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[Intervention Review]

Antifibrinolytics for heavy menstrual bleeding

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ABSTRACT

Background

Heavy menstrual bleeding (HMB) is an important physical and social problem for women. Oral treatment for HMB includes antifibrinolytic drugs, which are designed to reduce bleeding by inhibiting clot-dissolving enzymes in the endometrium.

Historically, there has been some concern that using the antifibrinolytic tranexamic acid (TXA) for HMB may increase the risk of venous thromboembolic disease. This is an umbrella term for deep venous thrombosis (blood clots in the blood vessels in the legs) and pulmonary emboli (blood clots in the blood vessels in the lungs).

Objectives

To determine the effectiveness and safety of antifibrinolytic medications as a treatment for heavy menstrual bleeding.

Search methods

We searched the Cochrane Gynaecology and Fertility (CGF) Group trials register, CENTRAL, MEDLINE, Embase, PsycINFO and two trials registers in November 2017, together with reference checking and contact with study authors and experts in the field.

Selection criteria

We included randomized controlled trials (RCTs) comparing antifibrinolytic agents versus placebo, no treatment or other medical treatment in women of reproductive age with HMB. Twelve studies utilised TXA and one utilised a prodrug of TXA (Kabi).

Data collection and analysis

We used standard methodological procedures expected by Cochrane. The primary review outcomes were menstrual blood loss (MBL), improvement in HMB, and thromboembolic events.

Main results

We included 13 RCTs (1312 participants analysed). The evidence was very low to moderate quality: the main limitations were risk of bias (associated with lack of blinding, and poor reporting of study methods), imprecision and inconsistency.

Antifibrinolytics (TXA or Kabi) versus no treatment or placebo

When compared with a placebo, antifibrinolytics were associated with reduced mean blood loss (MD -53.20 mL per cycle, 95% CI -62.70 to -43.70; $I^2 = 8%$; 4 RCTs, participants = 565; moderate-quality evidence) and higher rates of improvement (RR 3.34, 95% CI 1.84 to 6.09; 3 RCTs, participants = 271; moderate-quality evidence). This suggests that if 11% of women improve without treatment, 43% to 63% of

women taking antifibrinolytics will do so. There was no clear evidence of a difference between the groups in adverse events (RR 1.05, 95% CI 0.93 to 1.18; 1 RCT, participants = 297; low-quality evidence). Only one thromboembolic event occurred in the two studies that reported this outcome.

TXA versus progestogens

There was no clear evidence of a difference between the groups in mean blood loss measured using the Pictorial Blood Assessment Chart (PBAC) (MD -12.22 points per cycle, 95% CI -30.8 to 6.36; $I^2 = 0\%$; 3 RCTs, participants = 312; very low quality evidence), but TXA was associated with a higher likelihood of improvement (RR 1.54, 95% CI 1.31 to 1.80; $I^2 = 32\%$; 5 RCTs, participants = 422; low-quality evidence). This suggests that if 46% of women improve with progestogens, 61% to 83% of women will do so with TXA.

Adverse events were less common in the TXA group (RR 0.66, 95% CI 0.46 to 0.94; $I^2 = 28\%$; 4 RCTs, participants = 349; low-quality evidence). No thromboembolic events were reported in any group.

TXA versus non-steroidal anti-inflammatory drugs (NSAIDs)

TXA was associated with reduced mean blood loss (MD -73.00 mL per cycle, 95% CI -123.35 to -22.65; 1 RCT, participants = 49; low-quality evidence) and higher likelihood of improvement (RR 1.43, 95% CI 1.18 to 1.74; $I^2 = 0\%$; 2 RCTs, participants = 161; low-quality evidence). This suggests that if 61% of women improve with NSAIDs, 71% to 100% of women will do so with TXA. Adverse events were uncommon and no comparative data were available. No thromboembolic events were reported.

TXA versus ethamsylate

TXA was associated with reduced mean blood loss (MD 100 mL per cycle, 95% CI -141.82 to -58.18; 1 RCT, participants = 53; low-quality evidence), but there was insufficient evidence to determine whether the groups differed in rates of improvement (RR 1.56, 95% CI 0.95 to 2.55; 1 RCT, participants = 53; very low quality evidence) or withdrawal due to adverse events (RR 0.78, 95% CI 0.19 to 3.15; 1 RCT, participants = 53; very low quality evidence).

