

ORIGINAL ARTICLE

PROGNOSIS AND PREVENTION OF UTERUS BLEEDINGS IN EARLY POSTPARTUM PERIOD FOR WOMEN WITH IDIOPATHIC ARTERIAL HYPOTENSION

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ABSTRACT

The aim: To establish the effectiveness of thromboelastography (TEG) and tranexamic acid (TXA) for prognosis and prevention of early postpartum period bleedings (PPB) for postpartum women with idiopathic arterial hypotension (IAH).

Materials and methods: Coagulological research was conducted (coagulogram screening, dynamic function of platelets under the influence of adenosine diphosphate (ADP) (visual assessment), measurement of soluble fibrin-monomer complexes (FMC) and TEG of 36 in parturient women during the I childbirth period with arterial hypotension. 14 parturient women with normal fibrinolysis were included into the first observation group; The second group includes 22 parturient women with TEG results which show signs of hyperfibrinolysis. Further, in cases when stronger fibrinolysis was detected during the late pushing phase of childbirth period, the TXA by amount of 1,0 g IV (bolus) was injected due to bleeding prevention. TEG was repeated during early postpartum period.

Results: the inhibition of platelet aggregation activity with ADP was observed in every parturient woman with IAH in the first partum period. In 61,1% cases with TEG hyperfibrinolysis were shown, which was accompanied by significant increase in FMC levels in blood. The use of TXA as PPB prevention for parturient women with IAH and hyperfibrinolysis during TEG was fully oppressing the fibrinolytic activity and was not affecting the coagulation part of hemostasis.

Conclusions: hemostasis testing during childbirth based on TEG gives the ability to prognose the hemorrhagic complications in parturient women with IAH and administer their prophylaxy using TXA.

KEY WORDS: idiopathic arterial hypotension, thromboelastography, thrombocytopeny, fibrinolysis system, tranexamic acid, childbirth

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INTRODUCTION

Women with idiopathic arterial hypertension (IAH) experience bleeding during their first postpartum period (PPB) at frequency of 10,6% [1]. Parturient woman with IAH poorly tolerate blood loss which results in rapid development of vasomotor collapse. The ruptures of soft tissues of the birth canal are characterized by increased bleeding from vessels of small and medium calibre. History provides information on formation of soft bruises and petechiae on skin and mucous membranes, nasal bleedings, menometrorrhagiae – bleedings associated with thrombocyte dysfunction [2, 3]. High nitric oxide concentration (NO), is a strong antiaggregant, which plays key role in IAH pathogenesis [4], can play important role in changes of vascular-platelet pathway of hemostasis. Decreased thrombocyte function leads to increased uptake of thrombin, and to depletion of procoagulants and platelets as a consequence. Meanwhile, every action that is aimed at blood clotting system activation, activates the fibrinolytic system. Fibrinolysis activation is detected due to increased release of tissue plasminogen activator from endothelial cells with fast plasmin formation [5]. Due to this fact deep circulatory disorders which occur as a consequence of deceleration of capillary blood flow and endothelial dysfunction due to excessive nitric oxide

formation in women with arterial hypertension contribute to increase in fibrinolytic activity of the vascular wall.

As known standard screening coagulogram gives no information about platelet link parameters, mechanical (hemostatic) clot properties and fibrinolytic activity. As well viscosimetric method of thromboelastography (TEG) highlights the coagulation dynamics over time, its parameters provide detailed information about the coagulation process and can reflect both hypo- and hypercoagulation.

TEG provides a global assessment of the coagulation system from the initiation of clot formation and development to fibrinolysis in vivo, including the interaction of cellular and plasma components, including platelet function. In the diagnosis of hyperfibrinolysis, the TEG method is considered as the most sensitive [6, 7].

