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[Intervention Review]

Antifibrinolytic drugs for treating primary postpartum haemorrhage

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ABSTRACT

Background

Postpartum haemorrhage (PPH) - heaving bleeding within the first 24 hours after giving birth - is one of the main causes of death of women after childbirth. Antifibrinolytics, primarily tranexamic acid (TXA), have been shown to reduce bleeding in surgery and safely reduces mortality in trauma patients with bleeding without increasing the risk of adverse events.

An earlier Cochrane review on treatments for primary PPH covered all the various available treatments - that review has now been split by types of treatment. This new review concentrates only on the use of antifibrinolytic drugs for treating primary PPH.

Objectives

To determine the effectiveness and safety of antifibrinolytic drugs for treating primary PPH.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register, [ClinicalTrials.gov](https://www.clinicaltrials.gov), the WHO International Clinical Trials Registry Platform (ICTRP) (28 May 2017) and reference lists of retrieved studies.

Selection criteria

Randomised controlled trials (RCTs), including cluster-randomised trials of antifibrinolytic drugs (aprotinin, TXA, epsilon-aminocaproic acid (EACA) and aminomethylbenzoic acid, administered by whatever route) for primary PPH in women.

Participants in the trials were women after birth following a pregnancy of at least 24 weeks' gestation with a diagnosis of PPH, regardless of mode of birth (vaginal or caesarean section) or other aspects of third stage management.

We have not included quasi-randomised trials, or cross-over studies. Studies reported as abstracts have not been included if there was insufficient information to allow assessment of risk of bias.

In this review we only identified studies looking at TXA.

Data collection and analysis

Two review authors independently extracted data from each study using an agreed form. We entered data into Review Manager software and checked for accuracy.

For key review outcomes, we rated the quality of the evidence as 'high', 'moderate', 'low' or 'very low' according to the GRADE approach.

Main results

Three trials (20,412 women) met our inclusion criteria. Two trials (20,212 women) compared intravenous (IV) TXA with placebo or standard care and were conducted in acute hospital settings (labour ward, emergency department) (in high-, middle- and low-income countries).

One other trial (involving 200 women) was conducted in Iran and compared IV TXA with rectal misoprostol, but did not report on any of this review's primary or GRADE outcomes. There were no trials that assessed EACA, aprotinin or aminomethylbenzoic acid.

Standard care plus IV TXA for the treatment of primary PPH compared with placebo or standard care alone

Two trials (20,212 women) assessed the effect of TXA for the treatment of primary PPH compared with placebo or standard care alone. The larger of these (The WOMAN trial) contributed over 99% of the data and was assessed as being at low risk of bias. The quality of the evidence varied for different outcomes, Overall, evidence was mainly graded as *moderate* to *high quality*.

The data show that IV TXA reduces the risk of **maternal death due to bleeding** (risk ratio (RR) 0.81, 95% confidence interval (CI) 0.65 to 1.00; two trials, 20,172 women; *quality of evidence: moderate*). The quality of evidence was rated as moderate due to imprecision of effect estimate. The effect was more evident in women given treatment between one and three hours after giving birth with no apparent reduction when given after three hours (< one hour = RR 0.80, 95% CI 0.55 to 1.16; one to three hours = RR 0.60, 95% CI 0.41 to 0.88; > three hours = RR 1.07, 95% 0.76 to 1.51; test for subgroup differences: $\text{Chi}^2 = 4.90$, $\text{df} = 2$ ($P = 0.09$), $I^2 = 59.2\%$). There was no heterogeneity in the effect by mode of birth (test for subgroup differences: $\text{Chi}^2 = 0.01$, $\text{df} = 1$ ($P = 0.91$), $I^2 = 0\%$). There were fewer **deaths from all causes** in women receiving TXA, although the 95% CI for the effect estimate crosses the line of no effect (RR 0.88, 95% CI 0.74 to 1.05; two trials, 20,172 women, quality of evidence: moderate). Results from one trial with 151 women suggest that **blood loss of ≥ 500 mL** after randomisation may be reduced (RR 0.50, 95% CI 0.27 to 0.93; one trial, 151 women; *quality of evidence: low*). TXA did not reduce the risk of **serious maternal morbidity** (RR 0.99, 95% CI 0.83 to 1.19; one trial, 20,015 women; *quality of evidence: high*), **hysterectomy to control bleeding** (RR 0.95, 95% CI 0.81 to 1.12; one trial, 20,017 women; *quality of evidence: high*) receipt of **blood transfusion (any)** (RR 1.00, 95% CI 0.97 to 1.03; two trials, 20,167 women; *quality of evidence: moderate*) or maternal **vascular occlusive events** (any), although results were imprecise for this latter outcome (RR 0.88, 95% CI 0.54 to 1.43; one trial, 20,018 women; *quality of evidence: moderate*). There was an increase in the use of brace sutures in the TXA group (RR 1.19, 95% CI 1.01, 1.41) and a reduction in the need for laparotomy for bleeding (RR 0.64, 95% CI 0.49, 0.85).

