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## **USE OF CARBETOCIN TO PREVENT HYPOTONIC POSTPARTUM BLEEDING AND ASSOCIATED COMPLICATIONS, REDUCE HYSTERECTOMY COUNT.**

**Summary.** This literature review is aimed at summarizing the results of using carbetocin, its benefits, and its safety in practice in the prevention of hypotonic bleeding in the early postpartum period. The scientific information available in MEDLINE, Embase, Elibrary, and Google Scholar was systematically sought using the search terms "hypotonia," "bleeding," "postpartum period," "hysterectomy," and "use of carbetocin." The authors have analyzed four investigations involving 2 567 patients. Hysterectomy is one of the most common complications of hypotonic hemorrhage in the postpartum period. To reduce blood loss and to prevent possible complications, various mechanical and pharmacological methods are applied. These include the use of carbetocin, a drug used to control postpartum hemorrhage and bleeding after giving birth. It is an analogue of oxytocin; it causes contractions in the uterus. The distinguishing characteristic of and predominance over oxytocin is:

- 1) 100 mcg of carbetocin is equal to 50 units of oxytocin.
- 2) After the introduction of carbetocin, uterine contractions become more frequent, and after two minutes, a sharp contraction occurs.
- 3) Prevention of uterine atonia in women in labor with an increased risk of postpartum bleeding, both in caesarean sections and in natural childbirth.

Carbetocin is well tolerated; side effects include headache, dizziness, increased blood pressure, chest pain, nausea, and, rarely, pain in the area of injection. The literature describes the effective use of this drug to reduce bleeding, which ultimately reduces the number of births completed by hysterectomy.

**Conclusion:** The results of the analysis made by the authors point to the safety and efficacy of carbetocin. Nevertheless, it is necessary to conduct further investigations to confirm these results in a large number of patients for the more effective application of this substance.

**Keywords:** carbetocin, hypotonic bleeding, hysterectomy, and the use of carbetocin to reduce the outcomes of hysterectomies.

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## **ПРИМЕНЕНИЕ КАРБЕТОЦИНА ДЛЯ ПРОФИЛАКТИКИ ГИПОТОЧЕСКИХ ПОСЛЕРОДОВЫХ КРОВОТЕЧЕНИЙ И СВЯЗАННЫХ С НИМ ОСЛОЖНЕНИЙ, УМЕНЬШЕНИЕ КОЛИЧЕСТВА ГИСТЕРЭКТОМИИ.**

**Резюме.** Данный обзор литературы направлен на обобщение результатов применения карбетоцина, его пользы и безопасности в практической деятельности при проведении профилактики гипотонических кровотечений в раннем послеродовом периоде. Проведены систематический поиск и анализ научных работ в MEDLINE, Embase, Elibrary, GOOGLE scholar, используя поисковые термины «гипотония», «кровотечение», «послеродовый период», «гистерэктомия»,

«применения карбетоцина». Мы анализировали 4 исследований, включающих 2 567 пациентов. Одно из самых частых исходов гипотонических кровотечений в раннем послеродовом периоде является гистерэктомия. Для снижения кровопотери и предотвращения развития возможных осложнений используют различные механические и фармакологические способы. Один из таких фармакологических способов применение карбетоцина, который является агонистом окситоцина длительного действия, отличительным характером от окситоцина и преобладанием над ним является:

1) 100 мкг карбетоцина равен 50 ЕД окситоцина.

2) после введения карбетоцина сокращения матки учащаются, и через две минуты наступает резкая схватка.

3) предупреждение атонии матки у рожениц с повышенным риском послеродового кровотечения, как при КС, так и при ЕР. Карбетоцин хорошо переносится; среди побочных эффектов встречаются головная боль, головокружение, повышение АД, боль в груди, тошнота, редко боль в области инъекции. В литературе описано эффективное применение данного препарата для снижения кровотечений, что в итоге уменьшает количество родов законченных гистерэктомией.

**Заключение:** Результаты проведенного нами анализа говорят о безопасности и эффективности применения Карбетоцина. Тем не менее, необходимо проведение дополнительных исследований для подтверждения данных результатов с большим количеством пациентов для более эффективного применения данного препарата.

**Ключевые слова:** карбетоцин, гипотонические кровотечения, гистерэктомия, применение карбетоцина для уменьшения исходов родов закончившихся гистерэктомией.