TXA versus herbal medicines (Safoof Habis and Punica granatum)

TXA was associated with a reduced mean PBAC score after three months' treatment (MD -23.90 pts per cycle, 95% CI -31.92 to -15.88; $I^2 = 0\%$; 2 RCTs, participants = 121; low-quality evidence). No data were available for rates of improvement. TXA was associated with a reduced mean PBAC score three months after the end of the treatment phase (MD -10.40 points per cycle, 95% CI -19.20 to -1.60; I^2 not applicable; 1 RCT, participants = 84; very low quality evidence). There was insufficient evidence to determine whether the groups differed in rates of adverse events (RR 2.25, 95% CI 0.74 to 6.80; 1 RCT, participants = 94; very low quality evidence). No thromboembolic events were reported.

TXA versus levonorgestrel intrauterine system (LIUS)

TXA was associated with a higher median PBAC score than LIUS (median difference 125.5 points; 1 RCT, participants = 42; very low quality evidence) and a lower likelihood of improvement (RR 0.43, 95% CI 0.24 to 0.77; 1 RCT, participants = 42; very low quality evidence). This suggests that if 85% of women improve with LIUS, 20% to 65% of women will do so with TXA. There was insufficient evidence to determine whether the groups differed in rates of adverse events (RR 0.83, 95% CI 0.25 to 2.80; 1 RCT, participants = 42; very low quality evidence). No thromboembolic events were reported.

Authors' conclusions

Antifibrinolytic treatment (such as TXA) appears effective for treating HMB compared to placebo, NSAIDs, oral luteal progestogens, ethamsylate, or herbal remedies, but may be less effective than LIUS. There were too few data for most comparisons to determine whether antifibrinolytics were associated with increased risk of adverse events, and most studies did not specifically include thromboembolism as an outcome.

PLAIN LANGUAGE SUMMARY

Antifibrinolytics (such as tranexamic acid) for treatment of heavy menstrual bleeding

Review question

Antifibrinolytic agents are designed to reduce bleeding by inhibiting endometrial clot-dissolving enzymes (in the uterine lining); Cochrane researchers reviewed the evidence about the effect of these medications (such as tranexamic acid, TXA) versus placebo and other medical therapies in women with heavy menstrual bleeding (HMB: defined as more than 80 millilitres (> 80 mL) of blood loss per menstrual cycle).

Background

Antifibrinolytic agents (such as tranexamic acid, TXA) are commonly used to manage HMB. However, historically there has been concern that they may cause dangerous blood clots in the legs or lungs. There are a variety of other medications that can be used to treat HMB. We compared the benefits and risks of the treatments.

Antifibrinolytics for heavy menstrual bleeding (Review)

Study characteristics

We found 13 randomized controlled trials (RCTs) comparing an antifibrinolytic medication with a different medical therapy, in a total of 1312 women with heavy menstrual bleeding. The evidence is current to November 2017.

Key results

Antifibrinolytic medication may improve HMB in women aged 15 to 50 years old, without substantially increasing the rate of adverse events. Evidence suggests there is a 40% to 50% reduction in the amount of menstrual blood lost per menstrual cycle for participants taking TXA. Antifibrinolytic treatment was better at improving HMB loss than other medical treatments, except for the levonorgestrel intrauterine system (LIUS), a plastic device placed in the uterus which releases hormone to prevent conception.

The evidence suggests that if 10.9% of women taking placebo report an improvement in HMB, 36.3% of women taking TXA will do so.

TXA probably improves quality of life for women with HMB.

We did not find any evidence that side effects (including life-threatening blood clots) were increased in women taking antifibrinolytic treatment compared to placebo or other treatments for HMB. Two studies measured venous thromboembolic events: unfortunately these studies did not have enough participants to distinguish a real effect of a certain size from pure luck.

Quality of the evidence

The evidence was of very low to moderate quality. The main limitations were: risk of bias, due to participants/investigators being aware of which medication they were receiving (known as lack of blinding), or the study's methods not being reported very clearly; imprecision (i.e. repeated measurements being far apart from each other), and inconsistency (i.e. as the sample size increases, the sampling distribution becomes increasingly wide around the true parameter value).