Five randomized controlled trials were published in 2011 by Cochrane systematic review, which provided the results of using TXA for preventing PPB, two of which were included in meta-analysis, which combined 453 researches in total. Authors arrived at the conclusion that TXA reduces the level of postpartum bleeding, but further research is necessary to establish the effectiveness of routine TXA administration to postpartum bleeding prevention [8, 9]. H. Yang et al. (2001)

Table I. Coagulation system and TEG values in parturient women with primary arterial hypotension at first stage of labor

Indicators (norm)	I group, n=14	II group, n=22	p-II
PT, sec (14.0-16.0)	14.02±0.75	14.93±0.78	0.65
APTT, sec (25.0-35.0)	29.44±2,31	33.46±1,45	0.44
Fibrinogen, mg / ml (2.0-4.0)	3.97±0.21	3,91±0.55	0.21
Platelet count×109/л (180.0- 320.0)	178.33±19,33	173,07±32,8	0,78
SFMC, mg/100 ml (6.5-7.5)	9,87±1,85	17,37±2,30	<0.001
Aggregative function of platelets with ADP (visual assessment),sec(12.0-19.0)	23.7±3.3	26.7±4,3	0,65
Indicators TEG			
R, min (4.0-11.0)	5,72±0,92	6.37±1.36	0.54
K, min (1.0-4.0)	1,62±0.45	2.03±0.6	0.49
MA, mm (54.0-72,0)	65,21±5,45	42.66±7,11	<0.001
α-Angle, Degree (47.0-74.0)	67,42±4,88	62.77±6.25	0.12
CI (-3.0 - +3.0)	2,7 [1,7; 2,9]	-1.0 [-2.1; -0.04]	<0.001
G, dynes / cm ² (6.0-13.2)	9,52±1,81	3.81±0.99	<0.001
LY30, % (0-8)	1,8 [0,1; 6,0]	41.5 [22.6; 62.2]	<0.001

compared the efficiency of TXA use for PPB prevention during childbirth through the natural birth canal depending on the dose of medication. Researchers came to the conclusion about the more efficient way of using 1 g of TXA for postpartum bleeding prevention [10]. The evidence of the significant role of coagulopathy in the genesis of bleeding in postpartum women with IAH proves the necessity for conducting the research on effectiveness of using TXA during childbirth.

THE AIM

To establish the effectiveness of using TEG and TXA for PPB prognosis and prevention in parturient women with IAH.

MATERIALS AND METHODS

Based on the informed consent (protocol №1 excerpt from the meeting of the committee on research ethics of Danylo Halytsky Lviv National Medical University from 20.01.2020) the research was conducted in 36 postpartum women with IAH. Inclusion criteria for all the patients into the examination are based on confirmed IAH diagnosis conducted by daily pressure monitoring: the level of systolic blood pressure (Systolic BP) <100 mmHg, diastolic blood pressure (Diastolic BP) <60 mmHg, absence of congenital heart and vascular diseases, connective tissue dysplasia in form of Marfan syndrome, Ehlers-Danlos syndrome, collagenosis, hypothyroidism, adrenal insufficiency, infectious diseases, rheumatic disease.

All patients underwent coagulological studies and TEG. Native citrate plasma was used to perform thromboelastograms. For coagulological studies, blood was sequentially centrifuged in two modes (7 min at 110g and 20 min at 2000g) to obtain platelet-depleted plasma.

For the overall assessment of the state of the hemostasis system, the following studies were performed: prothrombin time (PT), activated partial thromboplastin time (APTT), deter-

mination of fibrinogen concentration by gravimetric method, study of dynamic platelet function under the influence of ADP (visual assessment), determination of soluble fibrin monomer complexes (SFMC) [11]. Platelet count was performed by hardware using the standard method.

TEG was performed on a TEG 5000 Haemoscope Corp., Niles IL thromboelastograph. To the thromboelastograph cuvette was added 340 µl of citrate blood and 20 µl of 0.2 M CaCl₂ solution. The following indicators of the sedimentation system were analyzed: reaction time (R, min); coagulation or clot formation time (K, min); the angle tangent to the TEG from the start of the clot formation (α-Angle, degrees); maximum amplitude (MA, mm); coagulation index - the blood potential of the patient in general (CI); the time of initial formation of fibrin (SP, min); clot stability and strength (G, dynes / cm²); LY30-characteristic of the clot dissolution process 30 min after reaching MA or the degree of fibrinolysis 30 min after the clot formation. The R and K values were recorded within 10 min after initiation of the thromboelastograph, α-Angle, MA, G, and LY30 settling in the cuvette for 30 minutes. Normal control values (reference interval) of thromboelastogram indices for citrate native blood samples are taken from the literature and provided by the manufacturer [12, 13].

