DOI: 10.38095/2181-466X-20221042-161-165 УДК 618.36-07:613.1-616.1

PREVENTION OF MASSIVE OBSTETRIC BLEEDING WITH PROTHROMBIN COMPLEX CONCENTRATES

U. Yu. Yusupov, R. Sh. Ummatova, N. U. Babadjonova
Republican Specialized Scientific and Practical Medical Center for Obstetrics and Gynecology, Tashkent, Uzbekistan

Ключевые слова: Умон-комплекс, коагулопатическое кровотечение, гемостазиограмма, транексамовая кислота, система свертывание крови (ССК), массивные акушерские кровотечения (МАК), обьем циркулирующей крови (ОЦК), концентрат протромбинового комплекса (КПК), преждевременное отслойка нормально расположенной плаценты (ПОНРП).
Таянч сўзлар: Умон-комплекс, коагулопатик қон кетиш, гемостазиограмма, транексамик кислота, қон ивиш тизими, кўп миқдорда акушерлик қон кетиши, айланма қон хажми, протромбин комплекси концентрати, нормал жойлашган плацентанинг муддатидан олдин ажралиши.
Key words: Umon-complex, coagulopathy bleeding, hemostasiogram, tranexamic acid, blood clotting system (BCS), massive obstetric bleeding (MOB), circulating blood volume (CBV), prothrombin complex concentrate (PCC), premature detachment of a normally located placenta (PDNLP).

The article concludes that, compared with tranexamic acid, the Uman-complex is much more effective for the prevention and control of massive obstetric bleeding, and also does not lead to thrombotic complications after its use.

ПРОТРОМБИН КОМПЛЕКСИ КОНЦЕНТРАТЛАРИ БИЛАН КЎП МИҚДОРДА АКУШЕРЛИК ҚОН КЕТИШИНИНГ ОЛДИНИ ОЛИШ

У. Ю. Юсупов, Р. Ш. Умматова, Н. У. Бабаджонова
Республика ихтисослаштирилган акушерлик ва гинекология илмий-амалий тиббиёт маркази, Тошкент, Ўзбекистон

Ушбу мақолага кўра, Умон-комплекси транексамик кислота билан солиштирганда, кўп миқдорда акушерлик қон кетишини назорат килиш ва олдини олишда сезиларли даражада самарали эканлиги аниқланди. Бундан ташқари фойдаланишдан кейин тромботик асоратлар кузатилмади.

ПРОФИЛАКТИКА МАССИВНЫХ АКУШЕРСКИХ КРОВОТЕЧЕНИЙ КОНЦЕНТРАТАМИ ПРОТРОМБИНОВОГО КОМПЛЕКСА

У. Ю. Юсупов, Р. Ш. Умматова, Н. У. Бабаджонова
Республиканский специализированный научно-практический медицинский центр акушерства и гинекологии, Ташкент, Узбекистан

Согласно данной статье, установлено, что Уман-комплекс значительно эффективен в борьбе с массивным акушерским кровотечением и его предотвращении по сравнению с транексамовой кислотой, кроме того после его применения тромботические осложнения не наблюдались.

Every situation that can be predicted can be prevented. Prevention of MOB should be carried out at the stage of preconception preparation. In the presence of a scar on the uterus, placenta ingrowth or placenta previa, it is necessary to monitor the integrity of the muscles of the uterus through ultrasound or MRI. In cases of suspicion of the above risks, plan observation and delivery in a level III clinic.

Prevention of PDNLP and pre-eclampsia should be carried out from the antenatal period, where it is necessary to assess uteroplacental blood flow, correct BCS from early pregnancy until delivery.

According to the WHO recommendation, MOB analysis should be carried out not only according to the protocols of confidential analysis of maternal deaths, but also according to NEAR MISS indicators (eng - “barely survived”), or all critical cases of massive obstetric bleeding that developed during pregnancy, during childbirth and during 42 days after them. Together, "near miss" and maternal mortality make up the so-called. maternal outcomes [4].

