The effect of mefenamic acid and naproxen on heavy menstrual bleeding: A placebo-controlled study

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Background. Heavy menstrual bleeding is a common complaint. Various therapeutic approaches have been suggested.

Aim. To compare the efficacy of mefenamic acid and naproxen in reducing heavy menstrual bleeding.

Methods. Women referred to an outpatient centre for treatment of heavy menstrual bleeding were recruited. Participants who met the inclusion criteria were evaluated for 6 menstrual cycles. During 3 control cycles they recorded the amount of their bleeding on the Pictorial Blood Assessment Chart to confirm that their menstrual bleeding was heavy. One hundred and twenty participants were then randomly assigned to receive mefenamic acid, naproxen or placebo, and asked to fill in the same questionnaires during 3 intervention cycles. The data were analysed using SPSS version 15 for Windows.

Results. Participants receiving mefenamic acid experienced a marked decrease in bleeding during the 3 months of intervention, an initial sharp decrease being followed by a further lesser decrease ($p<0.05$ within group). Bleeding lessened dramatically in the first month of the intervention in participants receiving naproxen, and dropped still further in the second and third months ($p<0.05$ within group). In the placebo group there were slight changes in bleeding during the intervention ($p>0.05$ within group). However, the total decrease in bleeding was greatest in the naproxen arm, and the differences between the groups were statistically significant ($p<0.05$ between groups).

Conclusion. All three interventions had positive effects on the mean amount of bleeding, although naproxen was more effective than mefenamic acid and much more effective than placebo.

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Heavy menstrual bleeding (defined as loss of 80 ml blood or more during each menstrual cycle, in the absence of pathological causes of abnormal bleeding such as tumours, hormonal, thyroid or coagulation disorders, infections, or foreign bodies such as the intrauterine contraceptive device (IUCD)[1]) is a common complaint, affecting close to 30% of women of reproductive age.[2] It has been reported that two-thirds of all hysterectomies, in addition to a large number of endoscopic endometrial ablations, are performed for this indication.[3] Moreover, the prevalence of anaemia has been shown to be higher among women who lose more than 80 ml blood in each menstrual cycle than among those who lose less.[4]

Laboratory investigations indicate that heavy menstrual bleeding is associated with two main factors: (*i*) an increase in fibrinolysis; and (*ii*) an imbalance in prostaglandins (PGs). It has been demonstrated that women who experience heavy menstrual bleeding have relatively high serum levels of prostaglandin E_2 and prostacylin, which induce vasodilatation and prevent the local accumulation of platelets,[5] and lower levels of prostaglandin $F_{2\alpha}$, which causes vasoconstriction.[6] Furthermore, women with heavy menstrual bleeding have more prostaglandin E receptors in their uteri than women who have lighter menstrual periods.[7] Therefore, it has been suggested that prostaglandin synthesis inhibitors could be an effective and appropriate treatment for heavy menstrual bleeding.[8]

Non-steroidal anti-inflammatory drugs (NSAIDs) are highly effective in the reduction of menstrual bleeding[9] and pain.[10] Mefenamic acid and naproxen have been shown to reduce blood loss by 30 - 50%, and only need to be taken during the menstrual period.[11] This research was conducted to compare their efficacy in reducing heavy bleeding.

Methods

This was a randomised, placebo-controlled clinical trial comparing the efficacy of mefenamic acid with that of naproxen in patients with heavy menstrual bleeding. Participants were recruited from an academic outpatient medical centre at Zeynabiyeh Hospital in Shiraz, Iran, during 2008 - 2009. The study was approved by the Medical Research Ethics Committee of Shiraz University of Medical Sciences, and all participants voluntarily consented to take part in the study, signed an informed consent form, and were assured that their information would be kept confidential.

We calculated that 40 women would be needed in each of the three study groups, with at least 25 per group completing the study, to have 90% power and to detect a 21% difference in menstrual blood loss at the statistical significance level of $p<0.05$.