The research was conducted on two groups of patients. The first one were those with normal fibrinolysis by TEG in 30 min. after clot formation during the first period of urgent childbirth. 22 parturient women with detected signs of hyperfibrinolysis with TEG were included into the second group. In case of further detection of hyperfibrinolysis signs during the pushing phase of childbirth (in average, from 10 to 15 minutes before the birth of the fetus) in order to prevent the bleeding, the TXA by amount of 1,0 g IV (bolus) had been injected and TEG had been administered repeatedly in early postpartum period. TXA belongs to antifibrinolytic medications. It possesses local and systemic hemostatic action during bleeding associated with the increase in fibrinolysis. Hemostatic effect is implemented by specific inhi-

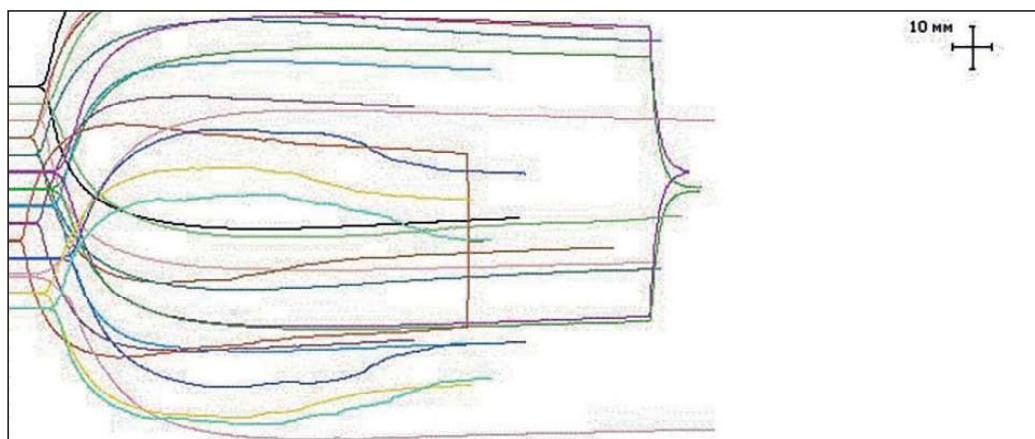


Fig. 1. TEG results in postpartum women with IAH during I childbirth period without sings of hyperfibrinolysis

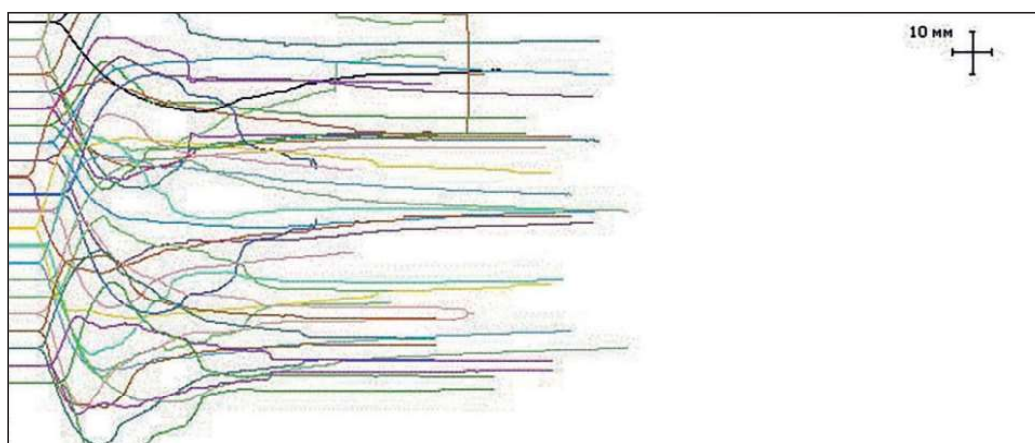


Fig. 2. TEG results in postpartum women with IAH in the first childbirth period with sings of hyperfibrinolysis