Serious changes have taken place in the Republic of Uzbekistan over the past three years. Increasingly, extragenital diseases are becoming the cause of maternal death (26.6%). However, massive obstetric hemorrhages continue to occupy a leading place in the loss of maternal life

(22.7%). Severe forms of preeclampsia also continue to be the most formidable life-threatening conditions (19%). Consistently high figures in the MOB structure continue to be occupied by congenital and acquired disorders of the blood coagulation system, the so-called. coagulopathy and systemic diseases (systemic lupus erythematosus). In the last decade, there has been an increase in the incidence of coagulopathic bleeding from 0.9% to 2.1% per 1000 births [2].

It should be noted that massive obstetric bleeding is characterized by the suddenness and speed of blood loss, which, in the presence of extragenital pathology and / or pathology of pregnancy, leads to the rapid development of coagulopathy, the development of shock and MODS (multiple organ failure syndrome). Almost any obstetric bleeding exceeding 25% of the CBV leads to the development of consumption coagulopathy, or more precisely, to coagulopathy due to acute loss of components that provide blood aggregation, or the so-called. syndrome of disseminated blood coagulation. First of all, in the laboratory, this is expressed by a significant decrease in all factors of BCS, including a decrease in the number of platelets and their aggregation properties [7].

The same occurs in severe preeclampsia, liver disease, and congenital and acquired coagulopathic conditions. However, in this contingent of pregnant women and puerperas, massive obstetric bleeding develops initially due to coagulopathic disorders.

In modern obstetric practice, the issue of assessing the state of the blood coagulation system is acute. Performing a standard hemostasiogram is difficult in most level II obstetric facilities, and takes more than 50 minutes in level III facilities. With MOB, laboratory assessment of the state of hemostasis should be accessible, reliable and fast. That is why, in the national standards in the Republic of Uzbekistan for combating bleeding, the bedside test (Lee-White test) continues to be relevant.

Thus, dynamic monitoring in the antenatal period should include: - systematic monitoring of the state of the BCS, the number of platelets and their aggregation properties, determination of the level of homocysteine, the content of antiphospholipid antibodies, genetic markers of thrombophilia, indicators of vascular resistance in the uteroplacental blood flow from the III trimester of pregnancy up to childbirth [2].

From the literature sources, autoplasma transfusion is actively used in a number of countries for the prevention of massive obstetric bleeding associated with coagulopathy. The use of fresh frozen plasma for bleeding caused by pathology in the BCS is the most pathogenic, because plasma contains all the necessary factors to ensure proper blood aggregation. The use of autoplasma does not carry the risk of infection of the recipient, prevents post-plasma transfusion complications, and is more cost-effective than the use of donor plasma preparations [6].

However, the procurement, storage and transportation of autoplasma, as well as donor plasma and its components, also presents significant difficulties. First of all, the duration of storage of autoplasma from the moment of harvesting to its use is unknown. And violations of the conditions for the duration of storage can lead to unpredictable consequences of its use. With regard to donor plasma or its components, it does not exclude the risk of infection of the recipient with formidable viral diseases, including HIV and hepatitis.

Tranexamic acid has also been successfully used in a number of countries to stop or prevent MOB. It should be noted that tranexamic acid is included in the WHO list of essential medicines. The antifibrinolytic effect of tranexamic acid consists in the reversible blocking of lysine binding sites on the plasminogen molecule, which prevents its conversion into fibrinolysin (plasmin), and also prevents the combination of plasmin and tissue plasminogen activator with fibrin. This provides suppression of fibrin degradation. In addition, tranexamic acid enhances collagen synthesis, which enhances the stability and strength of the thrombus. But, according to the researchers, the effectiveness of the action is significantly reduced 12-16 hours after the administration of the drug. Repeated administration of tranexamic acid prolongs the main effect of the drug. The most common complications in the form of nausea, vomiting, diarrhea, allergies and orthostatic collapse are observed in isolated cases. The most formidable complication in the form of deep vein thrombosis

was also recorded very rarely (3.5).

