Module 2

Role on Carbetocin in PPH

CONTENT

Introduction

Postpartum Hemorrhage (PPH)

Postpartum hemorrhage (PPH) is a major obstetric complication characterized by excessive bleeding following childbirth. It poses a significant risk to maternal health and is one of the leading causes of maternal morbidity and mortality worldwide. PPH is defined as blood loss of 500 mL or more within 24 hours after delivery, and it can be classified into primary (within the first 24 hours) and secondary (from 24 hours to 12 weeks postpartum) PPH. The primary cause of PPH is uterine atony, the failure of the uterus to contract adequately after delivery, but other causes include retained placental tissue, genital tract trauma, and coagulopathy.

Global Burden of PPH

The impact of PPH is particularly pronounced in low-resource settings, where access to quality obstetric care is limited, and the risk of maternal death is significantly higher. Despite global efforts to reduce the burden of PPH, its incidence remains high in both developed and developing countries. Continued research and innovation are necessary to identify novel strategies for PPH prevention, risk stratification, and management.

Current Management Strategies

Pharmacological Interventions

The current management of PPH involves a combination of pharmacological interventions, mechanical methods, and surgical procedures. Uterotonic agents such as oxytocin, misoprostol, and ergometrine play a pivotal role in the prevention and treatment of PPH by promoting uterine contractions and minimizing blood loss. Despite these measures, the incidence of PPH remains high, highlighting the need for continued research and innovation to identify more effective strategies.

Mechanical and Surgical Methods

Mechanical methods include the use of uterine balloon tamponade and surgical techniques such as uterine artery ligation, B-Lynch suture, and hysterectomy. These interventions are critical when pharmacological methods fail to control bleeding. However, they are often associated with higher morbidity and may not be readily available in all settings.

Carbetocin as a Uterotonic Agent

Pharmacological Properties of Carbetocin

Carbetocin is a long-acting synthetic analogue of oxytocin that has emerged as a promising agent in the prevention of PPH. Unlike oxytocin, carbetocin has an extended half-life, allowing for a more sustained effect on uterine contraction, and it does not require cold storage, making it more suitable for use in a variety of healthcare settings. Clinical trials have demonstrated that carbetocin significantly reduces the incidence and severity of PPH, thus improving maternal outcomes globally.

Mechanism of Action

Carbetocin acts by binding to the oxytocin receptors in the myometrium, promoting uterine contractions. This action helps to compress the blood vessels at the placental site, reducing blood loss. The prolonged uterotonic effect of carbetocin compared to oxytocin is due to its longer half-life, which provides a more sustained contraction of the uterus.

Clinical Pharmacokinetics

- Half-life: Approximately 40 minutes (IV administration).
- Duration of uterine activity: 120 minutes (IM injection), 60 minutes (IV injection).

Clinical Trials and Evidence

Study 1: Efficacy and Safety of Carbetocin in Prevention of PPH

A study conducted from September 2020 to January 2022 evaluated the efficacy and safety of carbetocin compared to oxytocin in preventing PPH in women undergoing caesarean section. This prospective, single-center, case-control, cross-sectional, observational study included 150 female patients randomized to receive either carbetocin or oxytocin. The results indicated that carbetocin significantly reduced blood loss and the need for additional uterotonic interventions compared to oxytocin.

Key Findings:

• Average blood loss in patients administered carbetocin was significantly lower compared to those who received oxytocin (451 mL vs. 800 mL).

• Carbetocin maintained better uterine tone and was more effective in preventing blood loss greater than 500 mL during cesarean section.

• The need for additional uterotonic interventions was significantly reduced in the carbetocin group.

Study 2: Comparative Analysis of Carbetocin and Oxytocin

Another study published in the Benha Journal of Applied Sciences evaluated and compared the effectiveness of carbetocin and oxytocin for PPH prophylaxis among high-risk women undergoing vaginal delivery and cesarean section. This randomized-controlled clinical trial included 200 singleton pregnant women with at least one risk factor for atonic PPH. The study concluded that carbetocin demonstrated superior efficacy in reducing blood loss and preventing PPH compared to oxytocin.
Key Findings:

• The estimated blood loss was significantly lower in the carbetocin group (826.8 mL) compared to the oxytocin group (1159.5 mL).

