Abstract

Theunissen FJ, Chinery L, Pujar YV. Current research on carbetocin and implications for prevention of postpartum haemorrhage.

Reprod Health. 2018 Jun 22;15(Suppl 1):94. doi: 10.1186/s12978-018-0529-0.

Background: Postpartum haemorrhage (PPH) is the leading cause of maternal mortality in low-income countries and is a significant contributor to severe maternal morbidity and long-term disability. Carbetocin may be an underused uterotonic for prevention of PPH. A number of studies are being conducted that may challenge the place of oxytocin as the first choice of uterotonics for prevention of PPH. This paper describes the current research into carbetocin and ranking of effectiveness of uterotonics that may provide important new information to assist healthcare decision makers to ensure that women receive an effective uterotonic for prevention of PPH.

Methods: We searched the WHO International Clinical Trials Registry Platform for current studies on effectiveness of carbetocin for prevention of PPH following vaginal delivery with sample sizes large enough to provide quality evidence to support potential changes to international guidelines. We also searched the Cochrane Library for current systematic reviews including carbetocin used in prevention of PPH.

Results: Susceptibility to degradation from exposure to heat is one of the key causes of reduced effectiveness of oxytocin in preventing PPH from uterine atony. Although heat stable and effective in preventing PPH, misoprostol is also subject to degradation due to exposure to moisture and produces some side-effects. Other uterotonics (including ergometrine and combinations of oxytocin, ergometrine and misoprostol) are also available and used with varying safety and effectiveness profiles and quality issues. Efforts to reduce maternal mortality from PPH include research studies seeking to identify safe, stable, effective uterotonics. Heat stable carbetocin is the subject of two major clinical studies into its effectiveness in preventing PPH following vaginal deliveries, information that could expand its application for prevention of PPH.

Conclusion: Heat stable carbetocin is being investigated as a potential alternative to oxytocin. This paper describes two current clinical trials on carbetocin and a network meta-analysis ranking of all uterotonic agents, including carbetocin, which combined may provide evidence supporting expansion of the use of the heat stable formulation of carbetocin in PPH prevention.

Begley CM, Gyte GM, Devane D, McGuire W, Weeks A. Active versus expectant management for women in the third stage of labour. Cochrane Systematic Review - Intervention Version published:

02 March 2015. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007412.pub4/full#0

Background: Active management of the third stage of labour involves giving a prophylactic uterotonic, early cord clamping and controlled cord traction to deliver the placenta. With expectant management, signs of placental separation are awaited and the placenta is delivered spontaneously. Active management was introduced to try to reduce haemorrhage, a major contributor to maternal mortality in low income countries.

Objectives: To compare the effectiveness of active versus expectant management of the third stage of labour.

Search methods: We searched the Cochrane Pregnancy and Childbirth Group Trials Register (30 September 2014) and reference lists of retrieved studies.

Selection criteria: Randomised and quasi randomised controlled trials comparing active versus expectant management of the third stage of labour.

Data collection and analysis: Two review authors independently assessed the studies for inclusion, assessed risk of bias and carried out data extraction.

Main results: We included seven studies (involving 8247 women), all undertaken in hospitals, six in high income countries and one in a low income country. Four studies compared active versus expectant management, and three compared active versus a mixture of managements. We used random effects in the analyses because of clinical heterogeneity.

There was an absence of high quality evidence according to GRADE assessments for our primary outcomes. The evidence suggested that for women at mixed levels of risk of bleeding, active management showed a reduction in the average risk of maternal primary haemorrhage at time of birth (more than 1000 mL) (average risk ratio (RR) 0.34, 95% confidence interval (CI) 0.14 to 0.87, three studies, 4636 women, GRADE:very low quality) and of maternal haemoglobin (Hb) less than 9 g/dL following birth (average RR 0.50, 95% CI 0.30 to 0.83, two studies, 1572 women, GRADE:low quality). We also found no difference in the incidence in admission of infants to neonatal units (average RR 0.81, 95% CI 0.60 to 1.11, two studies, 3207 infants, GRADE:low quality) nor in the incidence of infant jaundice requiring treatment (0.96, 95% CI 0.55 to 1.68, two studies, 3142 infants, GRADE:very low quality). There were no data on our other primary outcomes of very severe postpartum haemorrhage (PPH) at the time of birth (more than 2500 mL), maternal mortality, or neonatal polycythaemia needing treatment.

