Tranexamic acid for preventing postpartum haemorrhage (Review)

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ABSTRACT

Background

Postpartum haemorrhage (PPH) is a common and occasionally life-threatening complication of labour. Several options for preventing PPH are available, but further advances in this field are important, especially the identification of safe, easy to use and cost-effective regimes. Tranexamic acid, which is an antifibrinolytic that is used widely to prevent and treat haemorrhage, merits evaluation to assess whether it meets these criteria. Evidence of effectiveness in preventing PPH might also be extrapolated to use for treatment of PPH (as have other preventive measures).

Objectives

To determine, from the best available evidence, whether tranexamic acid is effective for preventing PPH.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group’s Trials Register (15 February 2011).

Selection criteria

All published, unpublished and ongoing randomised controlled trials (RCTs) evaluating the use of tranexamic acid alone or in addition to uterotonics in the third stage of labour or during caesarean section to prevent PPH.

Data collection and analysis

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We entered the data into Review Manager software and checked for accuracy.

Main results

We included two RCTs. One RCT of unclear quality (involving 273 women) compared tranexamic acid in two doses (0.5 g intravenously and 1 g intravenously) with aminomethylbenzoic acid (0.5 g intravenously) and with no treatment in women who had vaginal birth. We excluded the aminomethylbenzoic acid arm of this trial (92 women). A second RCT of 180 women who underwent caesarean section compared tranexamic acid (1 g intravenously given 10 minutes before incision) with placebo.

Blood loss greater than 400 ml was less common in women who received tranexamic acid after vaginal birth or caesarean section in the dosage of 1 g or 0.5 g intravenously (risk ratio (RR) 0.51; 95% confidence interval (CI) 0.36 to 0.72; two studies, 453 women). Mean
blood loss was lower in the group of women who received intravenous tranexamic acid postpartum (mean difference (MD) -75.17 ml; 95% CI -108.23 ml to -42.12 ml; two studies, 361 women).

No serious side effects were reported in women who received tranexamic acid in the three included studies.

Authors’ conclusions

Tranexamic acid decreases postpartum blood loss after vaginal birth and after caesarean section based on two RCTs of unclear quality which reported on only a few outcomes. Further investigations are needed to confirm efficacy and safety of this regimen for preventing PPH. These results also provide a basis for the investigation of tranexamic acid for the treatment of PPH.

PLAIN LANGUAGE SUMMARY

Tranexamic acid for preventing bleeding after delivery

Tranexamic acid is used to decrease blood loss in surgery and health conditions associated with increased bleeding. This review found that tranexamic acid is also effective in reducing blood loss after a mother gives birth. One study of 400 women (273 women were included in the analysis for purpose of this review), compared use of tranexamic acid in two different doses (1 g and 0.5 g given intravenously) to no such treatment. Tranexamic acid was given two to three minutes after the vaginal delivery of the baby, which is when the mother is most at risk of excessive bleeding related to the childbirth. In another study (involving 180 women), the use of tranexamic acid was compared with no treatment in women who were undergoing caesarean section. Tranexamic acid was given 10 minutes before incision. The mean blood loss was lower in women who received tranexamic acid compared to women who did not. The higher dose of tranexamic acid tended to cause mild side effects such as nausea and vomiting for a very few of the women. Women who received a lower dose of tranexamic acid had no side effects. More research is needed.