Inclusion criteria were as follows: (*i*) age 20 - 45 years; (*ii*) normal findings on cervical smear test; (*iii*) normal ovulatory cycles; (*iv*) no history of renal or hepatic impairment, thromboembolic disease, inflammatory bowel disease, peptic or intestinal ulceration, or coagulation or fibrinolytic disorders; (*v*) normal results for blood tests (including prothrombin time, partial thromboplastin time and thyroid-stimulating hormone); and (*vi*) not taking any hormones or NSAIDs. Exclusion criteria included: (*i*) infertility; (*ii*) being overweight or obese (body mass index (BMI) >25 kg/m^2) or underweight (BMI <18.5 kg/m^2); (*iii*) polycystic ovarian syndrome; (*iv*) vaginitis and/or pelvic inflammatory disease; (*v*) uterine polyps and/or fibroids; (*vi*) use of the ICUD; and (*vii*) being perimenopausal (increased serum follicle-stimulating hormone levels indicating the approach of menopause).

Gynaecological investigations, which included vaginal/abdominal ultrasound scans, hysteroscopy and endometrial biopsy, were performed in the luteal phase to rule out endometrial lesions and confirm normal ovulation. Patients who did not have ovulatory cycles were excluded from the study. In addition, a cervical smear test was done to exclude any organic causes of heavy menstrual bleeding. Patients with any of the exclusion criteria were referred for further evaluation and appropriate treatment. Women aged 20 - 45 years, who complained of regular heavy menstrual bleeding and met the inclusion criteria, were recruited.

One hundred and twenty participants were selected. The nominated women were randomly allocated to one of the three study groups in the following way: first, each questionnaire was assigned a number. Then three numbers were selected randomly in order to designate the first person in each group. After that, the 117 remaining questionnaires were divided into 39 groups consisting of three questionnaires in each group. Next, we randomly assigned each of these three questionnaires to one of the three study groups. At the end, there were three groups of 40 participants.

The participants were investigated for 6 consecutive menstrual cycles, during which all of them were asked to use pads of the same type, provided by the researchers. During the first 3 control cycles, they recorded the amount of their bleeding on the Pictorial Blood Assessment Chart (PBAC) to confirm that they had heavy bleeding. The PBAC was developed in 1990 by Higham *et al.* to evaluate menstrual bleeding, which is scored according to the visual appearance of stained towels, tampons and the presence of clots[12] (Table 1).

After the first 3 assessment cycles, the trial was explained to participants. They were assured of confidentiality and that their participation was entirely voluntary. Those who agreed to participate signed the informed consent form. All of them agreed to take tablets from days 1 to 5 of their menstrual period for the 3 consecutive intervention cycles.

The women in the first group received tablets containing 250 mg mefenamic acid (Rouz Darou Pharmaceutical Company, Tehran, Iran) 4 times a day (1 000 mg total daily intake), those in the second group tablets containing 250 mg naproxen (Rouz Darou Pharmaceutical Company, Tehran, Iran) 4 times a day (1 000 mg total daily intake), and those in the third group placebo tablets 4 times a day. The placebo, mefenamic acid and naproxen tablets were identical in appearance and their packages were coded according to the content by a person who was not in the research team, so they could not be identified by either the researchers or the participants until after completion of the study and statistical analysis, when the codes were broken. All participants completed the PBAC prospectively during the intervention cycles, and they were asked to record any adverse effects.

The participants were advised to take the tablets with food and a sufficient amount of water, and to use the pads that had been provided during both the control and intervention cycles. They were visited between cycles to make sure that they were not having any serious problems and to answer their questions. They were also given the researcher (MK)'s phone number and told to contact her at any time if they had had any concerns or questions. After completion of the 3 intervention cycles, all the participants were met for a final visit and to collect the questionnaires.

At the end of the 3 intervention cycles, data were analysed using SPSS version 15 for Windows. We used one-way ANOVA to compare menstrual blood loss in the three groups before and during the intervention. Descriptive statistics were used to summarise demographic data and adverse events. A p-value of <0.05 was considered statistically significant.

Results

Of the initial 120 participants, 93 completed the trial (32 in the mefenamic acid group, 33 in the naproxen group and 28 in the placebo group). Of the 8 participants in the mefenamic acid group who dropped out, 3 stopped using the study medication and 5 were lost to follow-up; in the naproxen group 4 stopped using the study medication and 2 were lost to follow-up; and in the placebo group 8 did not proceed due to the drug's ineffectiveness and 4 were lost to follow-up. However, the primary intention-to-treat analysis was based on data from 120 women (Fig. 1).