Active management also showed a significant decrease in primary blood loss greater than 500 mL, and mean maternal blood loss at birth, maternal blood transfusion and therapeutic uterotonics during the third stage or within the first 24 hours, or both, and significant increases in maternal diastolic blood pressure, vomiting after birth, after pains, use of analgesia from birth up to discharge from the labour ward and more women returning to hospital with bleeding (outcome not pre specified). There was also a decrease in the baby's birthweight with active management, reflecting the lower blood volume from interference with placental transfusion.

In the subgroup of women at low risk of excessive bleeding, there were similar findings, except there was no significant difference identified between groups for severe haemorrhage or maternal Hb less than 9 g/dL (at 24 to 72 hours). Hypertension and interference with placental transfusion might be avoided by using modifications to the active management package, e.g. omitting ergot and deferring cord clamping, but we have no direct evidence of this here.

Authors' conclusions: Although there is a lack of high quality evidence, active management of the third stage reduced the risk of haemorrhage greater than 1000 mL at the time of birth in a population of women at mixed risk of excessive bleeding, but adverse effects were identified. Women should be given information on the benefits and harms of both methods to support informed choice. Given the concerns about early cord clamping and the potential adverse effects of some uterotonics, it is critical now to look at the individual components of third stage management. Data are also required from low income countries.

Jo Durham, Alongkone Phengsavanh, Vanphanom Sychareun, Isaac Hose, Viengnakhone Vongxay, Douangphachanh Xaysomphou, and Keith Rickart. Misoprostol for the prevention of postpartum hemorrhage during home births in rural Lao PDR: establishing a pilot program for community distribution.

Int J Womens Health. 2018; 10: 215–227.

Purpose: The purpose of this study was to gather the necessary data to support the design and implementation of a pilot program for women who are unable to deliver in a healthcare facility in the Lao People's Democratic Republic (PDR), by using community distribution of misoprostol to prevent postpartum hemorrhage (PPH). The study builds on an earlier research that demonstrated both support and need for community-based distribution of misoprostol in Lao PDR.

Methods: This qualitative study identified acceptability of misoprostol and healthcare system needs at varying levels to effectively distribute misoprostol to women with limited access to facility-based birthing. Interviews (n=25) were undertaken with stakeholders at the central, provincial, and district levels and with community members in five rural communities in Oudomxay, a province with high rates of maternal mortality. Focus group discussions (n=5) were undertaken in each community.

Results: Respondents agreed that PPH was the major cause of preventable maternal mortality with community distribution of misoprostol an acceptable and feasible interim preventative solution. Strong leadership, training, and community mobilization were identified as critical success factors. While several participants preferred midwives to distribute misoprostol, given the limited availability of midwives, there was a general agreement that village health workers or other lower level workers could safely administer misoprostol. Many key stakeholders,

including women themselves, considered that these community-level staff may be able to provide misoprostol to women for self-administration, as long as appropriate education on its use was included. The collected data also helped identify appropriate educational messages and key indicators for monitoring and evaluation for a pilot program.

Conclusion: The findings strengthen the case for a pilot program of community distribution of misoprostol to prevent PPH in remote communities where women have limited access to a health facility and highlight the key areas of consideration in developing such a program.

Della Corte , Saccone G, Locci M, Carbone L, Raffone A, Giampaolino P, Ciardulli A, Berghella V, Zullo F. . Tranexamic acid for treatment of primary postpartum hemorrhage after vaginal delivery: a systematic review and meta-analysis of randomized controlled trials.

J Matern Fetal Neonatal Med. 2018 Sep 10:1-6. doi: 10.1080/14767058.2018.1500544

Background: Postpartum hemorrhage (PPH) is responsible for about 25% of maternal deaths worldwide. Antifibrinolytic agents, mainly tranexamic acid (TXA), have been demonstrated to reduce blood loss in patients with established PPH.

Objective: The aim of this meta-analysis of randomized controlled trials (RCTs) was to evaluate the effectiveness of TXA administration in women with established primary PPH after vaginal delivery.

Data Sources: The search was conducted using electronic databases from inception of each database through February 2018. Review of articles also included the abstracts of all references retrieved from the search. No restrictions for language or geographic location were applied.

Study Design: Selection criteria included RCTs comparing the use of TXA in women with established primary PPH after vaginal delivery with control (either placebo or no treatment). Trials in women undergoing cesarean delivery and trials in prevention of PPH were excluded. The primary outcome was the incidence of hysterectomy. The summary measures were reported as summary relative risk (RR) with 95% of confidence interval (CI) using the random effects model of DerSimonian and Laird.

