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The use of inhibitors of fibrinolysis in the treatment of obstetric hemorrhage due to placenta detachment

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Abstract

Purpose. Comparative evaluation of efficacy of aprotinin and tranexamic acid for the influence on the system of hemostasis, fibrinolysis, and the blood loss degree.

Results. There were studied the results of fibrinolysis inhibitor therapy in women undergoing cesarean section for premature detachment of the placenta. The condition of hemostasis was controlled by low-frequency piezoelectric thromboelastography. There were obtained data on a more pronounced antifibrinolytic and blood preserving effect of the tranexamic acid, which was reflected in the reduction of the intraoperative, general and postoperative blood loss in group of tranexamic acid by 19.8%, 13.4% and 47.6%. The need for transfusion was also the lowest in the group with the tranexamic acid, which showed its greatest "blood preserving" effect.

Conclusions. Early use of inhibitors of fibrinolysis in premature detachment of the placenta is pathogenetically justified and necessary, allowing to reduce the perioperative blood loss. Using low-frequency piezoelectric thromboelastography in obstetric bleeding makes it possible to detect quickly and reliably disorders in various levels of hemostasis, allowing to carry out their correction timely and fully.

Keywords: premature detachment of the placenta, hemostasis, fibrinolysis, aprotinin, tranexamic acid.

Bleedings during pregnancy and childbirth remain one of the main problems of modern obstetrics, substantially defining the structure of maternal mortality. In most cases, massive postpartum hemorrhages lead to the development of hemorrhagic shock and disseminated intravascular coagulation syndrome. This necessitates the further development of modern pathogenetically grounded methods of prevention and treatment of bleedings during pregnancy, childbirth and postpartum period [1].

Adaptation of hemostasis during pregnancy, enhancement of coagulation capacity is of systemic character and occurs in all hemostatic links. Changes in the vascular –platelet link consist in increasing the absolute number of platelets and their functional activity. There is increase in concentration and activity of many plasma coagulation factors, increased fibrinogen level more than 2 times [3]. Changes of the anticoagulant state level include reduction of synthesis of antithrombin III while increasing its activity [2,3]. Adaptation of the fibrinolytic system during pregnancy consists in deep suppression of the fibrinolytic activity and has important physiological significance for the stability of blood clotting, long-term and reliable hemostasis. This occurs mainly due to the functioning of the placenta, which is the main source of inhibitors of protease activators: the concentration of the inhibitor of plasminogen activator type II (PAI-2) in its tissues is increased 260 times compared to the plasma levels, PAI-1- 11 times [2.3].

However, there are a number of situations where the fibrinolytic link of hemostasis in pregnancy and childbirth shows no inhibition and increased activity due to various reasons. These cases are characterized by clinical implementation in the form of bleedings, which are certainly of coagulopathic nature and require corresponding specific therapy [1].

One of these causes of obstetric hemorrhage is the pathology of premature placenta detachment (PPD) that occurs in its untimely detachment during pregnancy or in I-II stage of labor [4]. The placenta contains excess thromboplastic (tissue factors) substances, which penetrate into the bloodstream in its premature detachment and cause the development of acute or fulminant DIC-syndrome with the systemic activation of fibrinolysis [5, 9]. That is why women with obstetric hemorrhage due to placenta detachment require obligatory inclusion of antifibrinolytic preparations - inhibitors of fibrinolysis and proteolysis in treatment protocols.

Currently there are several representatives of this group of drugs, the main ones are aprotinin and tranexamic acid. Aprotinin is a drug from natural raw materials; it is a polyvalent protease inhibitor of kallikrein, tripsin, chemotripsin, plasmin [1]. The tranexamic acid is a synthetic drug, competitive inhibitor of plasminogen, it blocks lysine binding sites not only in plasminogen, but also in plasmin, preventing its effects on fibrin. [1, 7].

