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Case report

TRANEXAMIC ACID FOR PREVENTION OF POSTPARTUM HEMORRHAGE IN AVERY YOUNG PRIMIPARA WITHVON WILLEBRAND DISEASE

ТРАНЕКСЕМИЧНА КИСЕЛИНА ЗА ПРЕВЕНЦИЈА НА ПОСТПАРТАЛНА ХЕМОРАГИЈА КАЈ МНОГУ МЛАДА ПРВОРОТКА СО ВОН ВИЛЕБРАНДОВА БОЛЕСТ

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Abstract

Von Willebrand disease (vWD) is an inherited disorder in the coagulation process. It occurs due to the quantitative or qualitative lack of the von Willenbrand Factor (vWF) coagulation factor. It is clinically presented by mucous bleeding, most commonly nasal, gingival, prolonged and heavy menstrual bleeding, and only in severe forms of the disease, there can be bleeding in the joints and muscles. Treatment of patients with vWD focuses on stopping or preventing episodes of bleeding using medications. With good treatment, patients can have a normal, healthy life.

Treating pregnant women with vWD is a particular challenge in many respects: pregnancy bleeding, bleeding in the course of delivery and 4-6 weeks after delivery. vWD may have varying degrees of clinical severity. Serious bleeding may occur in patients with miscarriage or intentional abortion in the first three months of pregnancy due to insufficiently high levels of factor VIII (FVIII). Bleeding in pregnant patients occurs less frequently due to increased concentrations of FVIII and vWF during pregnancy. Their values drop sharply during delivery and after delivery, so they can cause heavy bleeding. Postpartum hemorrhage can cause serious problems. Antifibrinolytic medications are also used to control postpartum bleeding in patients with vWD. Tranexamic acid (TxA) belongs to that group of medications and has a wide range of effects in hemorrhagic conditions.

We present a case of vaginal delivery and postpartum hemorrhage controlled by TxA in a very young primipara (14 years old) who was diagnosed with vWD and completed the pregnancy at 36th gestational week.

Keywords: tranexamic acid, delivery, postpartum hemorrhage, von Willebrand diseas

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Апстракт

Вон Вилебрандова болест (vWD) е наследно пореметување во процесот на коагулација. Настанува поради квантитативен или квалитативен недостиг од вон-Вилебрандовиот фактор (vWF) на коагулација. Клинички се манифестира со крварење од слузници, најчесто од нос, гингиви, продолжено и обилно менструално крварење, а само во тешки облици на болеста има крварење во зглобови и мускули. Третманот на пациентките со vWD се фокусира на запирање или спречување на епизодите на крварење со помош на лекови. Со добриот третман пациентите можат да водат нормален, здрав живот.

Водењето на бремените пациентки со vWD е посебен предизвик од повеќе аспекти: крварење во бременоста, во тек на породувањето и четири до шест недели по породувањето, при што vWD може да има различен степен на клиничка сериозност. Сериозни крварења може да се јават кај пациентки со спонтан или со намерен абортус во првите три месеци од бременоста, поради недоволно високи нивоа на фактор VIII (FVIII). Крварења кај бремените пациентки се јавуваат поретко, а тоа се должи на зголемената концентрација на FVIII и vWF за време на бременоста. Нивните вредности нагло опаѓаат за време на породување и по породувањето, така што можат да предизвикаат обилни крварења.

Постпарталната хеморагија може да предизвика сериозни проблеми. За контрола на постпартално крварење кај пациентки со vWD се користат и антифибринолитични лекови. Транексемичната киселина (TxA) спаѓа во таа група лекови и има широк спектар на делување во хеморагични состојби.

Прикажан е случај на вагинално породување и постпартално крварење, контролирани со TxA кај многу млада прворотка (14 години) со дијагностицирана vWD кај која бременоста е завршена во 36 гестациска недела.