Tabulation, Integration, And Results: Two trials including 14,363 women with established primary PPH after vaginal delivery were analyzed. Women who received TXA soon after the diagnosis of PPH had a significantly lower incidence of hysterectomy (0.5% vs 0.8%; RR 0.63, 95% CI 0.42-0.94), compared to those who did not. The risk of thrombotic events was not increased in the TXA group.

Conclusion: In women with established PPH after vaginal delivery, the use of TXA reduces the risk of hysterectomy and does not increase the risk of thrombotic events. We recommend 1 g plus a second dose of 1g if bleeding continues after 30min.

Loïc Sentilhes, Norbert Winer, Elie Azria, Marie-Victoire Sénat, Camille Le Ray, Delphine Vardon. Tranexamic acid for the prevention of postpartum hemorrhage after vaginal delivery: the TRAAP trial.

AJOG. January 2018.218(1)Supplement,S2–S3. https://www.ajog.org/article/S0002-9378(17)31650-2/fulltext

Objective: To test the impact of 1g of tranexamic acid (TXA) after vaginal delivery on the incidence of postpartum hemorrhage (PPH).

Study Design: In this multicenter double-blind randomized controlled trial with 2 parallel arms, women in labor for a planned vaginal delivery, at a term e”35 weeks, with a singleton live fetus were randomly assigned to receive 1 g intravenous tranexamic acid or placebo in addition to prophylactic oxytocin within 2 minutes after delivery. The primary outcome was the incidence of PPH defined by blood loss e”500 mL, measured with a graduated collector bag. Secondary outcomes were other measures of postpartum blood loss and potential adverse effects of TXA up to 3 months after delivery. Assuming a 10 % incidence of the primary outcome, two groups of 1,814 women were required to demonstrate a 30% decrease in primary outcome, with á=0.05 and 90% power.

Results: Of the 4079 women who were enrolled and provided consent, 3891 underwent vaginal delivery (modified intention-to-treat population).The primary outcome occurred in 156 women (8.1%) in the TXA group and in 188 women (9.8%) in the placebo group [relative risk (RR), 0.83; 95% confidence interval (95% CI), 0.68-1.01); P=0.07]. Incidences of PPH

defined by blood loss > 500 mL in the collector bag and of clinically-significant PPH according to caregivers were both reduced in the TXA group (respectively 6.6% versus 8.8%; P=0.01 and 7.8% versus 10.4%; P=0.004), as well as the need for additional uterotonics (7.3 versus 9.7%; P=0.003). Nausea or vomiting in labor ward were more common in the TXA group (7.0 % versus 3.2%; P<0.001). No significant differences were found for thrombotic events or other adverse outcomes (Table 1). Pre-specified subgroup analyses found that TXA reduced the primary outcome in women who had instrumental delivery [9.6% versus 14.5%; RR, 0.66; 95% CI; 0.44-1.00; P=0.0498] but not in those with spontaneous delivery; and in women with episiotomy [12.3% versus 17.3%; RR, 0.73; 95% CI: 0.53-1.00; P=0.049] but not in those without episiotomy.

Conclusion: Among women who delivered vaginally and received prophylactic oxytocin, TXA was associated with a lower risk of postpartum bleeding than placebo without higher risk of severe adverse events including thrombotic complications within 3 months after delivery.

WHO, USAIDS, mcsprogram. Updated WHO Recommendation on Tranexamic Acid for the Treatment of Postpartum Haemorrhage Highlights and Key Messages from the World Health Organization's. 2017 Global Recommendation. October 2017 www.mcsprogram.org https://apps.who.int/iris/ bitstream/handle/10665/259379/ WHO-RHR-17.21-eng.pdf; jsessionid=28 F40CC0945950143 F702928BAFB49B2?sequence=1

Key Messages

- The World Health Organization (WHO) recommends early use of intravenous tranexamic acid (TXA) within 3 hours of birth in addition to standard care for women with clinically diagnosed postpartum haemorrhage (PPH) following vaginal birth or caesarean section.
- Administration of TXA should be considered as part of the standard PPH treatment package and be administered as soon as possible after onset of bleeding and within 3 hours of birth. TXA for PPH treatment should not be initiated more than 3 hours after birth.
- TXA should be used in all cases of PPH, regardless of whether the bleeding is due to genital tract trauma or other causes.
- TXA should be administered at a fixed dose of 1 g in 10 mL (100 mg/mL) IV at 1 mL per minute (i.e., administered over 10 minutes), with a second dose of 1 g IV if bleeding continues after 30 minutes.
- TXA should be administered via an IV route only for treatment of PPH. Research on other routes of TXA administration is a priority.