

Mefenamic acid and diclofenac in the treatment of menorrhagia and dysmenorrhea in dysfunctional uterine bleeding: a randomized comparative study

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ABSTRACT

Background: There is a perception that Mefenamic Acid should be the preferred NSAID for menorrhagia. However, there are insufficient evidences to prove this. Further RCTs are required to compare individual NSAIDs.

Purposes of the study were to assess and compare the efficacy of mefenamic acid and diclofenac in control of menorrhagia in patients with DUB, to assess and compare their analgesic effects in dysmenorrhea associated with DUB and to study their adverse effects.

Methods: Sixty-eight patients were randomized into either Mefenamic Acid (n=34) or Diclofenac (n=34) group. Efficacy variables (Pictorial Blood loss Assessment Chart quantification, Number of pads used, Number of days of menstrual bleeding, Visual Analog Scale score) and adverse effects were recorded over three menstrual cycles.

Results: The median reduction of menorrhagia with Mefenamic Acid was 43.39% (Range: 2.86% to 94.4%) and for Diclofenac was 57.5% (Range: 9.9% to 93.58%). The Diclofenac group showed a statistically significant decrease in median bleeding volume, median number of pads used and median number of days of bleeding compared to the Mefenamic Acid group (p<0.05, CI = 95%) but did not show a statistically significant decrease in median VAS score compared to the Mefenamic Acid group. Adverse effects with both groups were mild.

Conclusions: Mefenamic Acid and Diclofenac individually managed to significantly reduce excessive bleeding compared to baseline. Diclofenac fared better than Mefenamic Acid in terms of control of excessive menstrual bleeding. Both these agents were able to reduce the menstrual pain and on comparison, were found to be equi-efficacious.

Keywords: Abnormal uterine bleeding, Diclofenac, Dysmenorrhea, Mefenamic acid, Menorrhagia, NSAIDs

INTRODUCTION

Menstrual disturbances constitute a major clinical problem, afflicting a large number of women leading to considerable physical and social morbidities in all societies.¹ Menorrhagia is one such disorder which may occur due to various causes. However, no specific cause of bleeding is identified in 50% of women presenting with menorrhagia and such cases are referred to as Dysfunctional Uterine Bleeding (DUB).²

Menorrhagia accounts for 5% to 25% of primary care consultations or outpatient referrals and about 10 to 15 percent women experience episodes of DUB at some time during the reproductive years of their life.³

The prevalence of other major disorder of menstruation, dysmenorrhea, varies from 45% to 95% reproductive age and is one of the most frequent causes of absenteeism from work and school.⁴

Menorrhagia has been objectively defined as 80 ml or more of Menstrual Blood Loss (MBL) per menstruation and continued losses of such quantity are associated with an increased incidence of iron deficiency anemia.^{5,6}

NSAIDs can be used as an effective first line treatment in abnormal uterine bleeding in women with no obvious pathological conditions. Probable mechanism through which they act maybe through inhibition of prostaglandin synthesis, which may also favourably alter the ratio between thromboxane A₂ (a vasoconstrictor and promoter of platelet aggregation) and prostacyclin (a vasodilator and platelet inhibitor).⁷ They are suitable for use in:

- Women who are trying to conceive.
- Menorrhagia coexisting with dysmenorrhea. Their use should be restricted for 3 menstrual cycles in the absence of improvement in symptoms.
- When symptomatic treatment is required while investigations and definitive treatment are being organized.⁸

Mefenamic Acid is the most commonly studied NSAID in menorrhagia.⁹⁻¹¹ Therefore, there is a perception among gynecologists that it is the most effective NSAID as far as menorrhagia is concerned. However, there are not many studies with other individual NSAIDs available to prove this perception. According to metanalysis, further studies are required to compare individual NSAIDs so that the optimum treatment to reduce heavy menstrual bleeding can be identified.⁹

Diclofenac is another NSAID that is used very commonly in the Gynecology department of our institution. However, no head-on comparative study was found in literature between the two agents – Mefenamic Acid and Diclofenac - in menorrhagia, with or without dysmenorrhea and this formed the basis of the present study.

METHODS

This was an open-label, randomized, parallel, prospective study.

