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Use of Octaplex in Obstetrical Hemorrhage – Preliminary Report From a Case Series

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ABSTRACT

Life-threatening hemorrhage can occur at any stage of pregnancy, labor, or puerperium. Octaplex, a prothrombin complex concentrate, is a highly promising agent raising new possibilities for the management of severe postpartum hemorrhage. We present a series of four cases illustrating our initial experiences with Octaplex in the management of acute obstetrical hemorrhage.

The hereby reported cases of hemorrhages were associated with primary, massive loss of blood due to various obstetrical conditions, such as uterine hypotonia postpartum or following Cesarean delivery, placenta accreta, or miscarriage with secondary bleeding disorders.

Administration of Octaplex enabled achieving hemostasis in all the cases.

However, due the lack of precise weighting of potential benefits and risks associated with poorly understood therapeutic effect of Octaplex in pregnant women, we postulate that it should be applied solely when maternal or fetal life is endangered and other established treatment modalities have failed.

KEYWORDS Octaplex, bleeding, obstetrical hemorrhage

Introduction

Postpartum hemorrhage (PPH) may occur in 1-5% of deliveries in developed countries, and still constitutes the most significant cause of maternal morbidity and mortality.[1-3] The degree of blood loss after childbirth varies depending on the type of delivery (vaginal vs. Cesarean). Typically, PPH is defined as a blood loss that exceeds 500 ml after a vaginal delivery or 1000 ml after a Cesarean.[1]

The search for agents that would normalize hemostasis in critical situations has been continued for a considerable length of time. Octaplex (PCC, Octapharma PPGmbH, Vienna, Austria) is a highly promising agent raising new possibilities for the management of life-threatening obstetrical hemorrhages.[4-5]

PCCs represent a heterogeneous combination of coagulation factors and counterbalancing inhibitor components. Typically, PCCs contain three (II, IX and X) or four (II, VII, IX and X) clotting factors derived from virus-depleted human plasma. The activity of the product corresponds to 25 IU of prothrombin complex per ml.[6-8]

Activated PCCs were first introduced in 1970s. Most modern PCCs are inactivated by adding small amount of unfractionated heparin (0.5-6 IU per IU of factor IX) and/or antithrombin that prevent clotting factor activation. Moreover, some PCCs may contain proteins C, S and Z to attenuate the risk for thrombogenesis; however, the clinical benefits associated with addition of these compounds remain unclear.[1,5,9]

As many PCCs contain small amounts of unfractionated heparin, they should not be administered to patients with heparin-induced thrombocytopenia.[10] However, there is no clinical evidence supporting a link between the use of PCCs and the risk for this condition. Nevertheless, PCCs are not recommended for patients with antithrombin deficiency or disseminated intravascular coagulation due to potential risk for thromboembolism; the only possible, rare exception pertains to patients with potentially life-threatening clotting factor deficiency, when no other alternative treatment is available. Furthermore, PCCs should be used with caution, after a careful benefit-risk analysis, in patients with active thrombosis, including individuals with a history of recent myocardial infarction.[11] Finally, the efficacy of PCCs has not been verified in pregnant or breast-feeding women or in pediatric populations.

Apart from the abovementioned major indications, PCCs are also used in an array of off-label indications, such as surgery- or trauma-related bleeding, reversal of anticoagulation therapy and other coagulation defects (e.g. von Willebrand disease, factor V or factor XI deficiency), and as rescue medicines in patients with intractable bleeding, persistent despite implementation of other therapeutic measures.

We present a case series illustrating our initial experiences with Octaplex in the management of acute obstetrical hemorrhage.