Клучни зборови: транексемична киселина, породување, постпартална хеморагија, Вон Вилебрандова болест

Introduction

Peripartum hemorrhage (PPH) accounts for about one-quarter to one-third of all maternal deaths. Worldwide, 7 women die of PPH every hour [1]. Von Willebrand disease is the most common inherited bleeding disorder among American women, with a prevalence of 0.6-1.3% [2]. The overall prevalence is even greater among women with chronic heavy menstrual bleeding, and ranges from 5% to 24% [3,4]. Among women with heavy menstrual bleeding, von Willebrand disease appears to be more prevalent among Caucasians (15.9%) than African Americans (1.3%) [5,6]. Von Willebrand disease (vWD) is the most common congenital hemorrhagic disease. It is presented in different types in 1% of the total population, equally in both genders [7]. It is classified into three types depending on the age and degree of vWF coagulation deficiency. The most common is type 1 (70-80%), while type 2 (20-30%) is less frequent. Both are inherited autosomal dominant. Type 3 occurs less frequently (1%) and is inherited autosomal recessively [8]. vWD occurs due to a quantitative (type 1 and type 3) or qualitative (type 2A, 2B, 2M, 2N) deficiency of vWF. vWF allows for easier platelet adhesion at the site of injured blood vessel and platelet aggregation. vWF is a carrier and stabilizer of factor VIII (FVIII) in the circulation, i.e. vWF forms a covalent complex with FVIII and prolongs its life in the blood plasma [9]. vWF is produced in megakaryocytes and endothelial cells. vWF, which occurs in endothelial cells, circulates in the plasma, and the other is found in the platelet alpha granules. FVIII is produced in hepatic cells [10]. vWD is characterized by a disorder of primary hemostasis, i.e. prolonged bleeding due to decreased platelet aggregation. vWD is clinically presented by mucosal bleeding. The main symptoms are nasal bleeding, gingival bleeding, bleeding of gums, heavy and prolonged menstrual bleeding, whereas joint and muscle bleeding is present only in severe forms of the disease with reduced FVIII values. In some patients the condition is completely asymptomatic, before serious bleeding following surgery or traumatic injury [11]. During pregnancy, the concentration of coagulation factors increases, including the FVIII complex, so that progression of gestation within the patient can lead to gradual decrease in bleeding time [12]. Severe bleeding may occur in patients with miscarriage or intentional abortion in the first three months of pregnancy due to insufficiently high levels of FVIII. Postpartum hemorrhage (PPH) can cause severe problems [13].

Treatment of vWD is only performed during active bleeding or before invasive procedure (surgical interventions) and only after the bleeding time is determined. At prolonged bleeding time in patients Desmopressin (vazopressin) for vWD type 1 is prescribed or FVIII/vWF concentrates for vWD types 2 and 3 [14,15]. Antifibrinolytic drugs are also used to control PPH in patients with vWD. Tranexamic acid (TxA) belongs to that group of medicines and has a wide range of effects in hemorrhagic conditions. TxA does not systematically affect coagulation, does not alter platelet count and function, nor it affects activated partial thromboplastin time (aPTT) and prothrombin time (PT) [16,17].

Clinical case

In December 2016 at the Clinic for Gynecology and Obstetrics in Skopje, a 14-year-old patient was admitted with vWD and first pregnancy at 36th gestation week. Information on family history could not be obtained due to separation of the parents andthe patient was raised by guardians. Personal history: vWD diagnosed in January 2015. Gynecological history: menarche at 11 years of age.

Medical history: due to prolonged menstrual bleeding (juvenile metrorrhagia) in a period of 3 months in January 2015, the patient was admitted and hospitalized at the University Clinic for Gynecology and Obstetrics-Skopje (UCGO). After ordination of hormone therapy (tabl. Microgynon 1x1/day) the bleeding stopped. After being discharged, the patient bled again despite the intensive regime with oral contraceptive (tabl. Microginon 21+7). Afterwards, she was sent to the Clinic for Children Diseases-Skopje. After performed children's hematologic examination in January 2015 she was diagnosed with vWD. The patient was recommended to use TxA (Tranexamic acid 500 mg to 6-8 hours) during bleeding (prescribed by a pediatric hematologist) and oral contraceptive Microgynon 21+7 (prescribed by a gynecologist-endocrinologist).

In April 2016 the patient's selected gynecologist after an ultrasound examination diagnosed the patient with pregnancy in second lunar month. During the ultrasound examination the patient was also diagnosed for uterus bicornis unicolis showingin left hemi-uterus GS with fetus with SA+ and right hemi-uterus decidually altered. Due to symptoms and signs of threatening miscarriage, a gestational therapy was provided (amp. Progesteron 1x1/week and tabl. Utrogestan 200 mg 2x1/day). The pregnancy was controlled by the patient's selected gynecologist and the patient was regularly examined by a pediatric hematologist. Due to the risk arising from the age and accompanying disease, the patient was sent to the UCGO-Skopje before her due date, in 36th gestational week. After the patient was admitted and examined with an ultrasound, the findings showed pelvic presentation of the fetus, with SA+, fetal biometry appropriate to the gestational age, good flow of feto-placental unit, CTG record without uterine activity, vaginal examination showed complete amniotic sac, without bleeding.