Since 2020, SSAPMC of Obstetrics and Gynecology of the Ministry of Health of the Republic of Uzbekistan has conducted clinical studies to evaluate the effectiveness of preventing bleeding in pregnant women at risk for massive obstetric bleeding registered in the Republic of Uzbekistan. concentrate prothrombin preparation Uman-Complex D.I. (Uman Complex D.i) by KEDRION S.p.A. (Italy).

The main group consisted of 10 pregnant women with a decompensated form of liver cirrhosis and 10 pregnant women with congenital thrombocytopenia, who, in order to prevent massive bleeding, 24-36 hours before delivery, received Uman-Complex PCC in the amount of two doses. The drug represents a balanced complex content of the three main human blood coagulation factors - II, IX, X. The pharmacological effect of the drug is hemostatic. PCC compensates for the lack of blood coagulation factors and eliminates hypocoagulation in patients with its deficiency.

The comparison group consisted of 20 patients with liver cirrhosis and congenital thrombocytopenia, who received tranexamic acid according to the standard scheme to prevent bleeding a day before the expected birth.

Clinical and laboratory studies included complete blood count (CBC), blood coagulation analysis (BCS) with platelet count, international normalized ratio (INR), bedside test (Lee White blood test), calculation of blood loss, volume of transfusion of blood components and so on.

The most common complication in pregnant women with a high risk of massive obstetric bleeding is placental abruption (PDNLP). This is primarily due to the low aggregation potential of the blood and dysfunction of endotheliocytes. Injury of the soft birth canal is an expected complication of childbirth, potentially threatening MOB only if it is diagnosed late, or if bleeding develops, which has a coagulopathic character. Since this contingent of women has the highest risk of developing coagulopathic bleeding, a comparative assessment of the effectiveness of the PCC Uman-complex and Tranexamic acid for the prevention of MOB was the purpose of our study.

Of the laboratory parameters, the decrease in Hb - (76-91) g/l, Ht<22, the number of erythrocytes <2.2 drew attention. In biochemical analyzes, there was a decrease in total protein <48 g/l, an increase in the normative indicators of direct and indirect bilirubin and enzymes. The state of BCS in pregnant women at risk for MOB indicates that there was a significant decrease in the number of platelets (111±21) thousand units; in pregnant women with liver cirrhosis, (99±29) thousand units. – in women with thrombocytopenia ($p<0.1$). Fibrinogen levels decreased to 1.5-1.8 g/l, platelet aggregation decreased to 45-60%. Clinically, this was manifested by gingival and nasal bleeding, post-injection hematomas and petichial hemorrhages on the mucous membranes and skin of varying degrees of intensity. The Lee-White bedside test exceeded 12 minutes (12.5-16.0) in almost all pregnant study groups.

All pregnant women of the main and compared groups were consulted before delivery by highly qualified hepatologists, infectious disease specialists and hematologists. All pregnant women were delivered conservatively through the natural birth canal at 35-38 weeks of gestation.

In the intensive care unit of the SUPSSAPMCOiG, 24-36 hours before the expected birth, intravenous administration of PCC Uman-complex - 400 IU and Tranexamic acid - 1.0 intravenously by drip was carried out, according to the scheme recommended by the manufacturers.

After the use of the drugs, clinical and laboratory monitoring of the clinical manifestations of hemorrhagic syndrome and laboratory blood parameters was carried out. After the introduction of two doses of the PCC Uman-complex, all patients noted the disappearance of gingival and nasal bleeding. After the introduction of tranexamic acid, gingival and nosebleeds were not observed in 7 out of 10 pregnant women, in three patients the intensity of bleeding from the gums and nose decreased significantly, but didn't disappear.