Case 1

A 31-year-old primipara (body weight 60 kg, 38th week of gestation) was admitted to the Department of Obstetrics and Gynecology due to the initiation of labor. She delivered a male newborn (birth weight 4410 g, Apgar scores 9 and 10 at 1 and 5 min, respectively) by Cesarean delivery. The decision on completing the pregnancy by Cesarean was associated with the risk of intrauterine hypoxia. Prior to the admission to the operating theatre, the patient had no complaints and her cardiovascular and respiratory function was normal. The Cesarean delivery was performed under spinal anesthesia. As uterine hypotonia was documented upon removal of the fetus, 5 units of oxytocin were given twice as an intravenous bolus (as recommended by the Polish Society of Gynecology and Obstetrics) to facilitate the involution. After expelling the placenta, additional 100 µg carbetocin (Ferring Pharmaceuticals, Germany), a long acting oxytocin agonist, mixed with 100 ml normal saline, were infused without resultant normalization of uterine contractions. Therefore, 0.4 mg of methylergometrine (Spofa Praha, Czech Republic) and 0.5 mg of sulprostone (Schering, Germany), a prostaglandin E2 analogue, were administered in a drip infusion due to further lack of uterine contractility. Continuous bleeding in the surgical field and lack of coagulation did not allow for the completion of the procedure despite normal uterine involution; secondary DIC resulting from severe, massive loss of blood was confirmed clinically. Bleeding, exceeding 1 250 ml, occurred 5 minutes after delivery. 1000 IU of Octaplex were administered by intravenous infusion with resultant evident reduction in bleeding (down to 200 ml). This enabled better insight into surgical field, identification of bleeding cause, and surgical hemostasis. A drain was placed in the peritoneal cavity. Throughout the procedure, the patient was given a total of 3 units of red blood cells (RBC) concentrate, 3 units of fresh frozen plasma (FFP), 6

units of cryoprecipitate, 1500 ml of crystalloids, and 1000 ml of colloids. Uterine involution was achieved, and the patient was transferred to the recovery room and then to the ward in good general status and without any major complications. The results of laboratory tests, including coagulation profile, are summarized in Tables 1 and 2.

Case 2

A 39-year-old multipara (body weight 55 kg, 3rd pregnancy, 31st week of gestation) was admitted to the Department of Obstetrics and Gynecology due to preeclampsia, central placenta previa and suspicion of placenta accreta. On admission, her blood pressure was 180/110 mmHg; moreover, she had proteinuria and generalized, puffy edema of lower legs and face. The patient reported decreased fetal movement, and deceleration was documented on cardiotocography. A decision on completing pregnancy with Cesarean was made due to the fetal risk and progressive signs of preeclampsia. The Cesarean delivery was performed under general anesthesia, and healthy male neonate (birth weight 2.34 kg, Apgar scores 9 and 10 at 1 and 5 min, respectively) was born. As massive hemorrhage resulting from placental invasion in lower uterine segment occurred shortly thereafter, a decision on intrapartum hysterectomy was made. However, the procedure could not be continued due to continuous loss of blood in the surgical field. 1500 IU of Octaplex were administered in an intravenous infusion, with resultant, albeit not complete, resolution of bleeding. Due to the lack of the signs of coagulation on laboratory testing and continued bleeding, 2 mg of NovoSeven (Novo Nordisk A/S, Denmark) was given as an intravenous bolus as an additional source of active factor VII (as recommended by the Polish Society of Anesthesiologists). Marked reduction of bleeding allowed for the continuation of hysterectomy, which was performed in accordance to the standard procedure and without complications. Two drains were placed in the peritoneal cavity and abdominal wall was closed in multiple layers. The patient lost 2 300 ml blood in total (including 1 500 ml prior to administration of Octaplex). Overall, 6 units of RBC concentrate, 6 units of FFP, 6 units of platelet concentrate, and 6 units of cryoprecipitate were transfused during the surgery. After the procedure, blood pressure was maintained at >90/40 mmHg without an inotropic or vasopressor agent. The patient, in good general status, was discharged home 7 days post-surgery. The results of her laboratory tests are presented in Tables 1 and 2.