The Purpose of our study was the comparative evaluation of the efficacy of the use of drugs aprotinin and tranexamic acid in bleedings associated with the placenta detachment; study of the effect of these two drugs on the hemostasis system, fibrinolysis, volume of intra- and postoperative blood loss, evaluation of the effectiveness of antifibrinolytic therapy; improvement of methods of diagnosis of the hemostatic system during obstetric hemorrhage.

Materials and methods.

There were studied the results of surgical treatment of 48 women , aged 18-42 with a pathology of premature detachment of the placenta in term of 28-40 weeks of gestation who underwent cesarean section for 2012-2014. The study was conducted at the maternity home №2 of Odessa, Ukraine. The operation was performed under total intravenous anesthesia with artificial lung ventilation (TIA with ALV). The women under investigation were comparable in age, severity of the condition, comorbidity.

The criteria for inclusion of patients in the study were: the presence of the pathology of premature detachment of the placenta and the indications for cesarean section, no hereditary or acquired coagulation disorders, lack of a history of allergic reactions, the consent of women to participate in the study.

Criteria of patients' exclusion from the study were: refusal of women from further participation in the study, individual intolerance of the main drugs used in the study, development of severe and/or unexpected adverse events during the study.

There were formed the following study groups:

A control group consisted of pregnant women (30 women) in the period 28-40 weeks of gestation with polyhydramnion.

Pregnant women with pathology of premature placental detachment were divided into two groups depending on the ongoing antifibrinolytic therapy:

Group 1 - pregnant women with PPD pathology (23 women) in the period 28-40 weeks of gestation who underwent intraoperative specific antifibrinolytic therapy by intravenous infusion of the inhibitor of proteolysis aprotinin in the dose of 300,000 kallikreininactivating units (KIU).

Group 2 - pregnant women with PPD pathology (25 women) in the period 28-40 weeks of gestation who underwent intraoperative specific antifibrinolytic therapy by intravenous infusion of the tranexamic acid 15 mg / kg.

All women were given infusion therapy with balanced crystalloid solutions 10-15ml / kg (sterofundin) and HES solutions of 10 ml / kg (tetraspan) depending on the amount of the blood loss. The degree of the blood loss was assessed using quantitative (visual assessment of the blood loss, blood collection container, followed by measuring the volume, gravimetric method) and clinical (control of hemodynamic parameters, shock index) methods of determination. Assessment of hemorrhage and infusion therapy was made in accordance with the orders of the Ministry of Health of Ukraine №782 of 29.12.2005 and №205 of 24.03.2014. There was also evaluated dynamics of the laboratory parameters (erythrocytes, hemoglobin, hematocrit, platelets) and the need for transfusion of the blood (red blood cell mass, fresh frozen plasma (FFP)). The state of hemostasis after surgery, in 24 and 72 hours was controlled by low-frequency piezoelectric thromboelastography using a complex hardware ARP-01M "Mednord" (certificate of the state registration №10561/2011 of 10.06.2011).

A portable analyzer of the blood rheology ARP-01M "Mednord" allows to control even minor changes in the physical state in the process of blood clotting, make calculations of the amplitude and chronometric constants characterizing the main stages of hemocoagulation and fibrinolysis, detect pathological changes of these characteristics for early diagnosis of various disorders. The principle of the device is to check viscosity characteristics of the blood or plasma in the process of coagulation by measuring damping of mechanical oscillations of the resonant element, which is in the study sample, placed into the thermostat cell. Stimulating piezoelectric transducer causes vibrations of the probe with a specified amplitude. Mechanical energy of oscillation damping of the probe, depending on the characteristics of the environment that change, is converted by the piezoelectric transducer into electrical potential and is registered by a potentiometer. This measurement of characteristics of the studied sample is continuous. The device provides output to PC graphics of changes in resistance of the investigated medium to the probe fluctuations mounted on vibroelectric sensor and software provides calculation of the amplitude and chronometric parameters.

Results and discussion

In the study of hemostasis by the low-frequency piezoelectric thromboelastography method the women with premature placenta detachment were obtained data at the preoperative stage; the results are shown in Table 1.

