UTEROTONIC MEDICATIONS FOR PREVENTION AND TREATMENT OF POSTPARTUM HEMORRHAGE

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EXECUTIVE SUMMARY

- Oxytocin is the medication of choice for **BOTH prophylaxis and treatment** of postpartum hemorrhage in high resource settings (i.e. hospitals in the United States and other developed countries), and has a favorable side effect profile relative to other uterotonics.
    - Oxytocin dosing is typically 10-40 units/500-1000 mL IV fluid or 10 units IM.
    - The most frequently studied prophylactic dose is 10 units/500 mL over 1 hour.
- Second line therapy for **treatment** of hemorrhage is a choice between Methergine® (methylergonovine maleate), Hemabate® (carboprost or 15 methyl PGF2 alpha) and Cytotec® (misoprostol) with the choice being made on institution assessment of availability and contraindications.
- Medication protocols for both **prophylaxis** and **treatment** should be standardized within each institution to provide ease of access and timely administration of medication according to processes that are well understood by all intrapartum and postpartum staff.

Table 1: Medications Summary

Prevention	Treatment
Oxytocin or 10-40 units/500-1000 mL IV infusion titrated to uterine tone OR Oxytocin 10 u IM when no IV access	Rapid infusion of IV oxytocin 10-40 units/500-1000 mL at ≥ 500 mL/hour, titrated to response
	Choose a standard second line agent from: Methergine 0.2 mg IM Hemabate 250 mcg IM or intramyometrially Misoprostol 600 mcg orally, 800 mcg sublingually

BACKGROUND

Pitocin® (oxytocin): Oxytocin is a synthetic version of the natural nonapeptide produced in the posterior pituitary. The drug comes in solution at a concentration of 10 units/mL. For postpartum use, including third stage of labor, oxytocin is dosed at 10-40 units per liter of IV fluid and given as an IV infusion. The rate of infusion should be sufficient to maintain uterine contractility. The plasma half-life of oxytocin is 1-6 minutes and the clinical response is rapid after IV infusion. Alternatively, the agent may be given as an IM injection (10 units). Intramuscular response to the drug occurs within 3-5 minutes, with a clinical response lasting about 2-3 hours. The drug may be stored at room temperature.

Experts appear to agree that oxytocin is still considered the prophylactic drug of choice in the developed world [1-4] A 2013 Cochrane systematic review stated that prophylactic usage of oxytocin, 10 units intravenous infusion or intramuscular injection, is still the most effective medication with the fewest side effects compared to ergot alkaloids (nausea and vomiting) and misoprostol (hyperpyrexia).[3] The WHO recommendations state that oxytocin intravenous infusion and bolus are acceptable, although if given by bolus it should be given slowly to avoid side effects.[1] If intravenous access is not available, intramuscular oxytocin 10 units can be given.[1] There is not a clear recommendation on the specific dosing, as studies utilize a different concentrations and rates. The most frequently studied prophylactic dose is 10 units/500 mL over 1 hour. A 2014 Cochrane Review also concludes that oxytocin is the first line agent of choice for treatment of primary postpartum hemorrhage.[5]

Alternative approaches to dosing of oxytocin at cesarean birth are an area of active investigation in the literature. Three discussions oxytocin dosing at cesarean suggest slow, small IV boluses of 1-3 units oxytocin over 15-30 seconds to initiate uterine contractility followed by ongoing infusion of 4–10 units per hour.[6-8] Concern for the hemodynamic effects of oxytocin has increased in recent years, especially in relation to historical practices of administering a 5-10 units IV bolus of oxytocin after delivery of the infant at cesarean in some settings. While the most commonly noted side effects are nausea, flushing, and hypotension, significant hemodynamic changes may be observed after IV boluses, including tachycardia, increased cardiac output and cardiac work, and myocardial ischemia.[6] These potential adverse effects are of increasing concern when the population of childbearing women is older and has more co-morbidities and cardiovascular disease is becoming a leading cause of pregnancy-related mortality.[9] Rapid IV boluses should be avoided in all patients and the use of small boluses of oxytocin should be used with caution in women with preexisting cardiovascular disease.