**Relevance.** One of the common outcomes of hypotonic bleeding in the early postpartum period is hysterectomy. The fundamental difference between secondary hypotonia and primary hypotonia is in the mechanisms (insufficiently studied), serious changes in the wall of the uterus not only of a functional nature but also irreversible morphological, excluding the possibility of using conservative treatment and requiring as rapid as possible surgical radical treatment (mainly hysterectomy). Uterine atonia is a risk factor for hysterectomy in early postpartum period and maternal mortality, along with uterine rupture and placenta accreta. According to a study by Jakobsson M. (2019), 32.7% of birth-related hysterectomies are due to hypotonic postpartum bleeding. In Italy, in study D, Arpe S. (2019), uterine atonia was the cause of 41.2% of cases of emergency hysterectomy related to pregnancy and childbirth. Therefore, various mechanical and pharmacological methods are used to reduce blood loss and prevent the development of possible complications. One such pharmacological method is the use of carbetocin, which is a long-acting oxytocin agonist characteristic of and predominant over oxytocin.

- 1) 100 mcg of carbetocin is equal to 50 units of oxytocin.
- 2) After the introduction of carbetocin, uterine contractions become more frequent, and after two minutes, a sharp contraction occurs.
- 3) Prevention of uterine atonia in women with an increased risk of postnatal bleeding, both in CS and NB.

Carbetocin is well tolerated; among the side effects are headaches, dizziness, high blood pressure, chest pain, nausea, and, rarely, pain in the injection area. The literature describes the effective use of this drug to reduce bleeding, which ultimately reduces the number of births ending in hysterectomy.

**Purpose of the study.** Demonstrating the efficacy and safety of carbetocin in clinical practice on the basis of the study of modern sources.

**Research materials and methods:** We conducted a systematic search and analysis of scientific papers in MEDLINE, Embase, Elibrary, and Google

Scholar, using the search terms "hypotension," "bleeding," "postpartum period," "hysterectomy," and "carbetocin applications."

**Results and discussions:** This literature review is aimed at summarizing the results of the use of carbetocin, its benefits and safety in obstetric activity in hypotonic postnatal bleeding, and reducing the number of outcomes by hysterectomy. We analyzed four studies involving 2,567 patients. The meta-analyses studied had a low risk of systematic error. As a result, when summarizing the results, we can note a decrease in the number of birth results in both CS and NB hysterectomy. But the studies did not specify such information as the amount of hemoglobin when entering the maternity complex. The presence of adverse events, such as increased blood pressure and nausea, was less in the control group, which can indicate the safety of the use of this method. The effectiveness of this method was determined by the change in the outcome of labor for hypotonic bleeding in the early postpartum period. Since it is challenging to predict the birth rate with precision, all relevant risk variables are included; preeclampsia, extra genital diseases, multiple pregnancy, induced births, CS, instrumental delivery, abortion history, repeat birth, anemia, low placentation, polyhydramnios, as well as anti-spasmodic, tocolytic, and disaggregating therapy during pregnancy.

According to a Begum M. (2014) study conducted in Saudi Arabia, placenta accreta (65%), uterine rupture (8%), and uterine atonia (27%) were the main causes of emergency hysterectomy following cerclage surgery. Most of the women were pluriparae. The analysis of uterine histological examination was omitted in the study by G.N. Maslyakova (2014) in relation to hypo plasm of uncertain genesis, which could not be halted by conservative methods In a retrospective analysis, the phenotypic signs of undifferentiated connective tissue dysplasia were identified in all mothers. The cause of hypotonic postpartum bleeding in women who do not exhibit obvious "obstetric" bleeding causes after childbirth is known to be undifferentiated connective tissue dysplasia. This

condition results in structural changes to the myometrium, specifically a deviation from the normal ratio of parenchyma to stroma. After the initial emergency delivery, atonic postpartum hemorrhage is most common in young women (average age 24) with undifferentiated connective tissue dysplasia.

The World Health Organization recommends several medications for the treatment and prevention of obstetric hemorrhage in order to stop hypotonic bleeding. Oxytocin and carbetocin are the first line's uterotonics. With a brief half-life, oxytocin is the most commonly employed uterotonic drug. Literary sources state that this drug's characteristic necessitates its continuous intravenous administration until a stable uterotonic effect is attained. This comes with a long list of negative side effects, such as hyper hydration, hyponatremia caused by antidiuretic effects, an irregular heartbeat, and more.