Descriptive analysis illustrated that there were no significant differences in socio-demographic data between the women who dropped out of the study and those who completed it. The mean age of those who completed the study was 30.6 years (standard deviation (SD)±1.6 years; range 19 - 43 years). Socio-demographic data (age,

Table 1. Scoring system for the Pictorial Blood Assessment Chart

Towels/pads: 1 point for each lightly stained towel; 5 points for each moderately soiled towel; 20 points if the towel is completely saturated with blood
Tampons: 1 point for each lightly stained tampon; 5 points for each moderately soiled tampon; 20 points if the tampon is completely saturated with blood
Clots: 1 point for small clot; 5 points for large clot

education, job, marital status, gravidity) were evaluated at baseline, and there were no statistically significant differences in any baseline parameters between the groups. There was no statistically significant relationship between demographic status and menstrual blood loss, and mean blood loss at baseline was similar in the three study groups, ranging from 117.6 to 121.2 ml per menstrual cycle ($p>0.05$ between groups) (Table 2).

There was a marked decrease in blood loss during the 3 months of intervention in the women receiving mefenamic acid ($p<0.05$ within group), and a dramatic decrease in the naproxen group ($p<0.05$ within group). In the placebo group, there were slight changes in blood loss during the intervention, and the differences between before and after intervention were not significant ($p>0.05$ within group) (Table 3).

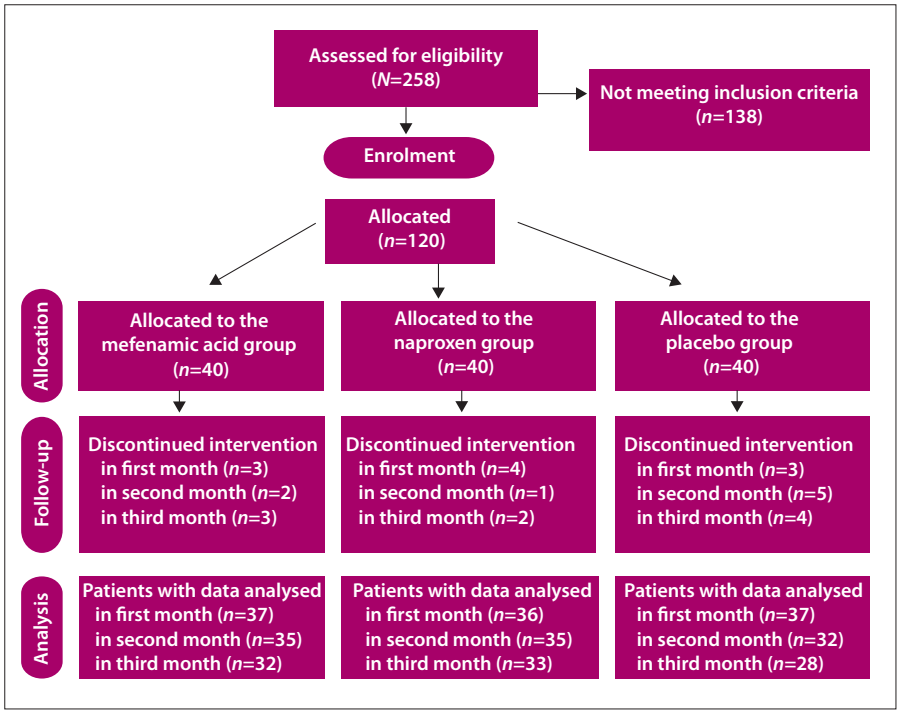

Fig. 1. Flow chart of the participants through each stage of the trial.

In both the mefenamic acid and naproxen groups the decrease in bleeding was most marked during the first month of intervention, bleeding continuing to decrease but to a lesser extent during the following 2 months. However, the decrease in the first month was greatest in the participants receiving napoxen ($p<0.05$ between groups) (Table 3). Despite the further decrease in bleeding in the mefenamic acid group, the reduction in the total amount of blood lost was much more remarkable in the naproxen arm, and the difference between the two groups was statistically significant ($p<0.05$ between groups) (Table 4).

In participants receiving the placebo, a slightly lower mean amount of blood was lost during the second month of intervention than during the first ($p>0.05$); during the third month, bleeding increased slightly again, though it was still less than it had been before intervention ($p>0.05$) (Tables 3 and 4). Furthermore, more patients who received naproxen and mefenamic acid than patients taking placebo were satisfied with the treatment.

Adverse events during the 3 months of intervention were reported by 11 participants in the mefenamic acid group, 6 in the naproxen group, and 1 in the placebo group ($p<0.05$) (Table 5). Nausea and diarrhoea were the most common side-effects.