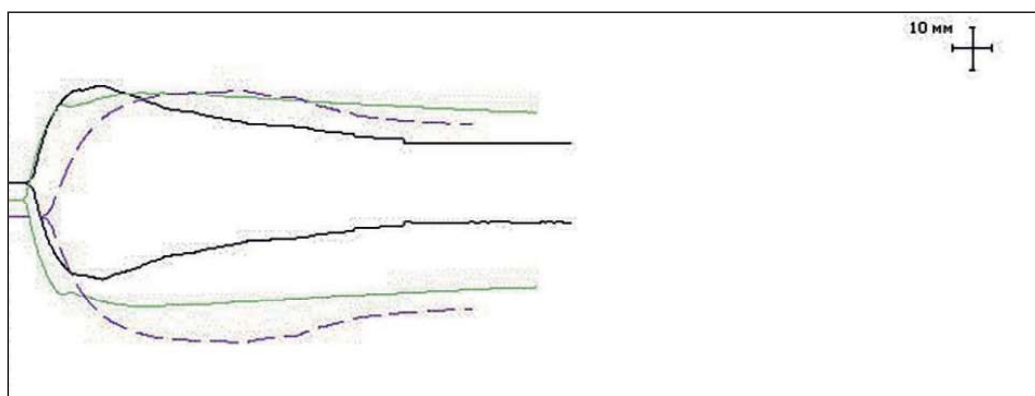


Fig. 3. TEG results for postpartum women with hyperfibrinolysis sings before and after TXA injection

bition of plasminogen activation and its conversion into plasmin.

We used the Shapiro-Wilk test to check the normality of quantitative distribution. In the case of the Gaussian distribution, the variational series were described using the arithmetic mean and standard deviation ($X \pm SD$). The rows that had non-Gaussian distribution were described using the median and 25th and 75th percentiles: Me [25%; 75%].

The significance of the difference between the two averages was determined in the normal distribution using the Student's t-test, and in the absence of a Gaussian distribution, the Mann-Whitney U-test. The difference was considered significant at $p < 0.05$.

Correlation dependencies were measured using Pearson's correlation coefficient (in quantitative terms) or Spearman's correlation coefficient (in rank indicators).

All statistical calculations were performed using RStudio v software. 1.1.442 and R Commander v.2.4-4.

RESULTS

Conducted studies have shown that screening coagulogram indicators of postpartum women with IAH were within normal limits and did not reliably differ in both groups (table I).

Thrombocytopenia was observed in 28,6% postpartum women in the I group and 36,4% of cases in the II observation group. Every postpartum woman with IAH had not only quantity changes in functional tests, but also quality changes of platelet hemostasis in the form of inhibition of aggregation activity with adenosine diphosphate (ADP). Quick inhibition of platelets aggregation with ADP (by 30,0 s) was in 41,7% of cases.

However, given that platelets are the basis for clot formation, vascular and platelet hemostasis disorders always are followed by changes of coagulation link. Classic standard tests provide the information only about separate links of hemostasis, which is why it was considered important to measure the density of the clot and the speed of its formation as well as lysis formation in parturient women with IAH using TEG. TEG results are shown in the table I and in fig. 1 and 2.

As it can be seen in fig. 1, 14 (38,9%) parturient women with IAH have TEG results within their normal limits. The latter reveals that in the case of changes in vascular-platelet chain and in the absence of coagulation chain disorders as well as sufficient thrombin level all following fibrinogenesis stages until the formation of crosslinked fibrin try to compensate the level of changes that was seen in the first stage. Excess of thrombin acts on fibrinogen accompanied by formation of fibrinopeptides A and B and fibrin-monomer. Consequently, FMC level in this group was slightly higher and exceeded the norm by 33,3%.

In 22 (61,1%) postpartum women with IAH there have been observed changes of TEG indicators (fig. 2). If the R value, K and α -Angle, which are signs of speed of the clot formation, were in their normal limits and did not differ in both groups, the density and clot efficiency was reliably lower in women from the second group, which contributed to its premature lysis. This indicates that platelets function in parturient women in this group is reduced significantly, this is why the basis for clot formation is not compensated by the increased thrombin formation. FMC for excess of thrombin do not have enough time to polymerize with the fibrin polymer formation, as well as the polymerization reaction has its stable speed at any given conditions [11]. The FMC level was significantly elevated and reliably higher than for parturient women in the first group for parturient women in the second group.

In order to prevent bleeding, parturient women of the II group, who were presented with signs of hyperfibrinolysis during TEG, were injected with TXA. In early postpartum period in order to control hemostasis, TEG was injected repeatedly.

