

Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding (Review)

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[Intervention Review]

Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding

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ABSTRACT

Background

Heavy menstrual bleeding (HMB) is an important cause of ill health in premenopausal women. Although surgery is often used as a treatment, a range of medical therapies are also available. Nonsteroidal anti-inflammatory drugs reduce prostaglandin levels which are elevated in women with excessive menstrual bleeding and also may have a beneficial effect on dysmenorrhoea.

Objectives

The primary objective of this review was to investigate the effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) in achieving a reduction in menstrual blood loss in women of reproductive years HMB.

Search strategy

We searched the Cochrane Menstrual Disorders & Subfertility Group trials register (searched 6 April 2004), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 1, 2004), MEDLINE (1966 to April 2004), EMBASE (1985 to April 2004), CINAHL (1982 to April 2004), and Current Contents (1993 to April 2004) and reference lists of articles. We also contacted manufacturers and researchers in the field.

Selection criteria

The inclusion criteria were randomised comparisons of individual NSAIDs with either each other, placebo or other medical treatments in women with regular heavy periods measured either objectively or subjectively and with no pathological or iatrogenic (treatment induced) causes for their heavy menstrual blood loss.

Data collection and analysis

Sixteen RCTs were identified that fulfilled the inclusion criteria for this review and data were extracted independently. Odds ratios for dichotomous outcomes and weighted mean differences for continuous outcomes were estimated from the data of nine trials. The results of the remaining seven crossover trials with data unsuitable for pooling were described in the Other Data section.

Main results

As a group, NSAIDs were more effective than placebo at reducing heavy menstrual bleeding but less effective than either tranexamic acid or danazol. Treatment with danazol caused a shorter duration of menstruation and more adverse events than NSAIDs but this did not appear to affect the acceptability of treatment. There were no statistically significant differences between NSAIDs and the other

treatments (oral luteal progestogen, ethamsylate, progesterone releasing intra-uterine system (IUS), oral contraceptive pill (OCC)) but most studies were underpowered. There was no evidence of a difference between the individual NSAIDs (naproxen and mefenamic acid) in reducing HMB.

Authors' conclusions

NSAIDs reduce HMB when compared with placebo but are less effective than either tranexamic acid or danazol. However, adverse events are more severe with danazol therapy. In the limited number of small studies suitable for evaluation, no significant difference in efficacy was demonstrated between NSAIDs and other medical treatments such as oral luteal progestogen, ethamsylate, OCC or IUS.

PLAIN LANGUAGE SUMMARY

NSAIDs help reduce heavy menstrual bleeding but tranexamic acid or danazol work better.

Women seek help for heavy menstrual bleeding (HMB) when it impacts on their quality of life although the menstrual loss can be assessed objectively. Levels of prostaglandin (naturally occurring fatty acids) are higher in women with heavy menstrual bleeding and are reduced by nonsteroidal anti-inflammatory drugs (NSAIDs). The review of trials found that NSAIDs are effective in reducing HMB but danazol and tranexamic acid are more effective. Danazol caused a shorter duration of bleeding and more adverse effects than NSAIDs but this did not stop women using it. These results are based on a small number of underpowered trials.

BACKGROUND

Excessively heavy menstrual bleeding (menorrhagia) is an important cause of ill health in women. One in 20 women aged 30 to 49 consult their general practitioner (GP) each year with heavy menstrual bleeding (Vessey 1992) and it accounts for 12% of all gynaecology referrals in the UK (Bradlow 1992).

Heavy menstrual bleeding is objectively defined as greater than, or equal to, 80 mls blood loss per menstrual cycle (Cole 1971; Hallberg 1966) but it is the woman's perception of her own menstrual loss which is the key determinant in her referral and indeed subsequent treatment. Many factors can cause abnormal menstruation (coagulation disorders, endocrine disorders, uterine abnormalities and other pelvic diseases) and these disorders are usually considered before decisions are made about treatment. Eighty per cent of women treated for heavy menstrual bleeding have no anatomical pathology and over a third of the women undergoing hysterectomies for excessive blood loss have normal uteri removed (Clarke 1995; Gath 1982). Hence medical therapy, with the avoidance of possibly unnecessary surgery, is an attractive alternative.