BACKGROUND

Description of the condition

Postpartum haemorrhage (PPH) remains a leading cause of maternal mortality, especially in developing countries (Ronsmans 2006). In confidential enquiries into maternal deaths in South Africa (2005 to 2007) (Confidential enquiries 2006), 383 maternal deaths due to PPH were reported and the majority of these were considered to be preventable. Of these deaths, 67 (17.5%) were caused by uterine atony, where uterotonic drugs were required to control the bleeding. Other cases of maternal death from PPH were due to uterine rupture (37 in women with previous caesarean sections and 43 in women without previous caesarean sections), retained placenta (88), inverted uterus (seven), and other genital tract trauma including caesarean section (141). The great majority were thus not due to uterine atony, and attempts to address the problem need to go beyond the use of uterotonic drugs. Because of the difficulty of randomised trials in women presenting with PPH, the use of tranexamic acid for preventing PPH in high-risk women could be regarded as a proxy for assessing its use for treating PPH. In particular, high-risk factors which may not be responsive to uterotonic drugs, such as placenta praevia and lacerations from instrumental delivery, may respond to tranexamic acid. If tranexamic acid is found to be effective in the prevention of PPH in such high-risk women, its use could be extrapolated to the treatment of PPH (as has been the case for most treatments for PPH, such as oxytocin and ergometrine).

Description of the intervention

Tranexamic acid could be used in addition to current prophylactic uterotonic drugs in the third stage of labour, given intravenously to reduce the blood loss. It is used in the dose of 10 mg/kg given intravenously immediately after delivery of the baby (Astedt 1987) or in a woman undergoing caesarean section, prior to the skin incision. Tranexamic acid acts within two to three hours after oral administration and immediately after intravenous administration, and its half-life is two to 10 hours (Jurema 2008). The oral route of administration is possible, but it is not ideal in the third stage of labour, when an immediate effect of the drug is required. The sublingual route may be an alternative, but has not to our knowledge been investigated.
**How the intervention might work**

Tranexamic acid potentiates the blood clotting system and is used to treat and prevent bleeding. The mechanism of action of tranexamic acid is related to its antifibrinolytic effect, which makes this drug potentially very effective in the third stage of labour. During placental delivery, rapid degradation of fibrinogen and fibrin occurs, as well as an increase in the activation of plasminogen activators and fibrin degradation products due to activation of the fibrinolytic system. This activation can last up to six to 10 hours postpartum, which may cause more haemorrhage. The antifibrinolytic effect of tranexamic acid in the third stage of labour could make it a safe and effective alternative or adjunct to other regimens currently used in the third stage of labour for prevention of PPH. Tranexamic acid could reduce blood loss associated with complications such as placenta praevia and lower genital tract trauma, as well as bleeding from the upper segment placental site. Use of tranexamic acid could potentially have prevented some PPH cases if it was given to women with the risk factors for PPH, as reported in the Cochrane review on treatment of PPH (Mousa 2007). Therefore, it may be particularly useful in preventing cases of PPH due to factors other than uterine atony, where uterotonic will not be effective.

Tranexamic acid is an effective agent for the reduction of blood loss, which has been widely used in various areas of medicine. It is an inhibitor of fibrinolysis that blocks the lysine-binding site of plasminogen to fibrin (Astedt 1987; Longstaff 1994). It has been used to decrease blood loss for many years in cases of haemorrhage, and is reported to reduce intraoperative and postoperative blood loss (Boylan 1996; Karski 1995; Katsaros 1996; Reid 1997; Vacharaksa 2002).

Tranexamic acid is associated with a significant reduction in objective measurements of heavy menstrual bleeding when compared to placebo or other medical therapies (NSAIDS, oral luteal phase progestagens and ethamsylate) according to a Cochrane review (Lethaby 2000).

The side effects described with the use of tranexamic acid include gastrointestinal symptoms such as diarrhoea, nausea and vomiting that occur in about 10% of patients. Rare complications include hypotension, thrombosis, blurred vision, renal cortical necrosis and retinal artery obstruction (Astedt 1987). However, another study reported no side effects associated with tranexamic acid (Belassy 1990). A Cochrane review on the use of antifibrinolytics for heavy menstrual bleeding reported no rise in side effects with tranexamic acid in comparison to placebo, NSAIDS, oral luteal phase progestagens or ethamsylate (Lethaby 2000). There are concerns about the risk of thromboembolic events associated with the use of tranexamic acid; however, there are no data available from randomised controlled trials (RCTs) which record the frequency of thromboembolic events (Lethaby 2000).