Case 3

A 31-year-old woman (body weight 67 kg, 2nd pregnancy, 1st labor, 40th week of gestation) was admitted due to labor to the Department of Obstetrics and Gynecology. Due to fetal risk documented as deep late decelerations on cardiotocographic examination, the patient was qualified to the Cesarean delivery on an emergency basis. The surgery was performed under spinal anesthesia. Male newborn (birth weight 3.63 kg, Apgar scores 10 and 10 at 1 and 5 min, respectively) was delivered. As uterine hypotonia was documented in the course of the Cesarean, dinoprost (Sanofi Synthelabo, Hungary) was administered in intravenous infusion. Furthermore, 20 units of oxytocin (Grindex, Latvia) were slowly infused and 0.2 mg methylergonovine (Spofa Praha, Czech Republic) was injected to further stimulate uterine contractions, but the bleeding did not resolve. As secondary bleeding disorder resulting from massive loss of blood and coagulation factors was assumed as a cause of the hemorrhage, 2 units of packed RBC concentrate and 2 units of FFP were transfused. As the total volume of lost blood amounted to approximately 1 200 ml, Octaplex (1 000 IU) was given as a rescue medication, with resultant decrease in the bleeding down to 250 ml. Additional 2 units of RBC concentrate and 2 units of FFP were given until complete resolution of the bleeding 14 min thereafter. The patient, in good general and local status and without any complications, was discharged home on postoperative day 3. The results of her laboratory tests are presented in Tables 1 and 2.

Case 4

A 37-year-old multipara (body weight 70 kg, 3rd pregnancy, 1st labor, 20th week of twin gestation) was admitted to the delivery room with the sings of ongoing miscarriage. Although she expulsed the first fetus by natural forces, anesthesiology team was called due to severe pain experienced during the second delivery. The obstetrical procedure was performed under spinal anesthesia, and only opioid (Fentanyl, Janssen, Sweden) was administered with desirable analgesic effect. Five units of oxytocin (Grindex, Latvia) were administered as intravenous bolus, followed by another 20 units in slow infusion in 500 ml 0.9% NaCl. As post-miscarriage uterine hypotonia was observed, 0.4 mg of methylergometrine (Spofa Praha, Czech Republic) was administered in intravenous infusion, followed by 100 µg of carbetocin (Ferring Pharmaceuticals, Germany) shortly thereafter. Additionally, dinoprost (Sanofi Synthelabo, Hungary) was given intracervically due to the lack of uterine contractility. Continuous loss of blood without clotting was observed despite normal uterine involution and lack of birth canal injury. As the secondary bleeding disorder was diagnosed, 2 000 IU of Octaplex were administered in intravenous infusion with resultant evident normalization of the hemorrhage. Furthermore, 2 units of RBC concentrate, 2 units of FFP, 6 units of cryoprecipitate, 1000 ml of crystalloids and 1250 ml of colloids were transfused in the operating theater, along with additional 2 units of packed RBC concentrate and 2 units of FFP in the recovery room. Total blood loss prior to administration of Octaplex amounted to approximately 1 450 ml. The patient was discharged home in good general status five days thereafter. The results of laboratory tests are presented in Tables 1 and 2.

Discussion

The presented cases in which perinatal bleeding disorders in patients with otherwise normal coagulation system were successfully controlled with Octaplex illustrate possible application of this agent in obstetrics. The hereby reported cases of hemorrhages were associated with primary, massive loss of blood due to various obstetrical conditions, such as uterine hypotonia postpartum or following Cesarean delivery, placenta accreta, or miscarriage with secondary bleeding disorders; administration of Octaplex enabled their rapid compensation.

Octaplex proved to be particularly useful in cases 1, 3 and 4, in which waiting times for blood preparations were relatively long which is unfortunately inherent to our hospital laboratory procedures. Therefore, we developed an algorithm for sudden hemorrhage management, including administration of Octaplex in the case of massive PPH. Administration of this agent in the hereby reported cases was reflected by permanent control of bleeding, enabling compensation of hemodynamic status with smaller amount of blood preparations and normalization of remaining laboratory parameters. Furthermore, we did not observe any adverse events associated with the administration of Octaplex.