A wide variety of medications are used to reduce heavy menstrual bleeding (HMB). A rationale for the use of non-steroidal anti-inflammatory drugs is given by the accumulation of data suggesting a role for the prostaglandins in the pathogenesis of HMB (Hagenfeldt 1987). The endometrium of women with excessive menstrual bleeding has been found to have higher levels

of prostaglandin E2 and prostaglandin F2a when compared with women with normal menses (Willman 1976). There is further evidence of deranged haemostasis (abnormal clotting) as the ratio of prostaglandin E2 to F2 (Smith 1981) and the ratio of prostacyclin (prostaglandin I2) to thromboxane (Makarainen 1986) are elevated. These substances are present both in the endometrium and myometrium, although the exact mechanism by which the excessive blood loss occurs remains speculative. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce prostaglandin levels by inhibiting the enzyme cyclo-oxygenase (Rees 1987; Smith 1981). In 1976, Anderson reported a reduction of menstrual blood loss when mefenamic acid and flufenamic acid were taken during the days of menstrual bleeding (Anderson 1976). Reduced menstrual loss (assessed subjectively) has also been reported after treatment with mefenamic acid (Wood 1980).

Individual NSAIDs used for the treatment of heavy menstrual bleeding include mefenamic acid, naproxen, ibuprofen, flurbiprofen, meclofenamic acid, diclofenac, indomethacin and acetylsalicylic acid. It is usually assumed that there are no differences in clinical efficacy between individual prostaglandin inhibitors, although there are individual women who seem to respond well to one agent but less well to another. This assumption has been tested in the review with the inclusion of individual NSAID comparisons for the treatment of HMB. NSAIDs also can have a beneficial effect on dysmenorrhoea, a symptom often related to heavy menstrual bleeding. Side effects of treatment, especially gastro-intestinal ef-

fects, are variable in frequency but are not usually severe.

OBJECTIVES

To determine the effectiveness of NSAIDs in achieving a reduction in menstrual blood loss in women of reproductive years with heavy menstrual bleeding.

We wished to test the following hypotheses:

- (1) Treatment with NSAIDs is more effective than placebo in reducing menstrual blood loss.
- (2) Treatment with NSAIDs is more effective than other medical therapies (anti-fibrinolytics, danazol, hormone treatment, LHRH/GNRH analogues) in reducing menstrual blood loss.
- (3) Individual NSAIDs have similar efficacy in reducing menstrual blood loss.
- (4) Treatment with NSAIDs is associated with a lower incidence of adverse events and higher adherence and greater acceptability than other medical therapies.
- (5) Treatment with NSAIDs is a cost-effective method of treating heavy menstrual bleeding.
- (6) Treatment with NSAIDs leads to an improved quality of life for women with heavy menstrual bleeding (in particular, an improvement in symptoms of dysmenorrhoea).

RESULTS

NSAIDs versus placebo

Menstrual blood loss (objective/subjective)

Mean menstrual blood loss was significantly different in the mefenamic acid (MFA) group compared to the placebo group in one small trial with 11 patients (WMD -124 mls, 95% CI -186 to -62) in the meta-analysis (MBL in the MFA group was 124 mls less than in the placebo group). There were no other trials with data suitable for pooling but six crossover trials were identified which reported a total effect at the end of the study (three trials compared mefenamic acid with placebo, two trials compared naproxen with placebo and one trial compared different dosages (600 mg and 1200 mg daily) of ibuprofen with placebo). In five of the seven post-treatment comparisons, the post-treatment mean MBL was significantly different from placebo. However, non significant results were also reported for low dose ibuprofen versus placebo (Makarainen 1986) and mefenamic acid versus placebo (Muggeridge 1983).

A highly significant difference was found in women's perception of "relief" (OR 0.08, 95% CI 0.03 to 0.18) of heavy menstrual bleeding between mefenamic acid and placebo groups (Grover 1990).

No additional information was made available from the author regarding the measurement of relief of HMB. In one of the crossover trials not included in the meta-analysis (Ylikorkala 1986), 79% of patients indicated that naproxen was "better" compared to 21% who indicated that the placebo treatment was "better" at reducing their HMB.