**Why it is important to do this review**

PPH remains an important cause of maternal morbidity and mortality. It is important to establish safe, inexpensive and easily available methods of PPH prevention. Administration of tranexamic acid intravenously in the third stage of labour may be one of these methods. A particular advantage of tranexamic acid is that its effect is not limited to upper segment placental site bleeding, thus its use does not rely on accurate diagnosis of the site of the bleeding. Current evidence on management of the third stage of labour according to a Cochrane review favours active management involving administration of a prophylactic oxytocin before delivery of the placenta, and usually cord clamping and cutting, and controlled traction of the umbilical cord, over passive management: allowing the placenta to deliver spontaneously or aiding by gravity or nipple stimulation (Prendiville 2000). Oxytocin is beneficial for the prevention of PPH. There are insufficient data in favour of ergot alkaloids alone compared to either oxytocin alone, or to ergometrine-oxytocin according to another Cochrane review of management of the third stage of labour (Cotter 2001).

Tranexamic acid is a cost-effective drug. A study on total hip arthroplasty reported saving blood transfusion and money (47 Euro per patient) in cases where tranexamic acid was used prophylactically prior to surgery (Johansson 2005). Using tranexamic acid before caesarean section may reduce the blood loss as well. Use of tranexamic acid for preventing PPH may contribute to reduction in blood product use, which is associated with multiple risks (transfusion reactions, transmission of blood-borne viruses), is expensive and may not be available when it is needed. In South Africa, most of the maternal deaths due to PPH occur in level one hospitals which do not all have emergency access to formal blood transfusion services. Cost savings could also be gained from avoiding the use of expensive haematological agents such as Factor VIIa, which is establishing its place in the treatment of massive PPH in modern obstetrics despite the extreme cost (Welsh 2008).

**OBJECTIVES**

To determine, from the best available evidence, whether tranexamic acid is effective for preventing postpartum haemorrhage.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**
We included all published, unpublished and ongoing RCTs comparing the use of tranexamic acid alone or in addition to uterotonics in the third stage of labour or prior or during caesarean section to prevent postpartum haemorrhage. We excluded quasi-RCTs (for example, those randomised by date of birth or hospital number) from the analysis.

**Types of participants**
Women after vaginal or caesarean section birth.

**Types of interventions**
Tranexamic acid used for the third stage of labour or at caesarean section to decrease blood loss compared with placebo or other agents such as uterotonics; comparisons of tranexamic acid dosages or routes of administration.

**Comparisons**
1. Tranexamic acid versus placebo/no treatment
2. Tranexamic acid versus uterotonics
3. Different dosages of tranexamic acid
4. Different routes of administration of tranexamic acid

**Types of outcome measures**

**Primary outcomes**
1. Blood loss 500 ml or more
2. Blood loss 1000 ml or more

**Secondary outcomes**
3. Mean blood loss (ml) (during Caesarean section mean blood loss from placental delivery till two hours postpartum)
4. Use of additional medical interventions to control postpartum haemorrhage (PPH)
5. Use of additional surgical interventions to control PPH
6. Maternal haemoglobin concentration (Hb) less than 6 grams/decilitre 24 hours to 48 hours postpartum
7. Maternal death or severe maternal morbidity such as seizure, thromboembolic events, need for intensive care unit admission, hysterectomy, organ failure
8. Mild side effects such as nausea, vomiting, headache, skin reactions
9. Thromboembolic events

**Search methods for identification of studies**

**Electronic searches**
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (15 February 2011).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

**Data collection and analysis**

**Selection of studies**
Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion.

**Data extraction and management**
We designed a form to extract data. For eligible studies, both review authors extracted the data using the agreed form. We resolved discrepancies through discussion. We entered the data into Review Manager software (RevMan 2011) and checked it for accuracy. When information regarding any of the above was unclear, we attempted to contact the authors of the original reports to provide further details.
Assessment of risk of bias in included studies

Both review authors independently assessed the validity of each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We resolved any disagreement by discussion.

