

Oxytocin Administration and the Prevention of Postpartum Hemorrhage

Heather E. Brooks

University of Wyoming - Fay W. Whitney School of Nursing

### **PICOT Question**

In postpartum women, does the administration of oxytocin after delivery versus no pharmacologic intervention after delivery lead to lower rates of postpartum hemorrhage evaluated during the postpartum period?

### **Introduction of Problem**

Postpartum hemorrhage (PPH) is a very prevalent issue related to maternal morbidity and mortality. It is one of the leading causes of maternal mortality, accounting for more than 10% of pregnancy related deaths. Along with that, hemorrhage related morbidity is the leading cause of high-level care needed from obstetric conditions (American College of Obstetricians and Gynecologists [ACOG], 2017; Gavigan et al., 2019). The Centers for Disease Control and Prevention (CDC) analyzed statistics from 1993 to 2014 which evaluated the number of cases of PPH with obstetrical procedures to control bleeding and with blood transfusions required. These obstetrical procedures include but are not limited to, surgical repair of a laceration, uterine artery ligation or embolization, obstetric tamponade of uterus or vaginal canal, or a hysterectomy in severe cases. This data showed that in 1993 there was approximately 4.3 per 10,000 hospital deliveries that resulted in procedures to control bleeding, compared to 21.2 per 10,000 as of 2014. As for PPH with blood transfusions needed it was approximately 7.9 per 10,000 in 1993 and jumped to 39.7 in 2014 (Centers for Disease Control and Prevention [CDC], 2019). The numbers show that the problem of PPH is increasing with time, even though we have many resources to prevent and treat this problem. It should be noted that postpartum hemorrhage, refers to a severe amount of blood loss noted after delivery. In the clinical setting this typically means more than 500 mL of blood loss within the first 24 hours after delivery. The American College of Obstetricians and Gynecologists (ACOG) defines postpartum hemorrhage as greater

than 1000 mL of blood loss with signs and symptoms of hypovolemia within the first 24 hours after delivery (ACOG, 2017; Evensen et al., 2017). This amount of blood loss can be devastating on the woman's body and can often be very difficult to control once it has begun possibly resulting in more serious procedures such as a hysterectomy or death in severe cases. This data shows the great need for more established clinical protocols for risk-factor analysis, prevention, and treatment of PPH so that we may reduce the number of cases.

### **Risk Factors of PPH**

It is important to note that although around 20% of women who experience PPH will not have any identifiable risk factors, there are a few risk factors that healthcare providers should be aware of and should evaluate for in each patient. Most of the risk factors are only apparent during or after the birth process and may not be identifiable beforehand. Some examples of such risk factors include uterine atony, lacerations, retained placenta, adherent placenta, or uterine inversion (Gavigan et al., 2019). According to a study conducted on 43,105 hospital deliveries, 1064 of those deliveries resulted in severe PPH of greater than 1500 mL. They evaluated those 1064 women for potential risk factors that made them more likely to have a PPH and the most common cause of PPH that they found was uterine atony, followed by retained placenta and abnormal placentation. In the final study evaluating risk factors, they included 2059 random controls without severe PPH in with the original 1064 PPH patients. Nyfløt, Sandven, Stray-Pedersen, Pettersen, Al-Zirqi, Rosenberg, Jacobsen & Vangen (2017) concluded that:

Severe PPH was more likely among women with the following medical and obstetric characteristics: primiparity, women who were married or cohabiting, previous severe PPH, previous uterine surgery, known uterine anomaly, multiple gestation, IVF/ICSI pregnancies, anemia, gestational diabetes mellitus, uterine fibroma, polyhydramnios,

receipt of anticoagulant medication, and severe pre-eclampsia or HELLP syndrome.

Severe PPH was more likely among women with these intrapartum and delivery characteristics: instrumental vaginal delivery, in-labor cesarean delivery, induced labor, labor augmentation with oxytocin, fever during labor, PROM, and infant birth weight  $\geq 4500$  g (Article 17).

Most of these risk factors may not be avoidable, but it is vital for the physicians and nurses to recognize risk factors so that they may act quickly if anything were to happen. The reality is that any postpartum patient has a risk for PPH, which is why there are certain preventative procedures that are being put into place in the clinical setting to prevent PPH.

### **Uterotonics vs. Placebo**

The active prevention of PPH is becoming more prevalent in the medical world today, with this prevention occurring primarily in the third stage of labor. The third stage of labor is the time between birth of the fetus and expulsion of the placenta, and the time in which the woman is most at risk for hemorrhage. The active management of the third stage of labor (AMTSL) is an effective intervention to prevent postpartum hemorrhage during and immediately after expulsion of the placenta. This method includes administration of uterotonics such as oxytocin, controlled cord traction and uterine massage after delivery of the placenta (Evensen et al., 2017; Joshi et al., 2014; Erikson et al., 2017). For the sake of this research, we will be focusing on the administration of uterotonics to help prevent PPH, but the combination of these three methods is the most effective strategy to prevent PPH (Evensen et al., 2017). Research comparing a placebo or no medication to an effective uterotonic is lacking, but the research showing the effectiveness of uterotonics in general is plentiful. The effectiveness of uterotonics in preventing PPH is only applicable if they are administered after delivery, specifically in the third stage of labor.