Table 1.

Value of thromboelastography indices in premature placental detachment (PPD) before surgery.

Indices	Women with premature placental detachment before surgery, M± m	
	1 group	2 group
A0, rel.units, initial index of blood aggregation state	228.91 ± 16.23	226.48±15.93
A1, rel.units, amplitude of the contact phase of coagulation	186.93 ± 16.41	190.57 ± 14.75
T1, min., time of the contact phase of coagulation	1.44 ± 0.18*	1.46 ± 0.19*
ICC, rel.units, intensity of the contact phase of coagulation	19.79 ± 1.10*	20.93 ± 1.05*
TAC, rel.units, thrombin activity constant	60.98 ± 3.24*	61.84 ± 3.26*
T3,min., time of coagulation	6.74 ± 0.58*	6.71 ± 0.57*
ICD, rel.units, intensity of coagulation drive	57.21 ± 2.53*	57.28 ± 2.55*
A4, rel.units	729.28 ± 21.39	722.28 ± 22.54
T4,min., time of clot polymerization	15.86 ± 0.84	15.70 ± 0.88
ICP, rel.units, intensity of clot polymerization	22.49 ± 1.35	23.62 ± 1.39
T5,min., time of clot formation	35.39± 2.07	35.08 ± 2.11
MA, rel.unit, maximal s clot density	660.68 ± 25.08*	667.69 ± 26.31*
ITC, rel.units, intensity of total coagulation	21.85 ± 0.96	21.08 ± 0.98
RICL, %, retraction intensity and clot lysis	8.60 ± 0.18*	8.58± 0.19*

Note: p- reliable difference of the mean data by Student's criteria

*-$p<0.05$ in comparison with a control group

According to the thromboelastography data obtained in women with premature placenta detachment the following changes were observed. There is activation of the vascular-platelet

link of hemostasis and coagulation phase I, as evidenced by statistically significant ($p< 0.05$) changes in the indices: moderate shortening of time of contact T1 coagulation, increased intensity of the contact coagulation (ICC) characterizing the intensity of the contact kallikrein- kinino- cascade reaction of the blood, prothrombinase activity, aggregation activity of platelets and other blood cells. The pro-coagulating link of hemostasis is activated, as evidenced by a moderate growth of the index of thrombin activity constant (TAC), clotting time (CT), the intensity of coagulation drive (ICD). There are statistically significant changes of retraction intensity and clot lysis (RICL), reflecting the plasma state activity, the number of clot structured fibrinogen, degree of lability of plasminogen activators (tissue, urokinase, kallikrein, XIIa). Changes in this index are statistically significant and most pronounced. Thus, in premature placenta detachment pathology changes occur at different levels of hemocoagulation identified by the thromboelastography method that indicate small activation of the vascular - platelet, activation of plasma links with maximum hemostasis changes in fibrinolytic activity, which is reflected in the increased rate of RICL 27 times. These changes indicate to some extent a presence of the hypercoagulation with pathological activation of fibrinolysis and is a reaction of the regulation system of the blood aggregation to the areas of placenta detachment with release of tissue thromboplastin in the blood and directed at cessation of bleeding and processes of the placenta detachment.

After introduction of fibrinolysis inhibitor and after surgery the following changes were observed in groups under study according to thromboelastography indicators (Table 2).

Table 2.

Index dynamics of thromboelastography in women with premature placenta detachment after surgery and introduction of antifibrinolytic.