• The incidence of PPH and the need for additional uterotonics and blood transfusion were considerably lower in the carbetocin group.

• Uterine tone was better maintained in the carbetocin group.

Safety Profile of Carbetocin

Adverse Effects

While carbetocin is generally well-tolerated, some studies have reported side effects such as nausea, vomiting, headache, dyspnea, and itching. However, these adverse effects are typically mild and transient. The cardiovascular side effect profile of carbetocin includes a lower incidence of gastrointestinal side effects compared to the combination of oxytocin and ergometrine, but a higher occurrence of transient tachycardia has been noted.

Cardiovascular Considerations

Pre-eclampsia remains a contraindication to carbetocin use, and close monitoring of blood pressure is necessary for patients with suspected pre-existing cardiovascular disease. The cardiovascular side effect profile of carbetocin requires further research to better understand its impact in different populations.

Practical Implications and Applications

Advantages in Low-Resource Settings

The use of carbetocin in clinical practice offers several advantages, particularly in settings where cold storage for oxytocin is not feasible. Its stability at room temperature and longer duration of action make it a practical choice for preventing PPH in various healthcare environments, including low-resource settings.

Cost-Effectiveness

Recent studies suggest that carbetocin may be the most cost-effective uterotonic agent in resource-poor developing countries. Its single-dose administration reduces the need for continuous monitoring and additional interventions, thereby lowering overall healthcare costs.

Recommendations for Clinical Practice

Guidelines for Use

Based on current evidence, carbetocin should be considered as a first-line option for the prevention of PPH in high-risk women. Healthcare providers should be aware of its potential benefits and limitations, including the need for close monitoring in patients with cardiovascular conditions.

Further Research

Further studies are needed to confirm the efficacy and safety of carbetocin in low-risk populations and to explore its use in other therapeutic settings. Research should also focus on the long-term outcomes and potential side effects of carbetocin in diverse patient populations.

Conclusion

Carbetocin has proven to be a safe and effective option for the prevention of PPH, particularly in high-risk women. Its superior pharmacological profile, coupled with evidence from multiple clinical trials, supports its use as a first-line uterotonic agent for PPH prophylaxis. Further studies are needed to explore its efficacy and safety in low-risk populations and other therapeutic settings.
Summary:

• Carbetocin significantly reduces blood loss and the need for additional uterotonics compared to oxytocin.

• It is effective in maintaining uterine tone and preventing excessive bleeding after cesarean section and vaginal delivery.

• Carbetocin is a practical alternative to oxytocin, especially in low-resource settings due to its stability at room temperature.

Recommendations

1. Carbetocin should be considered as a first-line option for PPH prevention in high-risk women.

2. Further research is needed to confirm its efficacy and safety in low-risk populations.

3. Healthcare providers should be aware of the potential cardiovascular side effects of carbetocin and monitor patients accordingly.

Postpartum hemorrhage (PPH) remains a leading cause of maternal mortality and severe morbidity worldwide. The incidence of PPH has been increasing in many countries, with uterine atony identified as the primary cause. Active management of the third stage of labor, which includes oxytocin administration, uterine massage, and umbilical cord traction, has been associated with a 50% reduction in PPH incidence. Although oxytocin is the most effective medication with few adverse effects, a long-acting oxytocin analogue, carbetocin, has emerged and is recommended by some institutional guidelines to prevent PPH after both vaginal delivery and cesarean section.

Carbetocin is a synthetic analogue of oxytocin, sharing similar side effects but differing in molecular structure. This modification enhances its stability and receptor affinity, making it long-acting and potentially more effective in PPH management. Despite its promise, no randomized controlled trials have directly shown a decrease in PPH following carbetocin infusion after birth. However, compared to oxytocin, carbetocin has demonstrated a prophylactic effect, reducing the need for additional uterotonics by half following cesarean section. Economic analyses have also indicated that carbetocin is cost-effective, potentially reducing workload in busy units after cesarean sections. The advantages of carbetocin in vaginal delivery settings, however, remain unclear due to small and poor-quality studies.