Table 2. Menstrual blood loss in the three groups before the intervention

	Time		
Group	1st month (ml), mean±SD	2nd month (ml), mean±SD	3rd month (ml), mean±SD
Mefenamic acid	119.5±5.3	118.7±6.01	118.2±3.4
Naproxen	119.5±9.7	121.2±2.2	117.6±7.8
Placebo	118.7±6.0	120.02±6.2	119.6±5.9
p-value* (between groups)	0.61	0.59	0.4

*$p<0.05$ indicates a statistically significant difference.

Table 3. Menstrual blood loss in the three groups during the intervention

	Time		
Group	1st month (ml), mean±SD	2nd month (ml), mean±SD	3rd month (ml), mean±SD
Mefenamic acid	81.4±4.5	68.2±8.5	63.4±7.2
Naproxen	58.3±5.1	47.4±4.9	43.2±4.0
Placebo	115.8±8.6	110.7±6.5	113.1±5.6
p-value* (between groups)	0.001	0.01	0.02

*$p<0.05$ indicates a statistically significant difference.

Table 4. Changes in blood loss before and during the intervention

Group	Bleeding before intervention (ml)	Bleeding after intervention (ml)	Mean decrease in bleeding (%)
Mefenamic acid	118.8	71	40.0
Naproxen	119.5	49.6	58.5
Placebo	119.4	113.2	6.2

Table 5. Adverse events recorded in the three groups during the intervention

Group	Nausea *n* (%)	Vomiting *n* (%)	Heartburn *n* (%)	Abdominal pain *n* (%)	Diarrhoea *n* (%)	Allergy and itching *n* (%)
Mefenamic acid	4 (12.5)	0	2 (6.2)	2 (6.2)	3 (9.4)	0
Naproxen	2 (6.1)	0	1 (3.0)	1 (3.0)	2 (6.1)	0
Placebo	1 (3.6)	0	0	0	0	0

Discussion

Heavy menstrual bleeding is one of the most common reasons why women consult gynaecologists. In view of the various treatments available for heavy bleeding, and its potentially harmful consequences, more attention should be focused on medical ways to control it, so also avoiding operative procedures.[1]

Our study revealed that naproxen was more effective than mefenamic acid in reducing bleeding, and that it had fewer side-effects. Our results in the mefenamic acid group were better than those of Bonnar and Sheppard, who found that it resulted in a 20% decrease.[13] A small randomised trial by Fraser and McCarron comparing oral contraceptive pills, mefenamic acid, naproxen and danazol showed no significant differences in the amount of menstrual bleeding between groups.[14] We found that both naproxen and mefenamic acid reduced the amount of menstrual bleeding, but that the reduction in the total amount of blood lost was significantly greater in the naproxen arm. One reason for this difference could be Fraser and McCarron's small sample size, as they recruited only 12 - 14 participants in each group.

As can be seen from Tables 3 and 4, mean blood loss for participants receiving placebo decreased by 6.2% during the intervention. The drop was slightly greater during the second month of intervention than during the first and third months. It is not clear why the pattern of bleeding fluctuated in this group, and we assume that the 'placebo response' was responsible.

This study was a semi-quantitative clinical trial in which we used PBAC to measure blood loss. We therefore had to rely on participants' comments and reports. We were also unable to control use of the pads provided or adherence to the medications, so we had to rely on information given by the participants. In addition, we failed to evaluate haemoglobin concentrations at the end of the study, so we could not evaluate the effect of therapy with NSAIDs on the subjects' anaemia. Despite these shortcomings, we believe that our results warrant future study in this area. Another positive finding was that the majority of the women in the intervention groups were satisfied with the drugs used for treating their problem.

Conclusion

NSAIDs are known to be highly effective in reducing menstrual blood loss. They are cheap, easy to use, and have fewer side-effects than other drugs used for this indication; they are therefore used in the vast majority of cases of heavy menstrual bleeding. Because the duration of treatment for heavy menstrual bleeding with NSAIDs is short, the drug only being taken for the first 3 - 7 days of the menstrual cycle, they are less likely than other treatments to cause serious complications.

In view of the high prevalence of heavy menstrual bleeding and the importance of effective and timely treatment in preventing its negative effects on health, it is suggested that cheap, safe medical treatments be considered as first-line therapy. This study suggests that naproxen is more effective than mefenamic acid and has fewer side-effects, and that it should be considered as the first choice in dealing with this common problem.

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