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Chapter

Recent Advances in the Use of Uterotonics for the Prevention of Postpartum Hemorrhage

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Abstract

Primary postpartum hemorrhage (PPH) is one of the leading causes of maternal morbidity and mortality worldwide. The most common cause of primary PPH is uterine atony. Various uterotonics have been used over the years for the prevention of PPH. Oxytocin, Ergometrine, Misoprostol, and Carboprost have been extensively studied. Recently, Carbetocin, an analog of Oxytocin has been added to the armamentarium of postpartum hemorrhage. However, the optimal route and dose of these drugs are still being studied. Oxytocin induces superior myometrial contractions when compared with Ergometrine, Carboprost and Misoprostol. The effect of Oxytocin is reduced in myometrium of women with Oxytocin-augmented labor; however, it is still superior to the other uterotonics. Although the value of universal use of uterotonics to reduce postpartum hemorrhage after vaginal birth has been well established, their value in cesarean section has received little attention. It has been assumed that the benefits of oxytocics observed at vaginal birth also apply to cesarean section. The route of Oxytocin has been studied by various researchers. Intravenous (IV) infusion of Oxytocin has been preferred during cesarean section as an IV line would have been already secured and it has faster plasma peak concentration as in comparison to the Intramuscular (IM) route. Though IV bolus Oxytocin has been associated with a faster peak plasma concentration of Oxytocin, faster uterine contraction; it also has been associated with sudden hypotension. Carbetocin is also another promising drug. It has been prioritized due to its heat stable and long-acting properties. It also reduces the need for infusions. It is still an expensive drug in many countries. Carbetocin is administered as 100 mcg IM/IV/IV infusion. The dose in elective cesarean may be less as shown in some studies. Misoprostol by oral route has been recommended by WHO at 400–600 mcg in places where Oxytocin cannot be administered. Syntometrine has lesser blood loss compared to Oxytocin alone.

Keywords: blood loss, oxytocics, oxytocin, carbetocin, ergometrine, carboprost, sulprostone, tranexamic acid, ethamsylate, cesarean, vaginal delivery

1. Introduction

Post-partum hemorrhage (PPH) is a devastating condition causing severe maternal morbidity and mortality. Uterine atonicity is the commonest cause of PPH and in

turn, PPH is the commonest cause of maternal death across the continents. Though there are many predisposing factors for uterine atony, many a time it is unpredictable.

Postpartum hemorrhage is defined as blood loss of more than 500 ml after vaginal delivery and more than 1000 ml after cesarean delivery within 24 hours of childbirth.

Though the upper limits to define PPH have been established, the average blood loss during vaginal and cesarean delivery is much less. In a study conducted in France, which included 7908 participants, it was found that the mean blood loss after vaginal delivery was 180.1 mL (\pm 224.7 mL) and Cesarean delivery was 557.9 mL (\pm 496.2 mL) [1]. In another study conducted in rural India, the mean blood loss following delivery was 304 ml (range 50–975 ml). This was measured by Brass V drape [2]. Active management of third stage of labor (AMTSL) with the use of prophylactic uterotonics has reduced the incidence of PPH. However, based on evidence the World Health Organization (WHO) now considers controlled cord traction and uterine massage as optional. Delayed cord clamping is preferred. The only component of AMTSL which has been advocated is the use of uterotonic [3].

1.1 Oxytocin receptors

Endogenous Oxytocin is secreted by the paraventricular and supraoptic nuclei of the Hypothalamus. It stimulates uterine contractions. Oxytocin receptors (OTR) are present not only in the uterus but also in other tissues namely limbic regions of the brain, spinal column, heart, intestines, immune tissue, uterus, and breast. The OTR belongs to a family of G Proteins coupled receptors [4].

The number of receptors over the uterus is low in the first trimester and increases gradually in the third trimester. They then reduce in number in the immediate postpartum period.

The lower segment also has a lower concentration of OTR in comparison to the funds of the uterus, while the cervix has the least concentration [5].