Patients in whom the diagnosis of DUB was established after history, examination and relevant investigations were considered for recruitment.

Inclusion criteria

- Newly diagnosed patients of DUB with or without dysmenorrhea.
- Age 18 - 40 years.

Exclusion criteria

- Presence of co-morbid conditions like hepatic impairment, coagulation defects.
- Intra Uterine Contraceptive Device use.

- Single episode of heavy menstrual bleeding and normal cyclical bleeding thereafter.
 - Endometrial/ cervical malignancy, pregnancy related disorder, Pelvic Inflammatory Disease, or any uterine mass on ultrasonography.
 - Known allergies to prostaglandin synthesis inhibitors.
 - Patients taking anticoagulants/ hormonal treatment.
- 68 patients were included (34 in each group, calculated based on previous studies.^{12,13} Block randomization was achieved by using computer (block size 2) to assign the patients into two groups:
- Group A: Mefenamic acid 500 mg tablet three times a day for five days starting on the first day of menstruation, for a total of three cycles.
 - Group B: Diclofenac 50 mg tablet two times a day for five days starting on the first day of menstruation, for a total of three cycles.

The therapeutic regime was decided on the basis of previous studies with these drugs.^{6,12,14-17}

The following baseline data was collected from each recruited patient:

Menorrhagia estimation

A Pictorial Blood Loss Assessment Chart was modified using real images of used sanitary pads soaked in fixed blood volumes namely 15mL, 30mL, 50mL and 100mL.¹⁸

On each visit the patient was asked three questions:

- “Identify which pad did you use each day of bleeding? (15/ 30/ 50/ 100mL)”
- “How many such pads did you use each day?” and
- “How many days did the bleeding last?”
- The product of the answers to these questions gave the total menstrual blood loss per cycle.

Dysmenorrhea estimation

A visual analog scale was shown to the patient and she was asked to grade her menstrual pain from 0 (no pain) to 10 (agonizing pain).¹⁹

After the first visit, the patients were asked to visit the OPD again after a week and the extent of menorrhagia and dysmenorrhoea was estimated. At this visit, she was instructed to visit again at the onset of menstruation in the next cycle, which was followed up after a week in a similar fashion. Finally, she visited at the onset of menstruation of third cycle and was followed up for the same parameters.

Patients were also asked to maintain a diary to report any adverse effects. Out of 68 patients, 13 withdrew during first treatment cycle (Figure 1). No contact could be established with them. 55 patients were therefore included