(1) Random sequence generation (checking for possible selection bias)

We describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:
- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We describe for each included study the method used to conceal allocation to interventions prior to assignment and assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:
- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3) Blinding of participants, personnel and outcome assessors (checking for possible performance bias)

We describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We consider studies to be at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:
- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel;
- low, high or unclear risk of bias for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We describe for each included study and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes.

Where sufficient information is reported, or was supplied by the trial authors, we re-include missing data in the analyses which we undertook.

We assessed methods as:
- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:
- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We describe for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:
- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Handbook (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. We explored the
impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

**Measures of treatment effect**

**Dichotomous data**
For dichotomous data, we presented results as summary risk ratio (RR) with 95% confidence intervals (CI).

**Continuous data**
For continuous data, we used the mean difference (MD) as the outcomes were measured in the same way in both trials. In future updates of this review, when more studies become available, we will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

**Unit of analysis issues**

**Cluster-randomised trials**
If, in future updates of this review, we identify cluster-randomised trials for inclusion, we will include them in the analyses along with individually randomised trials. We will adjust their sample sizes using the methods described in the Handbook using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

**Crossover trials**
Crossover trials are irrelevant for this intervention, and, therefore we have not included them.

**Multi-armed trials**
When analysing multi-armed trials, we have combined all relevant experimental intervention groups of the study into a single group and all relevant control intervention groups into a single control group. If the authors considered one of the arms irrelevant, we excluded it from analysis.

**Dealing with missing data**
For included studies, we have noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we have carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we have attempted to include all participants randomised to each group in the analyses, and to analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes are known to be missing.

**Assessment of heterogeneity**
We planned to use the I² statistic to measure heterogeneity among the trials in each analysis (with greater than 50% indicative of substantial heterogeneity). In future updates of this review, as more data become available we will assess statistical heterogeneity in each meta-analysis using the T², I² and Chi² statistics. We will regard heterogeneity as substantial if I² is greater than 30% and either T² is greater than zero, or there is a low P value (less than 0.10) in the Chi² test for heterogeneity.

**Assessment of reporting biases**
In future updates of this review, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006. If we detect asymmetry in any of these tests or by a visual assessment, we will perform exploratory analyses to investigate it.

**Data synthesis**
We carried out statistical analysis using the Review Manager software (RevMan 2011). We used fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect, i.e. where trials are examining the same intervention, and we judged the trials’ populations and methods sufficiently similar. In future updates of this review, if there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if we detect substantial statistical heterogeneity, we will use random-effects meta-analysis to produce an overall summary if we consider an
average treatment effect across trials clinically meaningful. We will treat the random-effects summary as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials. If we use random-effects analyses in future updates of this review, we will present the results as the average treatment effect with its 95% CI, and the estimates of $I^2$ and $\hat{I}^2$.

Subgroup analysis and investigation of heterogeneity

In future updates if we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it. We plan to carry out the following subgroup analyses:

- We will compare the outcomes such as mean blood loss greater than 1000 ml and thromboembolic events in subgroups of women delivered vaginally and by caesarean section. We will also compare the above-mentioned outcomes between subgroups with and without routine oxytocics.

For fixed-effect inverse variance meta-analyses we will assess differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups’ confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

In future updates we will perform sensitivity analyses for aspects of the review that might affect the results, for example where there is a risk of bias associated with the quality of some of the included trials; or to explore the effects of fixed-effect or random-effects analyses for outcomes with statistical heterogeneity; and to explore the effects of any assumptions made, such as the value of the ICC used for cluster-randomised trials.

We will perform sensitivity analysis for the primary outcomes (mean blood loss greater than 500 ml and greater than 1000 ml).

Results of the search

An updated search in February 2011 found three new reports. We have excluded all three studies (Gobbur 2011; Gohel 2007; Sekhavat 2009). This updated review now comprises two included studies and three excluded studies. For further details see Characteristics of included studies and Characteristics of excluded studies.