Other outcomes

No trials were identified for the meta-analysis to assess number of days of menstrual bleeding, change in quality of life, patient adherence and treatment acceptability. In the small van Eijkeren study, total incidence of adverse events was comparable between groups, mefenamic acid and placebo (van Eijkeren 1992). Of the crossover trials identified above, there was no change in dysmenorrhoea scores between treatment cycles, mefenamic acid vs placebo, (Muggeridge 1983), and no differences in the total incidence of adverse events between treatment cycles, naproxen vs placebo and ibuprofen vs placebo (Ylikorkala 1986; Makarainen 1986).

NSAIDs versus tranexamic acid

Menstrual blood loss (objective/subjective)

In the one study available for pooling with 48 patients, a weighted mean difference of 73 ml/cycle (95% CI 22 to 124) was found in the comparison of mefenamic acid and tranexamic acid (MBL in the tranexamic acid group was 73 ml less than in the mefenamic acid group). In the same study, there was no significant difference between the groups in the women's perception of change in their MBL. In a crossover trial, where data were not suitable for pooling, mean MBL was significantly less in the tranexamic acid cycles (155 ml) than in the flurbiprofen cycles (223 ml), $p < 0.01$ (Andersch 1988).

Number of days of menstrual bleeding

In the one study available for pooling, there were no significant differences between treatment groups.

Other outcomes

No significant differences were found between groups for the outcomes, change in quality of life and treatment acceptability, although these results were based on only one study. No trials were identified to assess the other outcomes.

NSAIDs versus ethamsylate

All outcomes, except for MBL measured objectively, were based on only one study.

Menstrual blood loss (objective/subjective)

No significant differences were found for both objective (two studies) and subjective measurement (one study) of MBL between the treatment groups, immediately after the intervention and at longer follow up (one study).

Number of days of menstrual bleeding

In the one study available for pooling, no significant differences were found for this outcome between treatment groups.

Other outcomes

In the one study available for pooling, no significant differences were found between treatment groups for the secondary outcome, change in quality of life, but a greater proportion of women found ethamsylate unacceptable compared to NSAIDs (OR 0.20, 95% CI 0.07 to 0.61). No trials were identified to assess the other outcomes.

NSAIDs versus danazol

Menstrual blood loss (objective)

Reduction of HMB was significantly greater in the danazol group (WMD 45 ml/cycle, 95% CI 19 to 71). No trials were identified which assessed women's perception of MBL after treatment.

Number of days of menstrual bleeding

The number of days of menstrual bleeding was significantly less in the danazol compared to the mefenamic acid groups (WMD 1.03, 95% CI 0.26 to 1.80).

Other outcomes

No significant differences were found for the outcomes, change in quality of life and treatment acceptability between groups, although these results were based on one study with 40 patients. In this same study, the risk of adverse events was significantly less in the mefenamic acid group (OR 0.17, 95% CI 0.05 to 0.6).

NSAIDs versus oral progestogen (luteal phase)

Two studies assessed MBL and duration of bleeding and one study with 35 patients assessed adherence and adverse events. No significant differences were found for any outcomes.

NSAIDs versus progesterone releasing IUS

Reduction of HMB was not significantly different between groups in one small trial with 16 patients but the number of days of menstrual bleeding was significantly longer in patients with the progesterone releasing IUS.

NSAIDs versus oral contraceptive pill

In the one study with data suitable for pooling (26 patients), no significant differences were found in the objective measurement of MBL between treatment groups. No other outcomes were assessed.

Mefenamic acid versus naproxen

No significant differences were found in the objective measurement of MBL (two studies) and total incidence of adverse events between treatment groups (one study), but the risk of gastrointestinal effects was significantly less in the mefenamic acid group when compared with the naproxen group in one study with 35 patients (OR 0.24, 95% CI 0.06 to 0.87).