In the case of obstetrical surgeries, which by default are associated with increased risk of hemostatic disorders, the benefits associated with the administration of Octaplex extend well beyond bleeding control.[7,11-13] Administration of this agent reduces demand for fluids and blood preparations, thus decreasing immunization- and infection-related risks and the probability of early and late complications associated with massive loss of blood and transfusion. This allows for early breaking of the vicious circle associated with hemodilution coagulopathy, and reduction of costs related to transfusion of erythrocyte concentrate and FFP.

Uncertainty related to Octaplex administration results from the lack of precise weighting of potential benefits and risks associated with poorly understood therapeutic effect in pregnant women. Despite preliminarily outlined potential indications for the use of this agent, it should be applied solely when maternal or fetal life is endangered and other established treatment modalities have failed.

Conclusion

Our initial clinical observations suggest that this agent is highly

effective in selected obstetrical situations, and thus can represent a non-standard salvage option in cases in which all traditional possibilities of hemostasis have failed.

Table 1. Complete blood count prior to and after administration of Octaplex.

Parameter	RBC (T/l)	HGB (g/dl)	HT (%)	PLT (G/l)
Case 1				
Prior to Octaplex	2.93	8.52	26.93	213.0
2 h after	3.03	9.25	28.79	208.0
12 h after	3.75	10.85	35.2	198.0
Case 2				
Prior to Octaplex	2.33	7.13	22.5	218.0
2 h after	2.98	8.93	28.24	148.0
12 h after	3.89	12.13	35.26	185.0
Case 3				
Prior to Octaplex	2.86	8.40	27.53	160.0
2 h after	3.28	9.15	28.17	130.0
12 h after	3.70	12.50	36.56	167.0
Case 4				
Prior to Octaplex	2.56	8.40	27.28	160.0
2 h after	3.03	9.80	29.12	212.0
12 h after	3.75	9.93	29.39	207.0

RBC – red blood cells (normal range 3.7-5.1 T/l), HGB – hemoglobin (normal range 12.0-16.0 g/dl), HT – hematocrit (normal range 37.0-47.0%), PLT – platelets (normal range 150-450 G/l)

Table 2. Coagulation profile prior to and after administration of Octaplex.

Parameter	AT III (%)	APTT (s)	PT ratio (%)	INR	Fibr (mg/dl)	D-dim (µg/ml)
Case 1						
Prior to Octaplex	92.0	39.20	123.00	1.22	3.89	286
2 h after	75.0	36.60	111.00	1.18	2.00	372
12 h after	93.5	35.60	110.00	1.10	3.18	500
Case 2						
Prior to Octaplex	82.75	42.90	129.00	1.29	2.95	325
2 h after	62.0	40.90	128.75	1.23	1.72	368
12 h after	116.0	32.80	118.00	0.98	3.24	800
Case 3						
Prior to Octaplex	89.9	38.15	126.75	1.27	4.27	423
2 h after	85.5	36.70	128.50	1.25	2.20	657
12 h after	98.7	35.75	119.00	1.15	3.50	467
Case 4						
Prior to Octaplex	89.7	41.40	134.00	1.30	2.70	765
2 h after	72.30	35.54	125.00	1.29	2.50	1270.3
12 h after	73.8	35.10	120.00	1.20	2.74	489.8

AT III – antithrombin III (normal range 80.0-130.0%), APTT – activated partial thromboplastin time (normal range 25.90-36.60 s), PT ratio – prothrombin ratio (normal range 80.0-120.0%), INR – international normalized ratio (normal range 0.80-1.20), Fibr – fibrinogen (normal range 2.10-4.40 mg/dl), D-dim – D-dimer (normal range 1-500 µg/ml)

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