As the result of using TXA, R, K and α – Angle indicators which show the speed of clot formation were $5,65 \pm 1,22$ min; $1,75 \pm 0,44$ min; $68,25 \pm 4,32^\circ$ accordingly were in their normal limits and did not reliably differ from the indicators before TXA injection ($p=0,58$; $P=0,61$; $p=0,54$). The indicators that characterize the mechanical properties of the clot are as follows: MA and G after TXA were $44,22 \pm 5,12$ mm; $3,64 \pm 1,21$ dyn/cmI, remained reduced and did not reliably differ from initial ($p=0,80$; $p=0,88$). Negative value of the coagulological index CI ($-1,2 \pm 0,21$), that indicates the predisposition to hypocoagulation, did not change reliably ($p=0,75$). Although, lytic index indicator LY30 after the injection of the preparation was normalised and showed $0,8 [0,0; 4,4]\%$ ($p<0,001$) (fig. 3).

It has been established that TXA detects hemostatic action without systematic and denominate effect on hemostasis, has no effect on coagulation link, and, as a consequence, does not increase the frequency of thromboembolic complications during postpartum period. The given data show the effectiveness of using the preparation to prevent PPB in postpartum women with IAH in the presence of hyperfibrinolysis signs according to TEG.

DISCUSSION

Violations at the level of the vascular-platelet link which should be considered as the effect of NO, a strong antiaggregant that plays key role in pathogenesis of parturient women with IAH [4]. The inhibition of adhesive-aggregation platelet function as the result of excessive nitric oxide formation contributes to decrease in the risk of microcirculation vessels thrombosis due to deceleration of capillary bleeding in arterial hypotension. The latter should be estimated as the protective reaction of the organism to a possible development of the sludge phenomenon in conditions of abrupt blood flow speed drop. Partially, this can be explained by the phenomenon of spontaneous formation of microtromboaggregates in the microcirculatory bloodstream at the reduced blood flow velocity in women with PAH, which attracts the most active platelets and naturally causes thrombocytopenia. Platelets not involved in the thrombotic process have reduced functional activity [3].

Changes in the initial link of hemostasis lead to changes in thrombin activity and affect the subsequent stages of fibrinogenesis. Finally, increased thrombin uptake leads to increased fibrinolytic physical activity. As a result, hyperfibrinolysis develops, and its efficiency depends not only on enzyme activity, but also on the mechanical properties of the fibrin clot [13].

High FMC concentration that in fact is the product of active thrombin effect, signifies the intensification of the intravascular coagulation, including uteroplacental blood flow. DIC syndrome possesses chronic or even latent course during pregnancy and for a long time clinically is not presented by any specific symptoms [14]. Hypoxia which intensifies during childbirth by reduction of uteroplacental perfusion during contractions contributes to the depletion of compensatory-adaptive mechanisms of hemostasis system with the development of activation of fibrinolytic system and occurrence of hemorrhagic complications.

Unlike the clotting system, fibrinolytic system is quite labile: hyperfibrinolysis can develop suddenly as the response to acute hypoxia, which leads to fibrinolytic bleeding [16]. The fibrinolysis increases due to endothelial activation and the action of tissue plasminogen activator, released by the endothelium as a result of chronic hypoxia in parturient women with PAH due to of uterine placental perfusion insufficiency [17]. Hyperfunction of the fibrinolytic system leads to rapid degradation of the clot and its preterm lysis, which can cause „hyperfibrinolytic” bleeding at labor and early postpartum period.

Coagulopathy, detected by TEG in parturient women with PAH, show that these patients are at high risk of uterine bleeding, and need appropriate preventive measures.

CONCLUSIONS

1. 61,1% postpartum women with IAH on the background of deceleration of platelet function (aggregation with ADP – $26,7 \pm 4,3$ s) The increased thrombin uptake is observed, which is represented by the increase in FMC levels ($17,37 \pm 2,3$ mg/100ml). And, according to TEG, fibrinolysis is activated (lytic index indicator LY30 – $41,5 [22,6; 62,2]$).
2. Hemostasis evaluation during childbirth based on TEG provides with the ability to prognose the hemorrhagic complications in postpartum women with IAH.

3. Administering the TXA antifibrinolytic to prevent PPB in postpartum women with IAH, based on TEG, oppresses the fibrinolytic activity (lytic index indicator LY30 – 0,8 [0,0; 4,4]) and does not affect the coagulation link of hemostasis (R, K, 6-Angel, MA, G, CI indicators do not reliably differ).
4. Administering TEG and TXA should be considered appropriate for PPB prognosis and prevention in postpartum women with IAH.

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Conflict of interest:

The Authors declare no conflict of interest.

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