Administration and Practical Considerations

According to the manufacturer's instructions, oxytocin should be administered as a short infusion, while carbetocin is given as a single intravenous bolus over one minute to minimize cardiovascular side effects. This bolus administration can be challenging for midwives immediately after delivery. Since laboring women at high risk often receive intravenous fluids as part of their care, a short infusion is more convenient than a slow manual injection. Studies have shown that short infusion of carbetocin results in similar uterine tone and comparable cardiovascular side effects to bolus injection during cesarean delivery.

Study Design and Methodology

This prospective, single-center, randomized double-blind controlled study was conducted at the Nanjing Drum Tower Hospital in China, from March to May 2018. Women expecting vaginal delivery were recruited, and the study included those with at least one risk factor for developing uterine atony. Participants were randomly assigned to receive either carbetocin or oxytocin. The primary outcome was the incidence of blood loss over 500 mL within 24 hours after delivery.

Results

The study found no significant difference in the primary outcome between the carbetocin and oxytocin groups. However, manual removal of the placenta was significantly less frequent in the carbetocin group. Subgroup analysis revealed that carbetocin was more effective in women with induced or augmented labor.

Discussion

The study showed that prophylactic intravenous infusion of carbetocin was not superior to oxytocin in reducing the risk of PPH during vaginal delivery in high-risk women. However, carbetocin was superior in reducing the need for manual removal of the placenta, especially in cases of induced or augmented labor. Carbetocin's longer half-life and higher efficacy in preventing uterine atony could be beneficial. Nevertheless, its cost and availability remain limitations.

Practical Implications

The mode of uterotonic administration is crucial in a clinical setting. Carbetocin has been administered via different routes and at varying speeds in various studies. This study is the first to compare the effect of intravenous infusion of carbetocin to oxytocin after vaginal delivery. Despite no major adverse events, a small decrease in blood pressure was noted after carbetocin infusion. Further studies on the route of administration of heat-stable carbetocin are needed.

Strengths and Limitations

The study's strengths include strict adherence to the study protocol for blood loss measurement and maintaining blinding until statistical analysis. However, the study was conducted in a single center, and the high rate of PPH interventions might not be generalizable. The subjective assessment of atony and bleeding speed for additional uterotonic agents or manual removal of the placenta is another limitation.

Conclusion

Carbetocin could be a good alternative to oxytocin in preventing PPH in the third stage of labor, particularly in women with induced or augmented labor. Its intravenous infusion allows midwives to focus on other important procedures immediately after delivery, making it a practical choice in busy clinical settings.

Postpartum hemorrhage (PPH) remains a significant cause of maternal mortality worldwide, particularly in developing countries. It is estimated that more than 100,000 maternal deaths occur annually due to PPH. Uterine atony, which accounts for 50% to 60% of PPH cases, is the predominant cause. The incidence of PPH increased from 1.5% in 1999 to 3.4% in 2009, with a similar rise in atonic PPH from 1% to 3.4%.

Active management of the third stage of labor, which involves the administration of prophylactic uterotonic agents, uterine massage, and umbilical cord traction, significantly lowers maternal blood loss and reduces the risk of PPH by up to 60%. Commonly used uterotonics include oxytocin and syntometrine (a combination of oxytocin and ergometrine), though the latter is associated with adverse cardiovascular and gastrointestinal side effects. Prostaglandins, such as misoprostol, are less effective but can be used in settings where oxytocin is unavailable.

Carbetocin: A Synthetic Oxytocin Analogue

Carbetocin is a synthetic long-acting oxytocin agonist with a prolonged half-life, offering a potential advantage over oxytocin in managing the third stage of labor, particularly in patients at high risk for PPH. The side effect profile of carbetocin is similar to that of oxytocin, making it a promising alternative.

Study Objective

The current study aims to compare the effectiveness and safety profile of a single intravenous (IV) bolus dose of carbetocin versus continuous IV infusion of oxytocin in patients at risk of atonic PPH.