In laboratory parameters, a slight increase in the number of platelets draws attention, but this was not significant. However, aggregation of blood increased significantly. This was manifested by an increase in fibrinogen levels up to 2.4-3.5 g/l, an increase in platelet aggregation up to 71-92%. Lee-White bedside test scores dropped to 6-8 minutes.

Complications observed in childbirth are presented in table No. 1. Injuries of the birth canal, both in the main and in the comparison group, were observed in two puerperas in the form of ruptures of the soft birth canal and perineum of the 1st degree. In all cases, the volume of blood loss did not exceed 150.0±30.0 ml. However, he draws attention to the fact that in women, in order to prevent bleeding in the prenatal period, the PCC Uman-complex was used, after restoring the integrity of the vaginal and perineal mucosa, reliable hemostasis was clinically fixed, despite a significant decrease in the number of platelets. In BCS, fibrinogen levels exceeded >2.8 g/l, platelet aggregation rates >84%. Blood clotting time according to Lee-White did not exceed 8 minutes.

In puerperas of the comparison group, who were treated with tranexamic acid to prevent bleeding, clinically hemostasis after restoring the integrity of the tissue in the perineum was manifested by slight spotting bloody discharge from the wound. The number of platelets, as in the main group, was below 76 thousand. Fibrinogen levels were in the range of 2.4-2.8 g/l, platelet aggregation was above 72%. The time of formation of a clot according to Lee-White is within 9-10 minutes.

The most formidable complication in the form of placental abruption in the first stage of labor was noted in a woman with liver cirrhosis, where tranexamic acid was used to prevent MOB, which required emergency abdominal delivery. The volume of blood loss before delivery was estimated at 200.0 ml. Two doses of FFP were administered intraoperatively. The total volume of blood loss was estimated at 650.0 ml.

A complication of the third stage of labor in the form of hypotension and atony of the uterus was recorded in only three women. The standard treatment of uterine hypotension was carried out, approved by the protocol of the Ministry of Health and the standard of the SURSSAPMCOiG. In one woman of the main group with liver cirrhosis, the volume of total blood loss was estimated at 350.0 ml. External-internal massage on the fist with the simultaneous use of uterotonics allowed for an increase in tone and stable hemostasis. Of the two patients in the comparison group, in one conservative methods of increasing the tone were sufficient to stop bleeding. The volume of blood loss was estimated at 500.0 ml, which required the additional use of uterotonics and repeated intravenous administration of trenexamic acid and infusion solutions to replenish the CVB. In one case, continued bleeding required surgical hemostasis. Laparotomy with uterine extirpation provided reliable hemostasis. Intraoperatively, in order to ensure reliable hemostasis, the patient additionally underwent intravenous transfusion of tranexamic acid-1.0 and FFP in the amount of two doses. The total blood loss in the patient of the comparison group was 1200.0.

Fibrinogen values in the patient of the main group after bleeding relief amounted to 2.4 g/l, platelet aggregation - 72%, Lee-White clotting time 8.35 sec. In the patient of the comparison group, who had enough conservative measures to ensure hemostasis, fibrinogen values were 2.1 g/l, platelet aggregation was 66%, the Lee-White clotting time was 9.20 sec.

In a patient with bleeding requiring surgical treatment, fibrinogen levels decreased to 1.8 g/L, platelet aggregation was 51%, the Lee-White thrombus formation time exceeded 12 minutes.

In pregnant women of both groups with thrombocytopenia, coagulopathic bleeding was observed during childbirth in one patient of the main group, and in three women of the comparison group. To stop bleeding in all patients, conservative measures were sufficient to increase the aggregation properties of blood. In one patient of the main group, after the placenta was released, one-stage bleeding in the amount of 400.0 ml was noted. Standard measures with repeated intravenous administration of oxytocin 10 units. and PCC Uman-complex made it possible to achieve reliable hemostasis five minutes after the administration of drugs.