Included studies

We found one RCT (Yang 2001) investigating the efficacy of tranexamic acid for preventing postpartum haemorrhage in women who had vaginal birth. This study included 400 women with term singleton pregnancy, vertex presentation, spontaneous delivery who received 10 units of oxytocin immediately following delivery of their babies’ shoulders. The women were allocated to four groups: group one received tranexamic acid 1 g intravenously; group two received 0.5 g tranexamic acid intravenously; group three received aminomethylbenzoic acid 0.5 g intravenously; and group four did not receive any treatment. The randomisation was not described in the study, which was not blinded. For more information see Characteristics of included studies. As the results of group three were not included in this review, the effective sample size for this review was 273 women.

We identified an RCT (Gai 2004) investigating the efficacy of tranexamic acid in reducing blood loss during caesarean section. This study included 180 primigravid women with term singleton pregnancy without severe medical or surgical complication, history of thromboembolic disorders, abnormal placenta, pregnancy complications (pre-eclampsia, macrosomia, polyhydramnios), or myoma. Women in the intervention group received 1 g of tranexamic acid by slow intravenous infusion 10 minutes prior to caesarean section incision. The randomisation was done using a randomised consecutive numbered chart. The study was not blinded. Women in this trial received routine uterotonic (10 units of oxytocin intravenously and 20 units of oxytocin into the uterine wall) after delivery of the baby.

Excluded studies

We excluded three trials (Gobbur 2011; Gohel 2007; Sekhavat 2009).

The first trial (Gohel 2007) on the use of tranexamic acid prior to Caesarean Section incision was quasi-randomised (the rule of odds and even was used for randomisation).

The second trial by Gobbur and co-authors (Gobbur 2011) was only published in abstract form. Neither randomisation, nor allocation concealment were described.

The third trial by Sekhavat and co-authors (Sekhavat 2009) was quasi-randomised (randomisation was done by the rule of odds and even) and did not supply any information on allocation concealment. The outcomes reported were not consistent with our...
The blood loss reported in this trial was reported only after caesarean section. The authors have reported the mean haemoglobin concentration after caesarean section, though in this review we decided to report the number of cases with haemoglobin concentration less than six milligrams per decilitre 24 hours after caesarean section.

Risk of bias in included studies

The studies were not blinded. Allocation concealment was not described. Thus, there is a considerable risk of bias in both included studies.

Effects of interventions

We have included one study (Yang 2001) of 273 women comparing tranexamic acid in two doses (0.5 g intravenously and 1 g intravenously) with no treatment given to women having vaginal birth; one study (Gai 2004) of 180 women comparing tranexamic acid (1 g intravenously) given 10 minutes prior to caesarean section.

Primary outcomes

As blood loss greater than 500 ml was not reported in included studies, we have taken the other authors’ outcome of blood loss greater than 400 ml (Gai 2004; Yang 2001) as a proxy for the primary outcome.

Blood loss greater than 400 ml was less common in women who received tranexamic acid after vaginal birth or caesarean section in the dosage of 1 g or 0.5 g intravenously (risk ratio (RR) 0.51; 95% confidence interval (CI) 0.36 to 0.72; two studies, 453 women). See Analysis 1.1.

Women who received tranexamic acid two to three minutes postpartum after vaginal birth in the dosage of 1 g or 0.5 g intravenously had less incidence of blood loss greater than 400 ml (RR 0.38; 95% CI 0.22 to 0.68; one study, 273 women). A similar effect was also observed in women who were undergoing caesarean section. Fewer women had blood loss greater than 400 ml after receiving 1 g of tranexamic acid 10 minutes before caesarean section in comparison to women who did not receive tranexamic acid (RR 0.61; 95% CI 0.39 to 0.96; one study, 180 women).

Secondary outcomes

Mean blood loss was lower in the group of women who received intravenous tranexamic acid postpartum (mean difference (MD) -75.17 ml; 95% CI -108.23 to -42.12; two studies, 361 women). This effect was observed after vaginal birth (MD 71.50; 95% CI -115.17 ml to -27.83 ml; one study, 181 women) and after caesarean section (MD -80.10; 95% CI -130.68 ml to -29.52 ml; one study 180 women). See analysis Analysis 1.2.