1.2 Cesarean versus vaginal delivery

The cesarean section brings about a varied situation in comparison to vaginal delivery. It could be done during active labor as in emergency cesarean section or when the woman is not in labor as in elective cesarean section. There is no consensus on the dose of Oxytocin in elective cesarean sections in comparison to cesareans done in active labor. The required dose of Oxytocin during elective cesarean section is less than the dose required during cesarean section done during active labor, however, there is no consensus about using a reduced dose. The guidelines for use of prophylactic uterotonics for vaginal delivery are being used for cesarean delivery. There are no specific guidelines for the use of uterotonics for cesarean delivery [6, 7]. Oxytocin may be required to be continued as an infusion for 2–4 hours after the commencement of administration for women undergoing cesarean section [8].

2. Uterotonics

Uterotonics have been used over the decades for both prophylaxis and treatment of PPH. The uterotonics are Oxytocin, Carbetocin, Ergometrine/Methyl ergometrine, Carboprost, Misoprostol, Dinoprostone, and Sulprostone. Combination of Oxytocin and methylergometrine are also used.

2.1 Oxytocin

The WHO recommends the use of Oxytocin as the first-choice prophylactic drug for the prevention of PPH. It can be used intramuscularly and when an intravenous line is in place, intravenously as an infusion. The recommended dose is 10 IU. It has a half-life of 1–6 minutes [9].

Various studies have used intravenous bolus of Oxytocin during cesarean and vaginal delivery.

Royal College of Obstetricians and Gynecologists (RCOG) guidelines recommend a bolus of 5 IU Oxytocin during cesarean delivery. Other studies have used doses as low as 1 IU and as high as 10 IU bolus during cesarean delivery. They have shown that Bolus Oxytocin did not have significant adverse effects as it was previously thought [10].

Intravenous bolus of 10 IU of Oxytocin has been used for the prevention of PPH during vaginal delivery. In a randomized control trial comparing intravenous bolus of 10 IU Oxytocin to intramuscular Oxytocin of 10 IU for prevention of PPH during vaginal delivery conducted in the Republic of Ireland, it was found that the incidence of PPH was lower in women administered intravenous bolus of Oxytocin in comparison to the intramuscular group (4.6 vs. 8.1%) [11]. In another large three-arm randomized control trial conducted in Egypt, comparing 10 IU of Oxytocin by intramuscular, intravenous bolus, and intravenous infusion, it was observed that the blood loss in the intravenous infusion group was 5.9% lesser than that occurring in the intramuscular group. The intravenous bolus group had 11.1% less blood loss in comparison to the intramuscular group. There were no significant differences in the adverse effects of Oxytocin among the three groups [12]. Intravenous bolus Oxytocin is shown to be a promising choice of uterotonic for the prevention of PPH without any significant adverse effects.

2.2 Carbetocin

Heat stable Carbetocin is a long-acting synthetic analog of Oxytocin. It has the benefit of being heat stable in comparison to the heat-sensitive Oxytocin. It does not require cold storage and has a good shelf life of 36 months at 30°C [13]. It is long acting having a half-life of 40 minutes. It is given in the dose of 100 mcg. Intramuscular, intravenous infusion, and intravenous bolus routes have been administered. Carbetocin, like Oxytocin, causes hypotension, tachycardia, and myocardial ischemia. It acts by 2 minutes of administration when given intravenously or intramuscularly [14–16]. The Champions trial conducted over 23 countries at 10 sites compared 100 mcg of Carbetocin to 10 IU of Oxytocin both given intramuscularly. It concluded that Carbetocin was noninferior to Oxytocin for the prevention of PPH and there was no significant difference between the adverse effects on both the groups [13].

It has now been recommended for prevention of PPH by the WHO [9]. It has not been recommended for therapeutic use in PPH. Carbetocin is for single use, it cannot be repeated. This is because it causes adverse effects with higher doses.