Patients and Methods

This prospective, randomized controlled trial included 380 women attending Minia Maternity University Hospital. Participants were pregnant women at 37 to 42 weeks gestation with at least one risk factor for PPH. Risk factors included high parity, BMI over 35, history of PPH, antepartum hemorrhage, anemia, pre-existing hypertension, and overdistended uterus. Women with coagulopathy or known allergies to carbetocin or oxytocin were excluded.

Sample Size Calculation

Sample size was calculated to prevent type II error. Based on historical data, the average blood loss in patients at risk of PPH receiving oxytocin was 710 ± 322 ml. Assuming carbetocin could reduce blood loss by 20%, a sample size of 81 patients per group was needed to achieve 80% power with a 5% significance level. To account for withdrawals, 190 patients were recruited for each group.

Randomization

Participants were randomized to receive either 100 µg of carbetocin diluted in 10 ml of Ringer's lactate or 20 IU of oxytocin in 1000 ml Ringer's lactate as an IV drip immediately after delivery of the anterior shoulder. Slow administration was ensured to reduce potential hemodynamic effects.

Outcome Measures

Primary outcome measures included estimated blood loss and hemoglobin deficit (difference between pre- and post-delivery levels). Secondary outcome measures included the need for additional uterotonics, interventional procedures, blood transfusion, and adverse effects.

Statistical Analysis

Data were analyzed using SPSS version 21. Quantitative data were described as mean ± standard deviation, while categorical data were presented as frequencies. Comparative statistics used the Student t-test for quantitative data and the chi-square test for categorical data. A P value of <0.05 was considered significant.

Results

The study included 380 patients divided into two groups of 190 each. There were no significant differences in patient characteristics or risk factors for PPH between the groups, except for placental abruption (19 cases in the carbetocin group vs. 4 in the oxytocin group, P = 0.01).

Primary and Secondary Outcomes

The primary outcome of estimated blood loss showed no significant difference between the carbetocin and oxytocin groups. However, the hemoglobin deficit was significantly lower in the carbetocin group (0.53 ± 0.36 vs. 0.69 ± 0.37, P = 0.002). The need for additional uterotonics, further surgical interventions, and blood transfusions was lower in the carbetocin group compared to the oxytocin group (38% vs. 60%, P = 0.002; 12% vs. 38%, P = 0.0002; 18% vs. 30%, P=0.04, respectively).

Adverse Effects

Adverse effects were fewer in the carbetocin group compared to the oxytocin group, with lower incidences of nausea, vomiting, and palpitations (6% vs. 18%, P = 0.009; 13% vs. 28%, P = 0.008, respectively). However, there were more cases of flushing in the carbetocin group (6% vs. 2%, P = 0.27).

Discussion

This study demonstrated that carbetocin is associated with a reduction in the need for additional uterotonics, interventional procedures, and blood transfusions, with a better side effect profile compared to oxytocin. These findings are consistent with previous studies, suggesting that carbetocin could be a better alternative to oxytocin for PPH prevention in at-risk women.

Practical Implications

The results of this study suggest that carbetocin should be considered in clinical practice as a more effective alternative to oxytocin for the prevention of PPH in high-risk patients. The lower requirement for additional uterotonics and interventions, along with a favorable side effect profile, makes carbetocin a viable option.

Strengths and Limitations

The strengths of this study include its randomized controlled trial design and the reporting of clinically relevant outcomes. However, the study's limitations include its relatively small sample size and the single-center setting, which may affect the generalizability of the results.

Future Research

Further research should focus on larger multi-center trials to confirm these findings and explore the cost-effectiveness of carbetocin in different healthcare settings. Additionally, studies should investigate the long-term safety profile of carbetocin, particularly in women with underlying cardiac conditions.

Conclusion

Carbetocin is a promising alternative to oxytocin for the prevention of PPH in at-risk women. It reduces the need for additional uterotonics, surgical interventions, and blood transfusions while offering a better side effect profile. Larger studies are needed to confirm these findings and establish carbetocin as the standard prophylactic agent in PPH management.

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