Mild side effects such as nausea and vomiting were reported in women who received 1 g of tranexamic acid intravenously, but no such effects were reported for women who did not receive any treatment (RR 4.63; 95% CI 0.23 to 95.14; one study, 181 women; not statistically significant) Analysis 1.3.

When comparing different dosages (0.5 g versus 1 g) of intravenous tranexamic acid, there were no statistically significant differences in blood loss greater than 400 ml (RR 2.04; 95% CI 0.80 to 5.21; one study) Analysis 2.1, or mean blood loss (MD -0.40 ml; 95% CI -41.06 ml to 40.26 ml) Analysis 2.2.

No other outcomes defined in our protocol were reported in included studies.

DISCUSSION

Tranexamic acid is used widely to prevent haemorrhage. However, we found only five studies investigating the efficacy of tranexamic acid for preventing of postpartum haemorrhage (PPH).

Our review has found a reduction in postpartum blood loss with the use of tranexamic acid after spontaneous delivery (Yang 2001). This included study is limited to 273 women and looked at the use of tranexamic acid in women having vaginal birth. One arm of this study (92 women) was not included in the analysis as we considered it irrelevant. This group of women was given aminomethylbenzoic acid, which was considered a placebo by the trial authors, though there was also a group that has not received any intervention. We have included the latter group. The study was unblinded, with unclear allocation concealment and sequence generation. Another limitation of this study is exclusion of five cases of macrosomia (fetal weight greater than 4000 g) after randomisation, which could have introduced bias. This study was limited to singleton pregnancies and spontaneous delivery, and it reported on very few of the outcomes.

Another study investigated the use of tranexamic acid in women having caesarean section. It was an unblinded study limited to 180 women (Gai 2004). Women received routine uterotonics, which included 10 units of oxytocin intravenously and 20 units of oxytocin into the uterine wall in this trial.

Only blood loss greater than 400 ml, which differed to the primary outcome selected for this review (greater then 500 ml), as well as mild side effects were reported in Gai 2004 and Yang 2001 trials. The reasons behind a choice of an outcome such as blood loss greater than 400 ml are not clear from these papers. The possibility exists that this end-point may have been chosen retrospectively. Both trials reported on mean blood loss.

All women in all studies received routine uterotonics. No comparison between tranexamic acid and uterotonics was provided, nor was the effect of tranexamic acid in the absence of uterotonics, which may potentially be greater, assessed.
We were unable to address concerns regarding thromboembolic episodes with the use of tranexamic acid in the postpartum period, as no data are available on this major outcome.

To identify the efficacy and safety, as well as rare and more severe side effects that may be associated with the use of this regimen, a larger study is necessary.

**Summary of main results**

Subject to methodological shortcomings, tranexamic acid given in the dose of 0.5 to 1 g intravenously was effective in reducing postpartum haemorrhage after vaginal birth and caesarean section with minimal side effects.

**Authors’ Conclusions**

**Implications for practice**

The limited evidence presented in this review suggests that tranexamic acid may be an effective drug for reducing postpartum haemorrhage (PPH). Confirmation of these findings would be preferable before tranexamic acid could be recommended for prophylactic use in women at high risk of PPH, or women for whom blood loss needs to be minimised, such as women with anaemia or those who are haemodynamically unstable.

Treatment of PPH is beyond the scope of this review, but in the absence of treatment trials, the results of this review, together with the extensive evidence of safety and effectiveness from the surgical disciplines, may contribute to clinical decisions to use tranexamic acid for the treatment of PPH unresponsive to conventional treatment, particularly when haemorrhage is suspected to be due to genital tract trauma.

**Implications for research**

Because of the risk of bias in two studies reviewed, an adequately sized, placebo-controlled trial is needed to confirm the positive findings of this review. Further research is needed to examine rare side effects that may be associated with the use of tranexamic acid. Studies assessing tranexamic acid for preventing PPH are also important to allow extrapolation to the role of tranexamic acid in the management of PPH (as has happened with the use of uterotonic such as oxytocin and ergometrine for the treatment of PPH).