2.3 Misoprostol

This is a prostaglandin E1 analogue. It has the advantage of being in a tablet form and does not need refrigeration. It also has a long shelf life of 2–3 years [17]. It can be

administered by oral, sublingually, buccal, vaginal, and rectally. Oral and sublingual route administration act faster than the vaginal and rectal routes. The overall serum concentration of buccal route is low. It has a half-life of 20–40 minutes [18]. A common practice is to moisten the Misoprostol prior to placing it vaginally. This has been found not to have any additional benefit in comparison to placing the tablet as it is [19].

Various doses and routes have been recommended for prophylaxis. Misoprostol 400 mcg and 600 mcg by oral route have been recommended by the WHO. According to a meta-analysis by the Cochrane database, the use of Misoprostol as a first-line agent may have increased blood loss in comparison to Oxytocin [20]. Adverse effects of shivering, diarrhea, and vomiting, though not life-threatening, can be worrisome for the patient [9].

2.4 Ergometrine and methyl ergometrine

Ergometrine and Methyl ergometrine i.e., the semi-synthetic form of ergometrine are long-acting uterotonic agents [21]. The onset of action is 2–3 minutes and the half-life is 30–120 minutes [9].

They act on the adrenergic and serotonin receptors on the uterus. It is given in the dose of 0.2 mg and can be administered by both IV and IM routes [22]. Ergot derivatives are known to have severe cardiovascular adverse effects like hypertension, tachycardia, myocardial ischemia, and infarction. They can also cause cerebrovascular accidents and demise. For these reasons, it is not used as a first-line drug for prevention of PPH. It is not recommended in those women who suffer from hypertensive disorders of pregnancy or cardiac disease.

2.5 Carboprost tromethamine

Carboprost tromethamine is the synthetic 15-methyl analogue of prostaglandin $F_{2\alpha}$. It is listed as a therapeutic drug for postpartum hemorrhage by the WHO [9]. It acts by increasing the intracellular calcium of the myometrial cells, which in turn enhances the myosin light-chain kinase activity and uterine contractions. This action is mediated via the Prostaglandin F receptor which is a G protein-coupled receptor in the myometrium [23]. Carboprost is administered as 250 mcg intramuscular injection. It can be given as an intramyometrial injection as well. However, this is an off-label route. It cannot be given intravenously. It has a half-life of 8 minutes and its action peaks by 15–30 minutes. It is mainly used as a second line of treatment of postpartum hemorrhage. It is associated with gastrointestinal adverse effects, such as vomiting and diarrhea. It can also cause bronchospasm and is contraindicated in asthmatics [22]. Due to its adverse effects, it is not recommended by the WHO for prevention of postpartum hemorrhage [9].

2.6 Sulprostone

Sulprostone is a derivative of Prostaglandin E2 and acts on the PGEP3 receptor of the myometrium. It has been used for the treatment of PPH. It is used as an intravenous infusion. The dose is 100 mcg/hr. and can be given at 500 mcg/hr. dose. It is contraindicated in bronchial asthma.

According to the French College of Gynecologist and Obstetricians, Sulprostone is the second-line drug to be used in case there is a failure of Oxytocin in the

management of postpartum hemorrhage [24]. This drug is used in European countries and is not available in US and Australia. It is not available in India either.

2.7 Combination of uterotonics

The combination of Methylergometrine 500 mcg and Oxytocin 5 IU, commonly known as Syntometrine, is used in some countries. It acts for 2.5 minutes and has a prolonged action of 3 hours. It is administered intramuscularly [9]. Though it has more adverse effects than Oxytocin alone like nausea, vomiting, and diarrhea, it is more effective in preventing PPH [25].

2.8 Misoprostol and oxytocin

This combination of oral misoprostol with intravenous/intramuscular Oxytocin aims to take the benefit of the fast-acting Oxytocin and the longer-acting misoprostol. Though the combination is promising, it is associated with more adverse effects of shivering, fever, nausea, vomiting, and diarrhea, in comparison to Oxytocin alone [9].

