Global Journal of Medical research: E
Gynecology and Obstetrics
Volume 14 Issue 1 Version 1.0 Year 2014
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Tranexamic Acid for Postpartum Haemorrhage: A Review

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GJMR-E Classification : NLMC Code: WS 360, WJ 190

Strictly as per the compliance and regulations of:

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I. Background

The 5thMillennium Development Goal is improving maternal health and more specifically decreasing by three quarters, the maternal mortality ratio by 2015. While important gains have been made, developing countries are still lagging due to the poor access to healthcare facilities, skilled healthcare workers, medications and blood products1.

The World Health Organisation defines post partum haemorrhage as a blood loss of greater than or equal to 500ml at the time ofor after delivery. Post partum haemorrhage remains the leading cause of maternal mortality and morbidity worldwide. The maternal mortality ratio worldwide is estimated at 210 maternal deaths per 100 000 live births, but is as high as 1100 in some developing, particularly African countries. This is in comparison to 7 maternal deaths per 100 000 live births in Australia and 21 in the United States2. Up to one third of these deaths may be attributed to obstetric haemorrhage, many of which may be prevented or minimized with timely access to medications and emergency care. Up to 1 percent of women having a vaginal birth and 5 percent of women having a cesarean section will require a blood transfusion, which exposes the woman to risks from transfusion reactions and transmission of blood-borne viral infections3. In many areas, blood products are simply not available.

The predominant causes of post partum haemorrhage are uterine atony, trauma to the genital tract and retained placental tissue after delivery. There are a number of factors that increase a woman's chance of having a post partum haemorrhage, however the majority of cases occur in women with low risk pregnancies.

Tranexamic acid is an antifibrinolytic that prevents the breakdown of fibrin deposits at bleeding sites in the body. By blocking lysine-binding sites on plasminogen molecules, the body's natural pro-hemostatic state post delivery is enhanced.

Tranexamic acid is already widely used in non-obstetric fields, to decrease bleeding from trauma and during elective cardiac and orthopedic surgery4,5. It has proven effectiveness in decreasing blood loss in patients with menorrhagia6. As there is very limited data from randomized controlled trials on the use of tranexamic acid for treating post partum haemorrhage, early reports of its success in preventing post partum haemorrhage, as well as evidence of its effective use in other areas of medicine allow extrapolation of the results to cases in which a post partum haemorrhage is already occurring. Tranexamic acid is cheap, easy to transport, store and use and evidence to date suggests that it is safe to use, even in pregnant women who are already at higher risk for thromboembolic events.

This report examines the existing data on the use of tranexamic acid in post partum haemorrhage, with an aim to recommend its use in limited settings as an adjunct to established interventions such as uterotonics.

II. Evidence

The most recent Cochrane review on the literature surrounding the effectiveness of tranexamic acid in either preventing or treating post partum haemorrhage was undertaken in 20113. Since then seven further small but promising trials have given further strength to the evidence that the medication is effective in obstetric bleeding related to delivery. As not enough evidence is available to identify an impact on maternal mortality, the outcomes specifically ascertained in this review are reduction in blood loss, avoidance of further interventions and decreased requirement for blood transfusion. Data on adverse reactions and associated events was also collected.

Nine of the elevenrandomized controlled trials identified for inclusion in this review were studies in which tranexamic acid was given prophylactically prior to lower segment cesarean section. Despite the fact that most gave inadequate or unclear data on randomization or blinding techniques (or were not blinded), the limited

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available data on the subject necessitates consideration of all trials in the review.

Of the two remaining trials, one looked at tranexamic acid given prophylactically in the third stage of labour, and a final more recent study trialed tranexamic acid versus a placebo in women who were already experiencing a post partum haemorrhage. In all trials women also received uterotonics, as per the world health organisation recommendation7.

A compiled result of the reduction of blood loss achieved with the use of tranexamic acid was not applicable due to the fact that all studies used different doses, treatment regimes and timelines for documenting the degree of haemorrhage. However, individually all studies displayed a statistically significant reduction in blood loss after delivery.