Indices	Women with premature placenta detachment immediately after surgery, M± m	
	1 group	2 group
A0, rel.units	276.69±19.54*	261.38±16.04*
A1, rel.units.	228.45±16.50	209.82±14.93
T1, min	1.18±0.21*	1.21±0.19*
ICC, rel.units	23.04±0.87*	22.93±0.92*
TAC, rel.units	76.36±4.02*	65.84±3.94*
T3, min	5.92±0.37*	6.13±0.54*
ICD, rel.units	70.26±3.02*	62.01±2.98*
A4, rel.units	819.68±19.42	794.76±17.84
T4, min.	14.96±0.59	15.16±0.63
ICP, rel.units	25.74±1.06	24.82±1.13
T5, min	31.64±1.89	33.71±1.92
MA, rel.units	703.31±21.09*	694.83±22.86*
ITC, rel.units	22.99±0.84*	22.04±0.96*
RICL	5.17±0.72*	2.06±0.31*

Note: p- reliable difference of the mean data by Student's criteria

*-$p<0.05$ in comparison with a control group

In the first study group treated with aprotinin infusion there was even greater activation of the vascular-platelet hemostasis level, the processes of aggregation and platelet adhesion, as evidenced by changes of T1 and ICC. There was also a change of the amplitude and chronometric indices of the activation of coagulation hemostasis level: increased rate of TAC, ICD, ICP, decreased T3. Thus, the first group of women with premature detachment of the placenta had even more pronounced activation of adhesion and platelet aggregation, a moderate pro-coagulating activation link hemostasis immediately after surgery. These

changes are a reaction to the blood loss and operation stress. Decrease of the RICL index by 40% confirms antiplasma aprotinin activity and its inhibitory effect on fibrinolysis, these changes were statistically significant.

In the second group of patients treated with infusion of the tranexamic acid, hypercoagulation changes were also observed in the vascular coagulation and platelet levels, as evidenced by changes of T1, ICC, TAC, ICD, T3. There was also a statistically significant decrease in RICL from 8.58±0.19% to 2.06±0.31%, which indicates a pronounced inhibitory effect of the tranexamic acid on fibrinolysis.

By the end of the third day of the postoperative period there was a marked moderate decrease of hypercoagulation manifestations in the vascular platelet and plasma levels with preservation of differences in the fibrinolytic activity: RICL index remained the highest in the first group- 1.96± 0.08%, and it was 1.12± 0.05% in the second group. Thus, the tranexamic acid causes the most pronounced inhibitory effect on fibrinolysis.

According to the changes in the coagulation system there was a decrease in blood loss: the reduction of the intraoperative, general and postoperative blood loss by 19.8%, 13.4% and 47.6% was determined in the group with tranexamic acid compared with the first group, and mostly in the postoperative period, as evidenced by laboratory blood indices (hemoglobin, hematocrit, erythrocytes, platelets). According to the amount of the blood loss, the need for transfusion of blood was different: 2 patients in the first group of aprotinin needed transfusion of erythrocytes mass and 3 women required fresh frozen plasma; 1 patient needed fresh frozen plasma and no one needed a transfusion of erythrocytes mass in the group of the tranexamic acid.

Conclusions:

1. Obstetrical hemorrhages due to the placenta detachment are accompanied by changes in the hemostatic system, which correlates with the degree of the blood loss and timely therapeutic interventions but increased fibrinolytic activity as evidenced by the increased RICL index 27 times is the most severe and constantly present in this condition.
2. As a result of application of various fibrinolysis inhibitors - aprotinin and tranexamic acid, it was found that the inhibitory effect of the tranexamic acid on fibrinolysis is more pronounced than that of aprotinin in the above dosage, which is also confirmed by a decrease in the volume of the blood loss in the second group with the tranexamic acid: intraoperative, general and postoperative blood loss by 19.8%, 13.4% and 47.6%. The need for transfusion

was also the lowest in the group with the tranexamic acid, which shows its greatest "blood preserving" effect.

3. Pathology of the premature placenta detachment is always accompanied by activation of fibrinolysis and requires obligatory application of antifibrinolytic preparations - tranexamic acid or aprotinin.

4. Application of low-frequency piezoelectric thromboelastography allows to diagnose timely and accurately disorders in the thrombocytic, plasmic and fibrinolytic levels of hemostasis, allowing to give fully and adequately the therapy aimed at correcting hemostatic disorders and restore the blood loss.

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