Before delivery, laboratory tests were made in the Center for Hemophilia within the Institute of Transfusion Medicine, Department: Hemophilia. The following tests

Table 1. Tests for diagnosis and monitoring of vWD – before delivery

Analysis (description of status)	Reference values	Results
Tests of hemostatic system		
Thrombocyte count [10exp9/L]	150-450	208
Hematocrit[%]	35-50	33.2
PT[sec)	9.8 (14) 14.2	11.33
aPTT[sec]	27.9(33) 37.7	27.25
TT[sec]	16.1(20) 24.1	15.42
Quantitative determination of coagulation factors		
Antihemophilic globulin (f.VIII)[%]	50-150	128.61
Von Willebrand factor Ris with activity [%]	50-150	126.91
Von Willebrand factor vWF Ag [%]	50-150	59.42
Tests for fibrinolytic system		
D-dimers [ng/mL]	0-500	1416.19
Aggregation and monitoring of anti-aggregation therapy		
ADP [%]	78-97	71
Collagen [%]	70-94	78
Ristocetin [%]	87-102	89
Blood test – White blood cells		
WBC [109/L]	3.5-10	8.5
LYM [109/L]	0.5-5	1.5
MID [10exp9/L]	0.1-1.5	0.5
GRAN [10exp9/L]	1.2-8	6.5
LYM% [%]	15-50	17.7
MID% [%]	2-15	5.5
GRA% [%]	35-80	76.8
Blood test – Red blood cells		
RBC [10exp12/L]	3.8-5.8	3.91
HGB[g/L]	110-165	12.1
MCV[fl]	80-97	85
MCH[pg]	26.5-33.5	30.9
MCHC [g/L]	315-350	36.4
RDW% [%]	10-15	15
RDWa [fl]	30-150	60.3
Blood test – platelets		
MPV[fl]	6.5-11	8.6
PCT[%]	0.01-9.99	0.17
PDW[fl]	0.1-99.9	13.5
LPCR[%]	0.1-99.9	21

were made: hemostatic system, quantitative determination of coagulation factors: FVIII and vWF (Ris with activity, vWFAg), tests for fybrinolitic system, aggregation and monitoring anti-aggregation therapy and overall blood test (Table 1).

After the results were obtained, a specialist in transfusion medicine provided an opinion on D-dimers appropriate for the gestational age, border value of vWF and RisCo activity, good aggregation of thrombocytes.

After a spontaneous start, with spontaneous breaking of the amniotic fluid sac, the early delivery of live fetus with footling breech presentation was completed vaginally with classic liberation of hands and extraction of head following the Smelli-Wheit method. Placenta and umbilical cord without irregularities. The episiotomy incision was sutured.

The delivery and postpartum bleeding were controlled with TxA, dosed by a pediatric hematologist (amp. Tranexemic acid 15mg/kg body weight (BW)/6-8 hours intravenous). The patient with BW=62 kg postpartum received1 g TxA (i.v.).

After delivery on the puerperium department the patient was examined consiliary by a pediatric hematologist and a treatment was given of TxA (amp. Tranexemic acid 3x1 g in the course of seven days, amp. Tranexemic acid 2x1 g after alleviation of bleeding and amp. Tranexemic acid 1x1 g until total termination of bleeding).

Uterotonic therapy was administered (amp. Methylergometrin 2x1 i.m. in the course of seven days, afterwards sol. Oxytocin 2x10IU/ml i.v. until termination of bleeding).

Two days after delivery at the Institute of Transfusion Medicine,Department for Hemostasis and Thrombosis, control laboratory analyses were made (Table 2).

According tothe results, a specialist in transfusion medicine said that there wasa hyper-coagulation condition with a strong hypo-agregability of thrombocytes with ADP and collagen.