DISCUSSION

Assessment of menstrual blood loss is difficult because of cycle to cycle variation in women (Haynes 1977). Haynes found that cycle-to-cycle variation was greater in patients with heavy menstrual bleeding (39 to 271 ml) than in women with normal menses. Consequently, trials were included in this review only if MBL (measured objectively) was greater than 80 ml/cycle for 2 or more cycles prior to the intervention although trials were also included where women had a subjective complaint of heavy menstrual bleeding. The alkaline haematin extraction method is the most commonly used objective method for assessment of blood loss and is used as the standard but a woman's own perception of her MBL is also important in the evaluation of effectiveness of treatment on MBL and so a woman's subjective assessment is also a valid assessment tool. However, many women who seek medical help for heavy menstrual bleeding will have normal blood loss (Haynes 1977; Fraser 1984) and results from one RCT have suggested that there is little response to therapy in women with MBL <35 ml (Fraser 1981). Since a proportion of the study participants with a complaint of heavy menstrual bleeding had normal menstrual blood loss, it is likely that some reported differences between treatment and placebo groups have been underestimated.

The clinical differences between individual NSAID preparations have not been previously explored thoroughly in randomised studies. Two studies in this review compared mefenamic acid with naproxen and no differences were found in post-treatment menstrual blood loss or incidence of adverse events although women treated with mefenamic acid were less likely to have gastro-intestinal effects. This latter finding, however, based on only one trial, is not supported by RCTs where NSAIDs are given for other medical conditions.

Although data comparing different types of NSAIDs were limited, there was no suggestion of differential efficacy, so in line with the widely accepted assumption that NSAIDs have similar clinical efficacy, studies comparing different NSAIDs with placebo or other treatments were combined. Evidence from the one trial in the meta-analysis and five of the six crossover studies confirms that NSAIDs are more effective than placebo in reducing MBL. The quality of the only study in the meta-analysis, however, was not high; 42% of randomised patients dropped out and the analysis was not intention to treat. A highly significant difference between NSAIDs and placebo in reduction of MBL is also perceived by the patients in one study which recorded the proportion of patients who were relieved of their heavy menstrual bleeding as the primary outcome.

In the comparisons of NSAIDs as a group with other medical treatments, both tranexamic acid and danazol were more effective than any of the NSAIDs in reducing MBL. Results from the only study in the meta-analysis assessing the effect on MBL of NSAIDs vs tranexamic acid were confirmed by a crossover trial

(Andersch 1988). A significant reduction was also found in the meta-analysis of NSAIDs vs danazol in two included studies; the third study (Cameron 1987) had incomparable groups at baseline with a significantly higher (almost double) pre-treatment MBL in the danazol group and the results must be regarded with caution.

There were no significant differences in reduction of MBL in the comparisons of NSAIDs with ethamsylate, oral progestogen given during the luteal phase, the progesterone releasing IUS and the oral contraceptive pill, although the trend in the mefenamic acid vs ethamsylate comparison and the mefenamic acid vs oral progestogen comparison suggested that mefenamic acid may be more effective ($p=0.0524$; $p=0.0562$). More studies comparing these treatments are needed.

In the comparisons of NSAIDs with other medical treatment, the number of days of menstrual bleeding was significantly shorter with danazol treatment and significantly longer with the progesterone releasing IUS although this latter result was based on only one small trial. This outcome was not compared with oral contraceptive treatment.

Incidence of adverse events was significantly more likely under danazol treatment. Although acceptability of treatment did not differ between danazol and mefenamic acid therapy (50% vs 47% refused to continue), the reasons given were not similar. 80% of this group of danazol patients refused to continue because of adverse effects but 100% of the mefenamic acid group unwilling to continue were unhappy about the lack of efficacy of their treatment. A significantly greater proportion of women in the ethamsylate group compared to women in the NSAID group (MFA) found their treatment unacceptable.

No trials were identified with data on cost or resource use of NSAID treatments.

The studies included in this review have examined effects over two or three menstrual cycles of treatment and one study with unpublished data has assessed effects one month after treatment was withdrawn. There is no randomised evidence of effects over a longer period but one observational study has examined the effects of mefenamic acid in 34 women over a 16 month period and reported persistent reductions of 25-35% in menstrual blood loss and improvement in quality of life (Fraser 1983).

Moreover, different dosage regimens for some of the medical therapies were not considered in the included trials. A longer duration of oral progestogen treatment (from days 5 to 26 of the menstrual cycle), and longer duration of treatment over a number of cycles with all medical therapies are necessary to adequately assess the comparisons considered in this review.