Uterotonics can actually make a woman more likely to experience PPH if used for induction or augmentation of labor (Erikson et al., 2017). In a metaanalysis of the Cochrane database, 23 different trials were evaluated, they included 10,018 women who had delivered their baby. Nine of the trials compared prophylactic oxytocin versus a placebo, six studies showed that prophylactic oxytocin versus no uterotonics or placebo may be effective in reducing the risk of blood loss of 500 mL after delivery. This evaluation showed a 0.51 average risk ratio and a 95% confidence interval 0.37 to 0.72, although they determined that it was low-quality evidence. In five of the studies, it showed that prophylactic oxytocin may also prevent blood loss of 1000 mL after delivery when compared to placebo. This had an average risk ratio of 0.54 and a 95% confidence interval 0.42 to 0.83 also with low quality evidence (Govind, 2020). Even though these studies show low quality evidence, that is simply when comparing a placebo to the use of uterotonics and not when comparing oxytocin to other uterotonics.

### **Oxytocin vs. Alternative Uterotonics**

Oxytocin is the most commonly given uterotonic in prevention of PPH, which does not necessarily mean that it is the only effective option. Other options for uterotonics include: carbetocin, ergometrine/methylergometrine, misoprostol or a combination of oxytocin with ergometrine (Gallos et al., 2019, Vol. 23 No. 9; World Health Organization [WHO], 2018). In addition to these options for prevention of PPH, there are many more medications that can be used for the active treatment of a PPH. In one network meta-analysis, the effectiveness of available drugs and combination of drugs to prevent PPH were evaluated. The meta-analysis included 87,466 women, and the study concluded that “ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were found to reduce the risk of PPH blood loss of  $\geq 500$  mL compared with the standard drug, oxytocin” (Gallos et al., 2019, Vol. 23 No. 9). Although all of

these combination drugs produced more favorable outcomes, ergometrine and misoprostol with oxytocin both had a poor ranking for side effects. Carbetocin showed a more favorable side effect profile, that is similar to oxytocin and showed to be just as effective if not more effective, than oxytocin. The authors disclosed that the studies conducted with carbetocin were small and of poor quality. In addition, it is important to consider cost-effectiveness, which was inconsistent and inconclusive in this analysis (Gallos et al., 2019, Vol. 23 No. 9). A variety of additional studies and meta-analyses concluded that carbetocin is as effective, or possibly more effective than oxytocin in prevention of PPH, but it was also determined that use would be dependent on cost-effectiveness (Jin et al., 2019; Maged et al., 2016; Voon et al., 2018). The World Health Organization (WHO) also evaluated the use of carbetocin versus oxytocin. The main reason for the analysis is due to the need for oxytocin to be in cold storage, which makes it difficult to use in less developed countries. Results of this study showed that carbetocin is as safe and effective as oxytocin, which resulted in their recommendation to use carbetocin in countries that have limited resources for storage. Carbetocin does not require cold-storage and retains its efficacy for three years, unlike oxytocin (Gülmezoglu, 2018; Shakur-Still & Roberts, 2018). However, more studies need to be conducted to ensure that carbetocin is a truly affordable option when cold storage is an issue. One systematic review was performed to evaluate the cost-effectiveness of carbetocin versus oxytocin. This particular study found a vial of 100 mcg of carbetocin to be \$18.20 versus a vial of 10 IU of oxytocin to be only \$0.18, yet they state that carbetocin may still be cost effective. In their facility, the use of carbetocin reduced the number of retreatments, staffing requirements, and potential medication errors when compared to oxytocin. This made carbetocin more cost effective despite the higher index cost, but ultimately remains dependent on the specific facility resources and the value that is placed on resources such as staffing (Hian et

al., 2018). Ergometrine/methylergometrine and misoprostol are also approved for prevention of PPH by both the WHO and the Federation of Obstetric and Gynecological Societies of India (FOGSI) (Joshi et al., 2014; WHO, 2019). The FOGSI states that oxytocin is their first line of therapy, but if not available IM methylergometrine or PO misoprostol may be used, but misoprostol should be used as a last choice (Joshi et al., 2014). The exact recommendations from the WHO will be discussed later in this paper. It is evident that although there are many options for uterotonics, oxytocin still remains the best option in terms of effectiveness, affordability, and side-effect profile. The use of oxytocin still may be dependent on the specific context and what is available for use.