III. Prophylactic use in Cesarean Section

The largest randomized controlled trial, by Abdul-Aleem8 included 740 women, 373 of who received 1 gram of tranexamic acid intravenously 10 minutes prior to elective cesarean section. The mean total blood loss was 241.6ml in the tranexamic acid group, compared to 510.0 ml in the control group.

Goswami9 demonstrated a dose dependent relationship, with the mean total blood loss at cesarean section 527.17 ml in the control group, 376.83 ml in patients who received 10mg/kg tranexamic acid prior to cesarean and 261.17ml in those who received 15mg/kg.

The remaining studies determined a reduction in blood loss between 375.78ml and 62.5ml with the preoperative administration of tranexamic acid.10-16

IV. Management of Post Partum Haemorrhage

Ducloy-Bouthors17 is the only randomized controlled trial that looks at using tranexamic acid as a treatment for women diagnosed with postpartum haemorrhage, rather than as a preventative measure. This is the most relevant study to date. With 144 women in the study the cohort was relatively small, but adequately powered to achieve significant results. These women had already had a postpartum haemorrhage of greater than or equal to 800ml at the time of randomization. Based on success in cardiac and orthopedic surgery, a high dose of 4grams of tranexamic acid over 1 hour, followed by 1gram/hour over 6hours was administered. Blood loss was measured at specified intervals from the time of randomization up until 6hours later. The control group had a median blood loss of 221ml compared to the group receiving tranexamic acid, which had a median blood loss of 173ml.

Throughout all seven trials there wasa trend towardreduced requirement for blood transfusion and further intervention when tranexamic acid was used, however these outcomes did not reach statistical significance.

V. Adverse Events

Mild transient side effects, most commonly nausea, were reported with greater frequency among participants who had received treatment with tranexamic acid. There were no reports of deep vein thrombosis in any studies. Two patients in the tranexamic acid arm of the Ducloy-Bouthers17 trial developed superficial thrombosis at the site of the venous catheter, however one patient who did not receive the medication was diagnosed with the same condition. None of the studies reported side effects of clinical or statistical significance. A review of the use of tranexamic acid in surgery did not demonstrate an increased risk of thromboembolic events. Despite these findings, it would be imprudent to use tranexamic acid in patients with history of thrombosis or other risk factor that would preclude the use of antifibrinolytics in normal practice18.

Tranexamic acid crosses the placenta, which in theory may have some impact on the unborn baby if it is given prior to cesarean section, but obviously is not relevant if used as a treatment for post partum haemorrhage. It is excreted in very small amounts in breast milk, but to date no adverse events in breastfed babies have been reported.

VI. Discussion

The available evidence for the use of tranexamic acid in postpartum haemorrhage remains limited, with the majority of the data of poor quality. However, support is mounting and the outcomes of all studies to date are cohesive in the finding that tranexamic acid does significantly reduce blood loss post partum. At this time, doses other than 1 gram intravenously, followed by a further 1gram if bleeding does not cease are not well supported. There is not yet enough evidence to support the routine use of tranexamic acid, or any suggestion that it may be used instead of traditional interventions including uterotonics.

A large study, the WOMAN trial (World Maternal Antifibrinolytic Trial) is currently being undertaken, and will hopefully provide stronger evidence for the use of tranexamic acid in clinically diagnosed postpartum haemorrhage19. The mediation is also being used with increasing frequency in other gynecological and obstetric conditions including bleeding after LLETZ and cone biopsy of the cervix, and in antepartum haemorrhage due to placenta praevia or diagnosed placental edge bleeds. More evidence is required to support the routine use of tranexamic acid in these conditions.

Situations in which post partum haemorrhage is ongoing after first line interventions, in cases where

bleeding may be due to factors other than uterine atony, and times when there may be a delay such as transferring a patient to theatre or to a larger centre for further treatment may be an appropriate instance to administer tranexamic acid.

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