

Massive obstetric hemorrhage due to abnormal placentation : uterotonic drugs, cell salvage and activated recombinant factor seven

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INTRODUCTION

Massive obstetric hemorrhage remains a leading cause of maternal morbidity and mortality even in well developed countries (1). Hemorrhage can be antepartum, intrapartum or postpartum. Most important causes are placental abruption, uterine atony, cervical lacerations, placenta previa and abnormal placentation (placenta accreta, increta and percreta). The present manuscript will focus on anesthetic problems related to abnormal placentation and will review the place of uterotonic drugs, activated recombinant factor seven (rFVIIa), cell salvage and a team approach in the management of this problem. Interventional radiology and surgical management will be discussed elsewhere in this issue by colleague Dr. Dewandre.

ABNORMAL PLACENTATION : PLACENTA ACCRETA, INCRETA AND PERCRETA

Placenta accreta is defined as an abnormally adherent placenta, without invasion in the myometrium. Placenta increta invades the myometrium and placenta percreta perforates the uterine muscle and invades the serosa or the surrounding pelvic structures, usually the bladder. As a result of the increasing incidence of C-section, the problem is increasing. The combination of a placenta previa and a previous uterine scar, significantly increases the risk. CHATTOPADHYAY *et al.* and CLARK *et al.* noted that when the uterus is unscarred the incidence of placenta accreta is 5% in case of placenta previa (2, 3). With a previous C-section, the incidence increased to 10% and when more than 1 previous C-section was performed more than 50% of patients had placenta accreta. Ultrasonography and magnetic resonance imaging may be useful when abnormal placentation is suspected. However, they both have a poor sensitivity and the diagnosis is often made upon opening the abdomen and uterus (4).

A TEAM APPROACH

The effective management of obstetric hemorrhage, especially in unplanned or emergent situations, relies on very simple but often overlooked principles that all concur to timely treatment :

- simultaneous, coordinated, multidisciplinary management (i.e., obstetricians, anesthesiologists, hematologists, laboratory and blood bank technicians, radiologists and any other specialty which may be required)
- simple and practical definition of hemorrhage : any abnormal bleeding (in rate and/or duration) should trigger at once the diagnosis of hemorrhage. This is particularly important after delivery where the border between physiologic bleeding and PPH must be clear-cut to avoid any treatment delay
- consensual, preplanned, step management available as a written operational protocol.

A summarized example of step management was recently described by MERCIER and VAN DE VELDE (5) and is based on the French guidelines. Essential are a simultaneous approach, rapid interventions, short time delays before the following step is performed and no fear to use interventional and aggressive surgical techniques when conservative management does not produce results rapidly. Early involvement of senior and experienced staff is essential.

Of course, this systematic step-by-step approach of PPH treatment has to be adapted to the

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individual situation, rate of bleeding and/or specific etiologies but it is useful in most circumstances to gain time, avoid omissions and prevent conflicting strategies within the multidisciplinary team.

UTEROTONIC DRUGS

Uterotonic drugs are essential in the prevention and management of obstetric hemorrhage. However all these drugs have significant side-effects. While knowledge about their uterotonic effects is good, many anaesthetists and obstetricians fail to realise the cardiovascular risks associated with these drugs. Caution is required when these drugs are administered especially in hypovolemic patients.

Oxytocin

The first-line drug to manage postpartum uterine atony is undoubtedly oxytocin. Endogenous oxytocin is a 9-amino acid polypeptide with short half-life due to rapid metabolism of the drug by the liver, kidneys and the enzyme oxytocinase. Exogenous oxytocin has a small antidiuretic effect because oxytocin is similar to the antidiuretic hormone (ADH), differing in only 2 amino acids. The usual dose is 5-20 IU given as a slow infusion over 15-30 minutes.