Table 2. Tests for diagnosis and monitoring of vWD – after delivery

Analysis (description of status)	Reference values	Results
Tests of hemostatic system		
Thrombocyte count [10exp9/L]	150-450	220
Hematocrit[%]	35-50	32
PT[sec]	9.8 (14) 14.2	13
aPTT[sec]	27.9(33) 37.7	33
TT[sec]	16.1(20) 24.1	22
Quantitative determination of coagulation factor		
Antihemophilic globulin (f.VIII)[%]	50-150	145
Von Willebrand factor Ris with activity [%]	50-150	66
Von Willebrand factor vWF Ag [%]	50-150	114
Tests for fibrinolytic system		
D-dimers [ng/mL]	0-500	799.0
Aggregation and monitoring of anti-aggregation therapy		
ADP [%]	78-97	24
Collagen [%]	70-94	1
Ristocetin [%]	87-102	4
Blood test – White blood cells		
WBC [109/L]	3.5-10	9.4
LYM [109/L]	0.5-5	1.4
MID [10exp9/L]	0.1-1.5	0.3
GRAN [10exp9/L]	1.2-8	7.7
LYM% [%]	15-50	15.0
MID% [%]	2-15	3.5
GRA% [%]	35-80	81.5
Blood test – Red blood cells		
RBC [10exp12/L]	3.8-5.8	3.75
HGB[g/L]	110-165	117
MCV[fl]	80-97	84.8
MCH[pg]	26.5-33.5	31.4
MCHC [g/L]	315-350	370
RDW% [%]	10-15	14.9
RDWa [fl]	30-150	60.0
Blood test – platelets		
MPV[fl]	6.5-11	9.1
PCT[%]	0.01-9.99	0.20
PDW[fl]	0.1-99.9	14.1
LPCR[%]	0.1-99.9	23.4

The control tests for hemostasis made before discharge resulted in border values of vWF and vWFAg, hypo-aggregability with ADP, normal values for collagen and ristocetine and secondary activated fybrinolisis (Table 3).

The bleeding of the patient was regularly monitored clinically with gynecological controls, ultrasound examinations, complete blood test analyses, and analysis of hemostasis and dosing of vWF. Postpartum ultrasound results: uterus bicornis with low retained contents in one hemicavum. After administering uterotonic therapy the control ultrasound examination was good - without residual contents in both cavums and thin endometrium.

During her stay in thehospital, the patient was monitored by a multidisciplinary team consisting of gynecologist-obstetrician, gynecologist-endocrinologist, and pediatric hematologist, specialist in transfusion medicine, social worker and psychologist.

Before discharge, a control hematological examination was made and a recommendation was given for TxA therapy (tabl. Tranexamic acid 500 mg/2x1 until termination of bleeding).

The hospitalization of the patient until delivery lasted 23 days. She was discharged in generally stable condition and advised for therapy and control of bleeding up to 6 weeks by the selected gynecologist. Before discharge, the guardian was informed in detail for the condition of the minor patient and the recommendations, and due to the bad socio-economic status of the patient, the social service for good implementation of doctor's recommendations was informed.

Table 3. Tests for diagnosis and monitoring of vWD – before discharge

Analysis (description of status)	Reference values	Results
Tests of hemostatic system		
Thrombocyte count [10exp9/L]	150-450	268
Hematocrit [%]	35-50	31
PT[sec]	9.8 (14) 14.2	13
aPTT[sec]	27.9(33) 37.7	30
TT[sec]	16.1(20) 24.1	18
Quantitative determination of coagulation factor		
Antihemophilic globulin (f.VIII)[%]	50-150	110
Von Willebrand factor Ris with activity [%]	50-150	44
Von Willebrand factor vWF Ag [%]	50-150	49
Tests for fibrinolytic system		
D-dimers [ng/mL]	0-500	1064
Aggregation and monitoring of anti-aggregation therapy		
ADP [%]	78-97	64
Collagen [%]	70-94	109
Ristocetin [%]	87-102	125
Blood test – White blood cells		
WBC [109/L]	3..5-10	6.3
LYM [109/L]	0.5-5	1.4
MID [10exp9/L]	0.1-1.5	0.4
GRAN [10exp9/L]	1.2-8	4.5
LYM% [%]	15-50	22.9
MID% [%]	2-15	6.4
GRA% [%]	35-80	70.7
Blood test – Red blood cells		
RBC [10exp12/L]	3.8-5.8	3.81
HGB[g/L]	110-165	110
MCV[fl]	80-97	82.0
MCH[pg]	26.5-33.5	28.9
MCHC [g/L]	315-350	353
RDW% [%]	10-15	14.9
RDWa [fl]	30-150	61.4
Blood test – platelets		
MPV[fl]	6.5-11	8.5
PCT[%]	0.01-9.99	0.22
PDW[fl]	0.1-99.9	12.5
LPCR[%]	0.1-99.9	18.6

Discussion

vWD is a rare disease that is given particular importance in gynecology and obstetrics because of the risk of PPH. According to Holmgren the incidence of severe primary PPH is approximately 3.5% for vaginal delivery, 8% for instrumental vaginal delivery and 13% for caesarean section [18].