In three patients of the comparison group, immediately after separation and separation of the placenta, bleeding was noted in the amount of 350.0-550.0 ml. Immediate standard measures to stop bleeding, which required repeated intravenous administration of uterotonics and tranexamic acid in a volume of 2.0, did not allow achieving stable hemostasis in two patients. Only after an additional transfusion of FFP in the amount of one dose, it was possible to stop the bleeding.

The indicators of BCS in the main group before the use of PCC Uman-complex recorded a

decrease in fibrinogen to 1.8 g/l, platelet aggregation 68%, clotting time according to Lee-White 10.40 sec. After the use of the PDA Uman-complex, fibrinogen levels increased to 2.4 g/l, platelet aggregation was 88%, the Lee-White clot formation time was 8 minutes. In the comparison group, all three patients with profuse bleeding had a decrease in fibrinogen <1.7 g/l, platelet aggregation was less than 70%, and the Lee-White clotting time was more than 12 minutes. After carrying out emergency standard measures to stop bleeding by additional administration of uterotonics and tranexamic acid, one and after the introduction of FFP, two puerperas managed to significantly increase the aggregation indicators of BCS. Fibrinogen levels exceeded 2.2 g/l, platelet aggregation up to 82%, the Lee-White time was reduced to <8.32 sec.

In the postpartum period, there were no repeated episodes of bleeding in both groups. However, on the 4th day after delivery, one patient of the comparison group had clinical signs of deep vein thrombosis of the leg of the right leg, which required a consultation with a vascular surgeon and additional treatment and rehabilitation measures to stop thrombosis. This patient had a sharp increase in platelet aggregation to 93% and a Lee-White clotting time < 5.20 seconds.

Thus, compliance with approved national protocols and local clinical standards for the prevention of massive obstetric bleeding in pregnant women and parturient women at risk should include drugs that increase blood aggregation properties. The most effective of them should be recognized as a concentrate of the prothrombin complex Uman-complex, which has proven itself as a tool that reliably provides a stable increase in blood aggregation characteristics. Compared to tranexamic acid, Uman-complex is much more effective for the prevention and control of MOB, and also does not lead to thrombotic complications after its use.

References:

1. Н. Н. Каримова, Ф. М. Аюпова Пути улучшения качества жизни женщин, перенесших послеродовое кровотечение // Вестник врача, № 3, 2019. С.62-67.
2. Н. Н. Каримова, О. Й. Поянов, Ф. К. Ахмедов, Н. Зокирова Некоторые биохимические механизмы дисфункции эндотелия у женщин, перенесших массивные кровотечения при родах // Вестник врача, № 2 (94), 2020. С.47-51. DOI: 10.38095/2181-466X-2020942-47-51
3. Мазурок В.А., Лебеденский К.М., Карелев А.Е.. Острая массивная кровопотеря. СПб.: Изд-во СПбМАПО.2009: 192с.
4. Мельник А.А. Механизм действия гемостатических лекарственных препаратов.\\ Новости медицины и фармации.- №10(622).-2017.
5. М. Н. Негматуллаева, Н. Р. Хамидова, Ф. К. Ахмедов, Д. И. Туксанова Факторы риска акушерских кровотечений // Вестник врача, № 3, 2019. С.83-85.
6. Савустьяненко А.В. Транексамовая кислота и особенности ее применения при тяжелых менструальных кровотечениях. \\ Новости медицины и фармации.- №20-22.-2012.
7. Сухих Г.Т., Серов В.Н., Савельева Г.М. и др. Профилактика и терапия массивной кровопотери в акушерстве (медицинская технология). М.2010.20с.
8. Транексамовая кислота: чем раньше, тем лучше.\\http:\\9thcall.ru\2017\11\10\txa\
9. Д.И. Туксанова Особенности изменения органного кровотока у женщин с осложненной преэклампсией // Вестник врача, № 4, 2018. С.61-66.
10. WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage.Geneva: World Health Organization; 2017,№2
11. Shakur H.et al.Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2) : a randomized, placebo-controlled trial.\\ Lancet.2010; 376 (9734): 23-32.doi: 10.1016.