Current research is being done to determine the best oxytocin dosages for treating and preventing postpartum hemorrhage. There was no difference observed in the frequency of postpartum hemorrhages when compared to intravenous prophylactic infusions of 10, 40, or 80 units of oxytocin in 500 ml of isotonic sodium solution given within one hour of delivery. For single parenteral administration, carbetocin is the synthetic counterpart of oxytocin.

The half-life of this medication when administered intravenously is around 40 minutes, which is 4–10 times longer than that of oxytocin. Less than 30 minutes after intramuscular injection, the peak plasma concentration is seen, and 80% of the plasma is bioavailable. Similar to continuously administering oxytocin for several hours, a single dose of 100 mcg is sufficient to sustain enough uterine contractions, preventing uterus atonia and severe bleeding.

Carbetocin is well tolerated; among the side effects are headaches, dizziness, high blood pressure, chest pain, nausea, and, rarely, pain in the injection area. The literature describes the effective use of this drug to reduce bleeding, which ultimately reduces the number of births ending in

hysterectomy. Multiple meta-analyses of randomized controlled trials have shown that carbetocin is an effective medication for use in obstetrics. They reported that the medication's administration had decreased mortality, transfusion requirements, hysterectomies, hypotonic bleeds, and patient hospital stays. A significant number of births through both NB and CS were included in these meta-analyses. Risk factors included prolonged labor, polyhydramnios, big fetuses, repeated pregnancies, and gestational diabetes mellitus. These sources all demonstrate how well carbetocin works in obstetric practice to stop hypotonic hemorrhage. This tool is helpful in such cases when the count continues for seconds because it has been demonstrated that the administration of carbetocin lowers the chance of developing uterine hypotension, hence minimizing the requirement for transfusion. Furthermore, there is always a chance of developing immunological incompatibility, which puts the recipient at risk for possible complications from blood transfusions. Additionally, blood components are naturally lacking. Geller E.J. and Clarke-Pearson D.L. conducted a study involving 204 patients. Two groups of patients were created: group 1 (the group that received carbetocin during the third stage of delivery) and group 2 (the group that did not receive carbetocin).

This study shows the effectiveness of the use of a single dose of 100 mcg of carbetocin, administered in the third period of childbirth. They witnessed that the uterus had significantly shrunk. In their conclusion, they suggested using this technique to lower the incidence of problems and stop hypotonic hemorrhage. Similar to oxytocin, carbetocin selectively binds to oxytocin receptors in the uterine smooth muscles, causing the cervix to contract rhythmically, increasing the frequency of existing contractions, and improving uterine muscle tone. This is the basis of carbetocin's mechanism of action. Carbohydrates speed up and intensify spontaneous uterine contractions in the postnatal uterus. Uterine contractions start to get stronger once the carbetocin is

introduced, and after two minutes, there is a strong contraction. Similar to the injection of oxytocin, which functions for several hours, a single dose of 100 mcg of carbetocin is sufficient to sustain appropriate uterine contractions, preventing uterus atonia and severe bleeding. Patients tolerate this material well; the most frequent adverse effects are injection-related nausea and soreness that go away on their own without the need for medication.

J. Chen, H. Cui, and Q. Na carried out a study that was randomized. 98 women who were at high risk of hypotonic postpartum hemorrhage were enrolled in the study. The intramuscular, single-dose administration of carbetocin was found to be a safe and efficient way to lower the level of uterine hypotonia, which in turn prevents hypotonic hemorrhage and enhances the quality of labor. A sizable meta-analysis of nine trials involving expectant mothers who were at high risk of hypotonic postnatal hemorrhage came to a similar conclusion. It also noted the same effectiveness in the use of NB and CS. It is important to highlight the benefits of applying carbetocin, which include its 80% bioavailability, efficacy, 30-minute peak concentration, and convenience of administration. To sustain sufficient uterine contractions and avoid uterine atonia and severe bleeding, a single dose of 100 mcg is all that is needed.

**Conclusion:** In all the studies that we analyzed, the efficacy and safety of carbetocin were noted, and there was a decrease in the number of births that ended in hysterectomy. But, despite this, additional studies are needed to confirm these results with a large number of midwives, since the birth ended safely after hypotonic bleeding, which preserves the reproductive and menstrual functions of each puerperium.

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