Bolus administration of oxytocin has important cardiovascular side-effects: peripheral vasodilation, tachycardia, hypotension and increased pulmonary artery pressures (6, 7, 8), which may cause or contribute to serious maternal morbidity or mortality in already compromised patients. Electrocardiographic changes have also been described following a bolus of oxytocin. A slow intravenous infusion has therefore been recommended. THOMAS *et al.* confirmed that a slow iv infusion of oxytocin was as effective as a bolus in the prevention of postpartum hemorrhage following caesarean delivery (8). There is also no advantage of an intramyometrial injection of oxytocin (9).

Prostaglandins

Prostaglandins of the E and F family are the most recent additions to the pharmacological treatment of uterine atony. Prostaglandins increase myometrial intracellular free calcium concentrations, ultimately leading to increases in myosin light-chain kinase activity. The most common side-effects of all prostaglandins are fever, diarrhea,

nausea and vomiting. Other side-effects can occur and are listed below.

Prostaglandin E₂

Prostaglandin E₂ (dinoprostone) causes bronchodilation, tachycardia, decreased systemic vascular resistance and hypotension. No changes in pulmonary vascular resistance occur.

Prostaglandin F_{2- α}

Prostaglandin F_{2- α} causes systemic and pulmonary hypertension in anaesthetized pregnant patients (10). Over bronchospasm can occur.

15-Methylprostaglandin F_{2- α}

15-Methylprostaglandin F_{2- α} (carboprost) is probably the preferred prostaglandin for refractory uterine atony. Unfortunately it may result in serious pulmonary/respiratory side-effects such as increased intrapulmonary shunting, bronchospasm, disturbed ventilation/perfusion ratios and hypoxemia.

Prostaglandin E₁

Prostaglandin E₁ (misoprostol) is given rectally and appears to be an effective treatment option devoid of serious cardiovascular and respiratory side-effects.

Ergot alkaloids

Ergot alkaloids such as methergine are effective treatment options but with serious side-effects such as nausea and vomiting but more importantly hypertension, extreme vasoconstriction, myocardial ischemia and pulmonary hypertension.

ACTIVATED RECOMBINANT FACTOR VII (rFVIIa)

rFVIIa is not a new drug. Two decades ago it was introduced to treat bleeding episodes or surgery-related bleeding in patients with congenital haemophilia A or B with acquired antibodies to factor VIII or IX (11). It is now also licensed for congenital factor VII deficiency and for Glanzmann's disease. More and more authors also advocate its use in various other situations with life-threatening haemorrhage such as uncontrollable bleeding after trauma, intracerebral haemorrhage,

bleeding disorders in cirrhotic patients, etc... (12). However randomised evidence to support these claims is limited and at best contradictory.

rFVIIa binds to tissue factor at the site of endothelial damage. When this occurs haemostasis is initiated. In high concentrations rFVIIa can also directly activate factor X on the surface of locally activated platelets. This latter mechanism results in a thrombin burst, enhanced platelet activation and the production of a fibrin plug resistant to fibrinolysis. So rFVIIa will only work if sufficient concentrations of platelets and fibrinogen are circulating in maternal plasma.

There is a series of case reports using rFVIIa as a last resort drug in massively bleeding, coagulopathic obstetric patients. HAYNES *et al.* produced a very nice overview of 44 reported cases and added their own experience with four patients (13). The dose used varied from roughly 20 to 120 mcg/kg, without clear evidence of a dose-response relationship. Interestingly, while significant medical treatment was used before rFVIIa in most cases, prior invasive surgical management was used in only a few. Prior radiological embolisation was attempted in only four and in no patient was a B-Lynch suture tried. Following rFVIIa administration, invasive surgery, such as hysterectomy or embolisation, remained necessary. Out of 48 cases, seven patients responded only partially to treatment and three died despite treatment. The largest reported single centre experience comes from Finland (14). AHONEN and JOKELA described 12 cases in which the drug was used. They reported a 50% incidence of partial failure and a 5% complete failure rate. All patients required radiological embolisation anyway. These authors specifically noted in the paper's conclusion that "the indications for rFVIIa administration rather than selective arterial embolisation remain to be determined".