The incidence of PPH is higher in all forms of delivery, and is particularly high in instrumental vaginal delivery, with three out of seven deliveries (43%) resulting in blood loss of more than 1000 ml. Although there is insufficient data to make generalizations, these results underscore the recommendation to avoid instrumental vaginal delivery in patients with vWD, in order to prevent lacerations of the delivery routes and episodes of severe bleeding [19].

The Nordic Hemophilia Council gives several recommendations regarding the treatment, which differ from those given by other authors. Thus, TxA treatment is recommended in all births where the patient has vWD, and other authors recommend TxA only when it is found that vWF activity levels are low during the third trimester of pregnancy [20-22].

A study done at Karolinska University in Sweden analyzed birth data from 14 different obstetric units over a period of 18 years (1995-2012). Results showed that low levels of FVIII in the third trimester of pregnancy may predict PPH [23-25].

Patients with type 3 vWD were at highest risk of severe PPH, although all were administered prophylactic treatment [26-29].

Onestudy included 59 births and wasconsidered relatively large because vWD wasa rare disease [30].

Similar sample sizes were reported in previous studies from England, Scotland and the United States [31,32].

There are cases where vWF deficiency is diagnosed after prolonged bleeding following a caesarean section. Many experts suggest that vWD patients may have vaginal delivery, while caesarean delivery is reserved only when there are obstetric indications [33,34].

Treatment

Treatment options for vWD include desmopressin, vWF-FVIII, cryoprecipitate concentrates and other therapies such as antifibrinolytic agents and estrogens.
Desmopressin (DDAVP) is a synthetic analog of vasopressin. DDAVP increases plasma FVIII and vWF levels temporarily in normal subjects and in patients with vWD. DDAVP is most effective in patients with type 1 vWD who have normal vWF. Multiple reports suggest that DDAVP is effective in preventing or controlling abortion and bleeding during delivery [35-38].

Transfusion therapy

FVIII/vWF concentrates are used to prevent or control pregnancy-related bleeding in patients with vWD unresponsive to DDAVP [39-41].
Cryoprecipitate should not be used during pregnancy because of the risk of transmitting viral or other bloodstream infections. They can be used in emergencies if vWF-FVIII concentrates are not available.
Antifibrinolytic agents are usually avoided during pregnancy, but are used to control postpartum hemorrhage in patients with vWD [42].
TxA is a synthetic derivative of the amino acid lysine. TxA is used to control or prevent bleeding from placental abruption, caesarean section or other obstetric causes, with no visible side effects in the mother or fetus [43-48]. Table 4 shows benefits and risks of TxA [49].
According to one investigation of TxA, it is shown that various fixed (0.5 g or 1 g) and adjusted to body weight (10mg/kg or 15mg/kg) doses of TxA are used for prevention.
Given the wide range of body weight in pregnant women in modern obstetric practice, it is crucial to determine the minimum effective dose of TxA to avoid undue or overdose. The rationale of this study states that the minimum effective dose of TxA required to achieve therapeutic plasma levels of TxA is 5-15mg/L, following administration of a single dose of TxA intravenously (i.v.) after the delivery of a newborn and the cutting of the umbilical cord before delivery of the placenta [50-52].

Conclusions

Prophylaxis in consultation with a hematologist is a standard way of treating vWD patients for successful termination of pregnancy.The optimal dose and duration of prophylactic therapy depend on the type and severity of vWD, mode of delivery, and vWF level at term of delivery.
If patients are not diagnosed before pregnancy and delivery, then there is a risk of life-threatening bleeding during childbirth or postpartum hemorrhage. Levels of FVIII and vWF should be determined in pregnancy, primarily in the third trimester, to facilitate delivery planning and in the event of postpartum hemorrhage.TxA has a wide range of action in hemorrhagic conditions. TxA reduces menstrual blood loss and is an alternative to menorrhagia.
TXA reduces postpartum blood loss and transfusion needs. TxA has been successfully used to control bleeding in pregnancy and delivery.

Conflict of interest statement. None declared.

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