3. Hemostatic drugs: tranexamic acid and ethamsylate

Antifibrinolytic drugs can reduce blood loss during delivery. Tranexamic acid is an antifibrinolytic drug. It binds to plasminogen molecule and blocks the lysin binding sites. It is administered intravenously as 1 gm after the administration of the prophylactic uterotonic.

Ethamsylate is another hemostatic drug that acts on the platelets and enhances their aggregation. It also improves capillary resistance. It is used as a 1 g intravenous dose. It can cause rash, nausea, vomiting, and hypotension [26, 27].

3.1 Estimation of blood loss after delivery

The diagnosis of postpartum hemorrhage itself can be challenging. The various methods commonly used to estimate the blood loss are the visual estimation of the blood loss, use of a funnel-shaped drape with an attached plastic sheet placed underneath the buttocks of the woman, otherwise known as the Excellent BRASS-V drape in which the blood collects, spectrophotometry and estimation of Hemoglobin concentration in the venous blood [28]. Other indirect methods include weighing soaked gauze pieces, mops and drapes, and adding blood collected in bowls and suction jars. The weight of the unsoaked mops and gauze pieces and drapes should be known. 1 g increase in the weight of the soaked material = 1 ml of blood [29].

An easier, quick, and efficient method to estimate the blood loss and to help in predicting the prognosis would be to use the Shock Index (SI). This is a simple bedside calculation using the ratio of heart rate (HR) and systolic blood pressure (SBP) [30].

$$SI = HR / SBP. \quad (1)$$

The normal SI range is 0.7–0.9 in pregnancy which is slightly higher than the non-pregnant SI which ranges from 0.5 to 0.7 [31]. If the SI is more than 1, it indicates cardiac decompensation and demands immediate treatment [32]. SI has been used to triage patients for referral, especially in low-resource settings. A value of ≥ 0.9 would

suggest referring the patient to a tertiary care center, ≥ 1.4 immediate intervention, and ≥ 1.7 adverse prognosis [33].

3.2 Choosing the right uterotonic

With multiple uterotonics to choose from, selecting the appropriate one demands knowledge of the contraindications and adverse effects of the specific drug.

According to the WHO guidelines for the management of PPH, uterotonics are to be used in the following order.

First line of treatment: Oxytocin is the first-line drug to be used. It is to be used in dose of 20 IU in 1 liter of fluid at 40 drops per minute. It should not exceed 3 liters.

Second line of treatment: If not responding to this treatment, or if oxytocin is not available then, ergometrine or fixed-dose ergometrine and oxytocin can be used as second-line treatment of PPH. Methyl ergometrine can be given 0.2 mg IM or IV, it can be repeated after 4 hours and a maximum of 5 doses can be given.

Third line of treatment: Prostaglandins can be used as third-line drug if the patient does not respond to the previous treatments. Carboprostcan is given as 0.25 mg IM and can be repeated every 15 minutes for a maximum of 8 doses [9].

4. Conclusion

Oxytocin is the first-choice drug for the prevention of postpartum hemorrhage.

Carbetocin is a heat stable, longer-acting uterotonic which can be used in places where the cold chain and cold storage cannot be assured. However, it is expensive in comparison to Oxytocin.

Misoprostol is a heat-stable tablet that can be used if Oxytocin is unavailable. However, it is likely to be inferior to Oxytocin in the prevention of PPH.

Carboprost, though effective in controlling blood loss after the delivery, is used for therapeutic purposes than prophylaxis due to its adverse effects. It also requires refrigeration.

Ergot derivatives are second-like choices as they have cardiovascular adverse effects. It also requires refrigeration.

Sulprostone though considered as second-line drug for PPH in France and other European counties, is not available in many places.

Combination of drugs Misoprostol and Oxytocin or Syntometrine, while potentially reducing blood loss, seem to have more adverse effects; thus, administering Oxytocin alone is more advantageous.

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