### **Intramuscular vs. Intravenous Oxytocin**

The last area to be evaluated is the effectiveness of intramuscular (IM) oxytocin versus intravenous (IV), both are common practices. Oxytocin is the most recommended uterotonic for prevention of PPH, but the most effective route has not been identified. In fact, part of the WHO's recommendation, states the 10 IU IV/IM is the recommendation for all births (WHO, 2019). The appeal of an IM injection versus IV administration is obvious, it requires less skill and equipment while still remaining a safe option for oxytocin administration. In addition, IM injections cannot infiltrate or be accidentally removed during the birthing process. However, multiple studies show that IM injections are not as effective as IV infusions or boluses. The use of an IM injection is not only less effective in preventing PPH but also more commonly requires the use of additional uterotonics when compared to IV oxytocin (Dyanna et al., 2019; Ebada et al., 2020). Along with that, IV administration has a faster onset and has higher peak plasma concentration than IM administration. One study evaluated the effectiveness of IV bolus, IV infusion and IM injection. The study showed there was 5.9% less mean postpartum blood loss in

those receiving an IV infusion, and 11.1% less in those who received an IV bolus. It also showed the risk of having >500mL of blood loss was significantly reduced in those receiving the IV infusion or bolus when compared to an IM injection (Dyanna et al., 2019). Incidence of blood transfusions and the need of manual removal of the placenta is also shown to be higher in those receiving an IM injection versus the IV infusion (Wu et al., 2020). All of the evidence points to IV administration being the best option, yet the decision to use it also has to be based on available resources, provider skill level, maternal comorbidities, and maternal preference. For example, if an IV is already in place after delivery, then IV administration makes the most sense. However, if there is not established IV access, it would be more time efficient to give an IM injection versus establishing that IV. Also, in environments lacking resources, IM injections may be easier because they require less supplies and provider skill. Finally, women with unstable cardiovascular conditions such as cardiovascular disease may not be an optimal candidate for either route. Some studies show the incidence of cardiac arrest, hypotension, myocardial ischemia, ECG changes, tachycardia, and chest pain to occur in those women after IV administration of oxytocin. It is unclear if this cause and effect are directly related and there are not any studies showing this result in those that received an IM injection (Wu et al., 2020; Ebada et al., 2020).

### **Clinical Recommendation**

The clinical recommendation for prophylactic use of oxytocin is outlined by multiple organizations. One widely used and respected recommendation comes from the World Health Organization (WHO). They have created a detailed packet explaining exactly what they recommend related to many different uterotonics, including oxytocin. The first overarching recommendation is that the use of a uterotonic for prevention of PPH is recommended for all



births, both vaginal and cesarean. This may include oxytocin, carbetocin, misoprostol, ergometrine/methylergometrine, or oxytocin and ergometrine combination dose. It is specified that to effectively prevent PPH, the practitioner should only use one of these options. Their second recommendation relates specifically to oxytocin, and recommends the use of 10 IU IV or IM for prevention of PPH for all births as the first choice. The use of misoprostol PO is also recommended as a secondary option to oxytocin, as well as carbetocin or ergometrine/methylergometrine in context-specific cases. Ergometrine and methylergometrine may be used in instances where hypertensive disorders can be excluded as increased blood pressure is a common side effect of the medication. Injectable prostaglandins such as carboprost, are not recommended by the World Health Organization due to lack of effectiveness in prevention of PPH as well as unwanted side effects (WHO, 2019). The World Health Organization is not alone in providing reliable recommendations for PPH prevention. The California Maternal Quality Care Collaborative (CMQCC) created an obstetric hemorrhage toolkit that is widely used among clinical settings, including at Cheyenne Regional Medical Center (CRMC) in Cheyenne, WY. This toolkit contains recommendations on the prevention and treatment of PPH and is often located on the hemorrhage cart and is equipped with various emergency items. The CMQCC's only pharmacologic recommendation for prevention of PPH is IV oxytocin 10 IU/500 mL over one hour, or 10 IU IM if IV access is not available. The remainder of the recommendations revolve around treatment of an active PPH, and include the use of methylergonovine, misoprostol and carboprost, and provide no recommendations for preventative use (Shields et al., 2015). Another recommendation is for each institution to develop clear protocol and staff education on the prevention and treatment of PPH. These clinical

recommendations are evidence based and the research behind them can be seen clearly in each document.

### **Conclusion**

Postpartum hemorrhage is a serious complication of vaginal and cesarean births that can be effectively prevented and treated with the use of uterotonics. Evidence shows that oxytocin is an effective choice for prevention and leads to lower rates of PPH when compared to placebo, no uterotonics and other uterotonics. Oxytocin is the most effective choice, has least amount of side effects and is the most affordable option, which makes it the recommended option in most clinical settings. An exception may be if cold storage is not accessible. In that case, other options such as carbetocin may be a better choice. It is evident that IV administration is the preferred and more effective route when IV access is established in a safe and timely manner. PPH is significantly lowered with the use of uterotonics and AMTSL in general, but access to these resources may be limited in many areas. There is a significant amount of research on this topic, but there is a gap in good quality studies with low risk of bias. More blinded studies should be conducted as well as studies with less bias when comparing oxytocin use versus placebo. Additional research on the utilization of IM versus IV should also be conducted, especially in relation to women with cardiovascular conditions. Overall, it should be widely recognized that the utilization of oxytocin in the third stage of labor can be an effective prophylaxis to PPH.

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