**Acknowledgements**

Cochrane Pregnancy and Childbirth Group team for technical support.

**References**

References to studies included in this review

Gai 2004  (*published data only*)


Yang 2001  (*published and unpublished data*)


References to studies excluded from this review

Gobbur 2011  (*published data only*)

Gobbur VR, Reddy SV, Bijapur UJ. Efficacy of tranexamic acid in reducing blood loss during lower segment caesarean section. 54th All India Congress of Obstetrics and Gynaecology; 2011 January 5–9; Hyderabad, Andhra Pradesh, India. 2011:92.

Gohel 2007  (*published data only*)


Sekhavat 2009  (*published data only*)


Additional references

Astedt 1987


Bekassy 1990

Boylan 1996

Confidential enquiries 2006

Cotter 2001

Egger 1997

Harbord 2006

Higgins 2011

Johansson 2005

Jurema 2008

Karski 1995

Katsaros 1996

Lethaby 2000

Longstaff 1994

Mousa 2007

Prendiville 2000

Reid 1997

RevMan 2011

Ronsmans 2006

Vacharaksa 2002

Welsh 2008

* Indicates the major publication for the study
### Characteristics of included studies [ordered by study ID]

**Gai 2004**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised controlled trial. Multi-centre (2 centres).</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>180 primiparas healthy women at term with singleton who underwent caesarean section</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>1 g (10 ml) of tranexamic acid diluted in 20 ml 5% glucose given intravenously slow infusion over 5 minutes 10 minutes before incision</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Blood loss, incidence of PPH (blood loss &gt; 400 ml), vital signs, uterine contractility, placental separation, neonatal manifestations, side effects</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>No placebo was used. Women in both control and study groups received 10 units of oxytocin intravenously and 20 units of oxytocin into the intrauterine wall. The same surgical team performed caesarean section in each hospital</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Randomised consecutive numbered chart.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Unclear.</td>
</tr>
<tr>
<td>Blinding (performance bias)</td>
<td>High risk</td>
<td>Not blinded.</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>The data seem complete.</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td></td>
</tr>
</tbody>
</table>

**Yang 2001**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised controlled trial.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>400 primiparous women with term singleton pregnancy, vertex presentation, spontaneous delivery. Had 10 units of oxytocin injected immediately post delivery. Tranexamic acid was given intravenously 2 to 3 minutes after the delivery</td>
</tr>
</tbody>
</table>
Yang 2001  (Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>4 groups: I - tranexamic acid 1 g intravenously (n = 94), II - tranexamic acid 0.5 g intravenously (n = 92), III - aminomethylbenzoic acid 0.5 g intravenously (n = 92), IV - no treatment (n = 87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Incidence of PPH, average blood loss, side effects.</td>
</tr>
<tr>
<td>Notes</td>
<td>Aminomethylbenzoic acid is an antifibrinolytic. There was no placebo used. Not blinded</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomly assigned to 4 groups.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>It was not mentioned.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>High risk</td>
<td>Not blinded.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Authors did not mention incomplete data. 35 cases of fetal macrosomia (&gt; 4000 g) were excluded from the study</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Women who were primipara with term singleton pregnancy, vertex presentation, spontaneous delivery, normal antenatal care, no antepartum haemorrhage, no above moderate PIH, no polyhydramnios, no abnormal birth process or other complications were enrolled in the 2nd stage of labour</td>
</tr>
</tbody>
</table>