- ***Side Effects***: The drug should not to be given as a rapid IV bolus as it is associated with hypotension and tachycardia, and other adverse hemodynamic changes. Side effects are rare in the absence of prolonged use at low doses. Nausea and vomiting

  have been reported. The most serious side effect from prolonged use of IV oxytocin is water intoxication with subsequent dilutional hyponatremia.

- ***Contraindications***: The only postpartum contraindication to use of oxytocin would be hypersensitivity to the drug.

Methergine® (methylergonovine maleate): Methergine is a semi-synthetic ergot alkaloid that is FDA-approved for routine management of the third stage of labor and postpartum atony. It is supplied in ampoules containing 0.2 mg of active drug in a volume of 1 mL or as a single tablet of 0.2 mg of active drug. The drug is given either as an intramuscular injection (1 ampoule) or orally (single tablet). When given as an oral agent, the onset of action is within 5-10 minutes with a bioavailability of 60%. When given as an intramuscular injection, the onset of action is 2-5 minutes and the bioavailability is 78% (about 25% greater than when given orally). The plasma half-life is about 3.4 hours. The agent should not be given by intravascular injection. The frequency of administration is 2-4 hours for IM administration and 6-8 hours when given orally. The IM preparation of the drug must be refrigerated when stored.

There is little data to evaluate which second line therapy is preferable and as stated in the WHO recommendations: "Decisions in such situations must be guided by the experience of the provider, the availability of the drugs, and by known contraindications." In the first iteration of the CMQCC guidelines, the taskforce recommended Methergine as the primary second line agent for treatment of uterine atony, since the third line agent, misoprostol was of a similar therapeutic class to Hemabate, and therefore would theoretically be providing efficacy by different physiologic pathways (CMQCC guideline version 1). This ambiguity in efficacy clearly supports more research to determine the most effective therapy.

- ***Side Effects:*** Side effects are rare in the absence of prolonged use. Most common side effects are nausea and vomiting. Chest pain, arterial spasm, myocardial infarction, and hallucination have been reported in cases of toxicity.
- ***Contraindications*:** Methergine should be used with extreme caution in the setting of hypertension or preeclampsia. Care should be exercised when there has been recent administration of other vasoconstrictive agents (i.e. ephedrine). In these settings, there may be an exaggerated blood pressure response to the use of this agent. Care should also be taken when CYP 3A3 inhibiting agents, such as macrolide antibiotics, protease inhibitors, or azole antifungals, have recently been used.

Hemabate® (carboprost or 15 methyl PGF2 alpha): Hemabate is FDA-approved for the treatment of postpartum hemorrhage secondary to uterine atony not responsive to conventional treatment (massage and oxytocin). The drug is supplied in 1 mL ampoules

containing 250 mcg of the drug. The dose is one ampoule given as an IM injection. The peak plasma level of the drug is reached about 30 minutes after injection. A successful clinical response is expected after a single injection in about 75% of cases. In refractory cases, additional dosing at 15-90 minute intervals may be beneficial. The total amount of drug given should not exceed 2 mg (8 doses). The clinical response may be enhanced with concomitant use of oxytocin. It may be less effective when used in the setting of chorioamnionitis. It should be noted that other uterotonic agents are also less effective in the setting of chorioamnionitis. The drug must be refrigerated when stored.

- ***Side Effects*:** Recognized side effects include nausea, vomiting, diarrhea, fever (up to 1 degree Celsius), bronchospasm, and hypertension.
- ***Contraindications*:** It is recommended that the drug be given with caution to patients with active hepatic or cardiovascular disease, asthma, or hypersensitivity to the drug.