With every drug that initiates coagulation, thromboembolic complications are a potential risk. The safety record of rFVIIa in its licensed indication is good to excellent with very few complications reported (12). In over 140 000 doses administered to haemophiliacs, only 23 patients suffered from embolic complications: myocardial infarction (n = 7), cerebral infarction (n = 4), pulmonary embolism (n = 4), venous thromboembolism (n = 3) and disseminated intravascular coagulation (n = 5).

However, is it so safe in off-license indications, especially in patients with risk factors for thrombotic complications? Numerous reports have been published in which thrombotic complications were described. Complications included myocar-

dial infarction, ischaemic stroke, necrotising enterocolitis, pulmonary embolism, etc. The incidence is estimated to be up to 1% of treated patients. However, in certain patient populations the risk may even be higher. Remember that pregnant patients are hypercoagulable. When rFVIIa is given early during potentially life-threatening bleeding *before* severe coagulation abnormalities are present, thrombosis may occur. In fact, in the excellent review by HAYNES *et al.* of all reported obstetric cases in which rFVIIa was used, thrombosis of the brachial artery occurred in one patient (13).

When massive obstetric haemorrhage occurs, sometimes desperate measures are required to save maternal lives. rFVIIa is a highly debated drug which may have its place in massive obstetric hemorrhage (15, 16). However, rFVIIa is not without risks especially when given too early in hypercoagulable patients. The randomised evidence that is available for its off-license use is at best contradictory and inconclusive. Although rFVIIa appears to be a miracle drug in certain patients, failure has been reported regularly. Caution is required and input from specialists in coagulation prior to its use is probably required. Recently, European guidelines have pointed out that "rFVIIa may be considered as treatment for life-threatening post-partum hemorrhage, but should not be considered as a substitute for, nor should it delay, the performance of a life-saving procedure such as embolization or surgery, nor the transfer to a referring center" (17).

CELL SALVAGE

The use of intra-operative cell salvage in peripartum hemorrhage is still controversial, although it is now regarded as an acceptable alternative to allogeneic transfusion by major obstetric anesthesia societies (18, 19). The current main reason of opposers is concern that the implementation of this technique may result in delay compared to homologous/allogeneic transfusion during emergency obstetric hemorrhage. Proposers consider that every spared allogeneic unit of RBCs is important to reduce administration errors, transmitted infections, immunological reactions and blood supply shortage (18, 19). It has been recently calculated that intra-operative cell salvage might theoretically reduce exposure to appropriately transfused allogeneic erythrocytes in about 20% of Cesarean delivery patients (20). Although large randomized controlled studies are lacking to rule out any risk of coagulopathy or even iatrogenic amniotic fluid

embolus, experimental and clinical data now strongly suggest that it is very unlikely to exist. Indeed, modern autologous techniques in combination with leucocyte depletion filter removed virtually all fetal squames and phospholipid lamellar bodies ; in addition, extensive clinical experience is similarly reassuring.

Intra-operative cell salvage (and/or preoperative autologous donation in scheduled cases) has undisputedly a role in obstetrics in patients with high risk such as placenta praevia/accreta, massive fibroids, or rare blood type and/or unusual antibodies. Intra-operative cell salvage can be also useful in Jehovah's Witnesses or in geographic areas where allogeneic blood is particularly problematic. In institutions where cell saver devices are available routinely for non-obstetric scheduled surgery, its use for unexpected peripartum bleeding can also be useful, provided that "attempting to set the cell saver up in a crisis will not divert staff away from vital resuscitation".

CONCLUSIONS

Major obstetric hemorrhage remains a life threatening complication of normal and complicated delivery even in well developed countries. Essential in reducing morbidity and mortality is a team approach. Conventional uterotonic management remains the cornerstone of successful management but unlimited and overenthusiastic use of these drugs may in itself cause life threatening complications. rFVIIa can in certain situations be life saving when all else has failed but should not be considered as a substitute for, nor should it delay, the performance of a life-saving procedure such as embolization or surgery, nor the transfer to a referring center. Cell salvage appears to be safe and extremely useful in major hemorrhage especially if major blood loss is expected to occur.

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