Although 16 trials met the criteria for inclusion, the inadequacies in some of the studies must be highlighted. The trials were all small and underpowered and for many outcomes the results were based on only one trial. Reduction of MBL in two of the nine

trials (Cameron 1987; Hall 1987) that were included in the meta-analysis was correctly reported as a median and range in the publications since the distribution of data was positively skewed with one or more extremely high values. Substitution of the mean for the median and the estimation of the standard deviation for these studies has enabled their inclusion in the meta-analysis but sensitivity analysis with and without the inclusion of the Cameron trial has not altered results. The Hall study was the only trial comparing MBL after treatment with two NSAIDs, mefenamic acid and naproxen. The Mann-Whitney U test reported in the publication of the trial agreed with the results of the meta-analysis finding no significant difference between the groups.

Two of the included trials had incomparable groups at baseline (Chamberlain 1991; Cameron 1987) but sensitivity analysis indicated that their inclusion in the meta-analysis did not substantially alter the results.

Assessments of carryover effects were made in two trials (Fraser 1981; Hall 1987). Fraser found in his crossover trial of mefenamic acid and placebo, somewhat surprisingly, that the MBL during placebo cycles was greater (but not significantly) in the group that took mefenamic acid first. Of considerable interest was the finding that blood loss in the mefenamic acid cycles was significantly less ($p<0.01$) when placebo was taken first, so that mefenamic acid appeared to have a greater beneficial effect when taken after placebo. There was evidence of a small carryover effect but this did not reach statistical significance. Hall also tested for carryover effects but none were found ($p=0.96$). It is generally accepted that menstrual blood loss returns to baseline levels very quickly after medical treatment is withdrawn and so the results from the crossover trials were unlikely to be affected by carryover effects.

In spite of the limited data, it appears that NSAIDs are more effective than placebo but less effective than tranexamic acid or danazol in reducing heavy menstrual bleeding. However, adverse events are more frequent under danazol therapy than NSAID therapy.

AUTHORS' CONCLUSIONS

Implications for practice

The review provides limited evidence of the efficacy of NSAIDs (of which the most commonly studied is mefenamic acid) as a treatment for reducing heavy menstrual bleeding in women with menorrhagia. The efficacy of NSAIDs, however is superseded by both danazol and tranexamic acid. Other medical treatments appear to be similarly effective compared to NSAIDs, although there is a suggestion that mefenamic acid may be more effective than either ethamsylate or oral progestogen. Danazol also reduces the number of days of menstrual bleeding but is more likely to cause adverse events when compared to NSAIDs. Gastro-intestinal ef-

fects, which are often found with NSAID treatment, are less likely with mefenamic acid than naproxen.

It is important to emphasize that a proportion of women with a convincing history of menorrhagia may not have excessive bleeding as defined by the alkaline haematin method. Treatments used to reduce blood loss in these women are not likely to be as effective.

The results of the review underscore the multiple assessments that are required in the evaluation of an optimum treatment. Efficacy is only one of these; other factors such as cost, convenience, beneficial and adverse effects on symptoms are also required.

Implications for research

Since mefenamic acid has been most commonly studied, further RCTs are required to compare individual NSAIDs so that the optimum treatment can be identified. One of the excluded trials (Vargyas 1987) reported a greater percentage reduction from baseline MBL in women using another fenamate, meclofenamic acid, when compared to other studies assessing mefenamic acid.

Because many of the analyses contained only one RCT, some of the comparisons were not able to be assessed thoroughly, in particular,

the effects of NSAIDs on dysmenorrhoea, adherence to and acceptability of treatment and incidence of adverse events. However, since NSAIDs are less efficacious than a number of other medical therapies, further RCTs are not likely to significantly change the findings in this review. Future studies comparing treatments for heavy menstrual bleeding should consider giving a longer duration of treatment over a number of cycles and a regimen of oral progestogen given during three of the four weeks of the cycle to adequately assess comparative effects between medical treatments.

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* Indicates the major publication for the study

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NOTES

An updated search was performed in September and October 2001 but no new eligible trials were identified.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [*therapeutic use]; Dysmenorrhea [drug therapy]; Menorrhagia [*drug therapy]; Randomized Controlled Trials

MeSH check words

Female; Humans