Cytotec® (misoprostol): This agent is a synthetic prostaglandin E1 analog. This agent is FDA approved for reducing the risk of NSAID-induced gastric ulcers. It comes in either 100 or 200 mcg tablets. This agent is not FDA-approved for uterine atony or obstetrical hemorrhage. Despite anecdotal evidence of efficacy, studies of the efficacy of misoprostol for prevention and treatment of obstetric hemorrhage have had mixed results. For the treatment of postpartum hemorrhage from uterine atony, Gibbons, et al. cited two large randomized controlled trials which demonstrated oxytocin had the best efficacy, for both prophylaxis and first-line treatment of postpartum hemorrhage caused by uterine atony, without the side effects of fever seen commonly (22-58%) with misoprostol.[2] They also noted that the second study found the addition of misoprostol to oxytocin did not improve outcomes.[2]

The drug is water-soluble and is quickly absorbed after sublingual, oral, vaginal, and rectal use. The time to peak plasma concentration is shortest for sublingual administration and the plasma concentration is higher than when given rectally. However, after rectal administration, plasma concentrations are maintained for a longer period. The drug undergoes a series of chemical reactions after ingestion, converting the agent to a prostaglandin F analog, making the drug very similar to hemabate (15 methyl PGF2 alpha). Therefore, it is unlikely that misoprostol would be effective if hemabate has failed, or vice versa. Unlike hemabate, misoprostol does not appear to exacerbate bronchoconstriction in patients with asthma. One of the major advantages of this agent is that the drug does not need to be refrigerated and may be easily stored on labor and delivery hospital units. Treatment of postpartum hemorrhage with 800 mcg sublingually is a reasonable therapeutic regimen in delivery setting where other medications are difficult to maintain and stock, or as a second line therapy when hemorrhage is unresponsive to oxytocin.[1]

Historically misoprostol was commonly administered rectally at a dose of 800-1000 mcg in US settings. Since our initial review, several articles have been published on the utilization of sublingual/oral misoprostol to treat and prevent postpartum hemorrhage, and there are relatively few studies using rectal misoprostol. Most of the research has been conducted outside the United States where the use of misoprostol is more prevalent due to its low cost, easy storage and availability.[10-12] In all the reports, shivering and temperature elevation, known side effects of misoprostol, were found to be increased in exposed patients. It appears to have more side effects than oxytocin and therefore will not replace oxytocin for prophylaxis therapy in most U.S. settings, where oxytocin is readily available.[3,13]

For cesarean birth a recent meta-analysis suggests the combination of oxytocin and 400 mcg sublingual misoprostol may be of benefit for prevention.[14] The four studies used for this comparison were all done overseas. The authors suggest the apparent effectiveness of the combined use of oxytocin and misoprostol may be explained by the differences in timing of onset and duration of action between the two medications. The committee strongly urges more study of equivalence and dosing of various medications and their efficacies in populations more reflective of our patients so that the proper medication, route, amounts and combinations can be determined. These findings are consistent with other recommendations.[1,15]

- ***Side Effects:*** Diarrhea, shivering, pyrexia and headaches are the most common side effects.
- ***Contraindications:*** Hypersensitivity to the drug.

RECOMMENDATIONS

1. All labor and delivery and postpartum units should have a standardized medications regimen.

2. All relevant uterotonic medications should be readily available for emergent use.

3. Special preparation for treatment such as kits and carts should be in place in all labor & delivery and postpartum units.

4. Clinicians should stay abreast of emerging literature regarding the use of uterotonic agents.

Prophylaxis

1. The first line agent for hemorrhage prophylaxis is an intravenous infusion of oxytocin, with the most commonly recommended and studied dose being 10 units/500 mL over one hour.

2. Intramuscular administration of 10 units is recommended when IV access is not available.

Treatment

1. For treatment of hemorrhage due to uterine atony the first line medication remains oxytocin.

2. Institutions should select a standard medication for second line treatment. Options include Methergine® (methylergonovine maleate), Hemabate® (carboprost or 15 methyl PGF2 alpha) and Cytotec® (misoprostol).

3. Sublingual misoprostol appears to be effective and may offer benefit over rectal administration, but misoprostol has not been demonstrated as effective as oxytocin in the most recent systematic review of treatment of primary postpartum hemorrhage.

EVIDENCE GRADING:

Level of Evidence: I B. Evidence obtained from at least one properly designed randomized controlled trial. Recommendations based on limited or inconsistent evidence.