Authors' conclusions

TXA when administered intravenously reduces mortality due to bleeding in women with primary PPH, irrespective of mode of birth, and without increasing the risk of thromboembolic events. Taken together with the reliable evidence of the effect of TXA in trauma patients, the evidence suggests that TXA is effective if given as early as possible.

Facilities for IV administration may not be available in non-hospital settings therefore, alternative routes to IV administration need to be investigated.

PLAIN LANGUAGE SUMMARY

Antifibrinolytic drugs to treat heavy bleeding after childbirth

What is the issue?

Antifibrinolytic drugs such as tranexamic acid (TXA) reduce breakdown of clots which form to stop bleeding and have been shown to reduce bleeding in surgery and to safely reduce mortality in patients with bleeding following injury without increasing the risk of adverse events. This review assesses the safety and effects of antifibrinolytic drugs in women with primary postpartum haemorrhage (PPH) (heavy bleeding within the first 24 hours after giving birth).

An earlier Cochrane review on treatments for primary PPH covered all the various available treatments; that review has now been split by types of treatment. This new review concentrates only on the use of antifibrinolytic drugs for treating primary PPH.

Why is this important?

Postpartum haemorrhage is one of the main causes of death of women after childbirth and can also cause anaemia and other serious complications.

What evidence did we find?

We searched for evidence on 28 May 2017 and found three trials which met the inclusion criteria for the review. Participants in the trials were women after birth following a pregnancy of at least 24 weeks' gestation with a diagnosis of PPH, regardless of whether they had a vaginal or caesarean section. We identified three trials (involving 20,412 women). However, one of the trials (based in Iran) did not report important outcomes, therefore, our findings are based on two trials (involving 20,212 women) conducted in hospital settings in high-, middle- and

low-income countries. One was a large trial that included more than 20,000 women, and both studies looked at the effectiveness and safety of intravenous (IV) TXA compared with placebo (dummy treatment) or no treatment. In both trials TXA was given in addition to usual care to treat bleeding. The trial contributing most of the information to the review was at low risk of bias.

Our results show that TXA reduces the risk of maternal death due to bleeding (*quality of evidence: moderate*). There were fewer deaths from all causes but the findings were uncertain (*quality of evidence: moderate*). In one trial with a small sample size additional blood loss of 500 mL or more was also reduced (151 women; *quality of evidence: low*). TXA had little or no effect on the risk of serious maternal illness (*quality of evidence: high*), or complications such as stroke or deep venous thrombosis (*quality of evidence: moderate*). Rates of hysterectomy to control bleeding (*quality of evidence: high*) and blood transfusion (*quality of evidence: moderate*) were similar for women receiving TXA versus placebo. There was an increase in one surgical intervention (brace sutures) in the TXA group and a reduction in another (laparotomy to control bleeding) but there were no clear differences between groups for other surgical and invasive procedures.

What does this mean?

TXA when administered intravenously was effective in reducing mortality due to bleeding when given within three hours in women with primary postpartum haemorrhage without increasing the risk of other complications.

Facilities for IV administration is not available in some settings so future research could look at whether TXA is effective and safe if given by other methods.