IV: intravenously  
PIH: pregnancy-induced hypertension  
PPH: postpartum haemorrhage
## Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gobbur 2011</td>
<td>This study was published only in abstract form. The randomisation and allocation concealment were not described. This study reported decreased blood loss in 50 women who received 1 g of tranexamic acid intravenously 20 minutes prior to Caesarean section, in comparison to 50 women who did not receive the drug. No side effects were reported in either group.</td>
</tr>
<tr>
<td>Gohel 2007</td>
<td>This was a quasi-randomised trial (randomisation by the rule of odds and even). This study reported decreased blood loss in 50 women who received 1 g of tranexamic acid intravenously 20 minutes prior to Caesarean section, in comparison to 50 women who did not receive the drug. No side effects were reported in either group.</td>
</tr>
<tr>
<td>Sekhavat 2009</td>
<td>This was a quasi-randomised trial (randomisation by the rule of odds and even). This study reported decreased blood loss from the end of Caesarean section till 2 hours postpartum in 45 women who received 1 g of tranexamic acid intravenously 10 minutes prior to Cesarean section, in comparison to 45 women who did not receive the drug. Haemoglobin level was significantly greater in tranexamic acid group. No side effects were reported in either group.</td>
</tr>
</tbody>
</table>
## Data and Analyses

### Comparison 1. Tranexamic acid versus placebo/no treatment

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss &gt; 400 ml</td>
<td>2</td>
<td>453</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.51 [0.36, 0.72]</td>
</tr>
<tr>
<td>1.1 Tranexamic acid in vaginal birth</td>
<td>1</td>
<td>273</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.38 [0.22, 0.68]</td>
</tr>
<tr>
<td>1.2 Tranexamic acid in caesarean section</td>
<td>1</td>
<td>180</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.61 [0.39, 0.96]</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>2</td>
<td>361</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-75.17 [-108.23, -42.12]</td>
</tr>
<tr>
<td>2.1 Tranexamic acid in vaginal birth</td>
<td>1</td>
<td>181</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-71.5 [-115.17, -27.83]</td>
</tr>
<tr>
<td>2.2 Tranexamic acid in caesarean section</td>
<td>1</td>
<td>180</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-80.10 [-130.68, -29.52]</td>
</tr>
<tr>
<td>Side effects (nausea and vomiting)</td>
<td>1</td>
<td>181</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>4.63 [0.23, 95.14]</td>
</tr>
<tr>
<td>3.1 Tranexamic acid 1 g</td>
<td>1</td>
<td>181</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>4.63 [0.23, 95.14]</td>
</tr>
</tbody>
</table>

### Comparison 2. Different doses of tranexamic acid

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss &gt; 400 ml</td>
<td>1</td>
<td>186</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.04 [0.80, 5.21]</td>
</tr>
<tr>
<td>Mean blood loss</td>
<td>1</td>
<td>186</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.40 [-41.06, 40.26]</td>
</tr>
</tbody>
</table>

### What’s New

Last assessed as up-to-date: 11 May 2011.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 February 2011</td>
<td>New search has been performed</td>
<td>Search updated. We identified and excluded three new trials (Gobbur 2011; Gohel 2007; Sekhavat 2009).</td>
</tr>
</tbody>
</table>


**HISTORY**

Review first published: Issue 7, 2010

**CONTRIBUTIONS OF AUTHORS**

N Novikova participated in designing the review, and writing the protocol and review. She undertook the initial data analysis. GJ Hofmeyr conceived the review, and provided guidance in designing the review. He also provided a clinical perspective, and performed duplicate data extraction.

For the current update N Novikova assessed the new studies, extracted the data and prepared the first draft of the review. GJ Hofmeyr performed duplicate data extraction and reviewed the drafts of the update.

**DECLARATIONS OF INTEREST**

None known.

**SOURCES OF SUPPORT**

**Internal sources**

- Effective Care Research Unit, University of Witwatersrand, University of Fort Hare, South Africa, South Africa.

**External sources**

- No sources of support supplied

**DIFFERENCES BETWEEN PROTOCOL AND REVIEW**

The methods text has been updated to reflect the latest Cochrane *Handbook* (Higgins 2011).

**INDEX TERMS**

**Medical Subject Headings (MeSH)**

Aminobenzoates [administration & dosage]; Antifibrinolytic Agents [*administration & dosage*]; Injections, Intravenous; Postpartum Hemorrhage [*prevention & control*]; Randomized Controlled Trials as Topic; Tranexamic Acid [*administration & dosage*]
MeSH check words

Female; Humans; Pregnancy