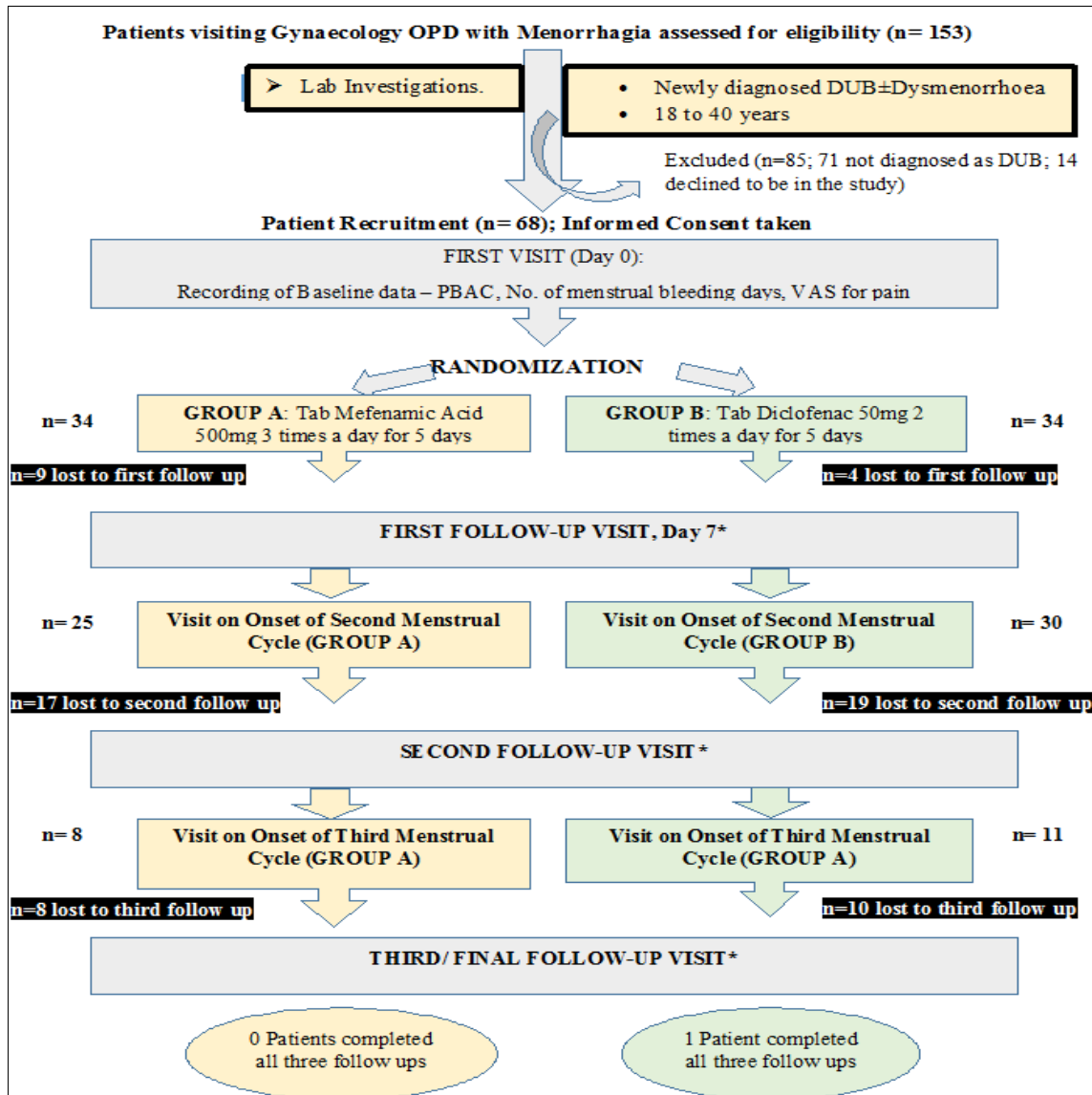
in a modified intention-to-treat analysis (Last Observation Carried Forward).

Statistical analysis

The data analyzed using GraphPad Prism 7. The demographic data was presented as Mean±Standard deviation. A p value of <0.05 was considered significant at a confidence interval of 95%.

RESULTS

The baseline demographic characteristics namely marital status, age and literacy were comparable between the two groups (statistically not significant) as shown in Table 1. Literacy was defined as the ability to read and write in any language (Literacy status was recorded as it could have bearing on the maintenance of diary for adverse effects).



*Bleeding volume by PBAC, No. of bleeding days, VAS score was recorded

Figure 1: Overview of the study.

History findings like age of onset of menarche, menstrual cycle duration, presence of associated dysmenorrhea, baseline quantification of menorrhagia by Pictorial Blood loss Assessment Chart and baseline dysmenorrhea quantification by Visual Analogue Scale score were also

comparable and statistically not significant as is seen in Table 2.

Laboratory parameters evaluated namely Total Leukocyte Count (to rule out inflammatory pathologies like PID),

Platelet Count (to rule out bleeding due to thrombocytopenia) and Liver Function Tests (to rule out bleeding due to hepatic disorders) before recruitment were also statistically not significant in the two treatment groups as seen in Table 3.

Table 1: Baseline demographic characteristics.

Parameter	Mefenamic acid Group (n=34)	Diclofenac Group (n=34)
Marital status	24 Married, 10 Unmarried	22 Married, 12 Unmarried
Age (Mean±SD) in years	27.23±7.17	28.47±7.32
Literacy	14 Illiterate, 20 Literate	13 Illiterate, 21 Literate

Table 2: History findings.

Parameter	Mefenamic acid Group (n=34)	Diclofenac Group (n=34)
Menarche (Years) Mean±SD	13.35±1.76	13.09±1.31
Menstrual Cycle Duration (Days) Mean±SD	28.32±3.16	30.03±2.91
Dysmenorrhea present	21 Patients	19 Patients
Baseline Visual Analog Scale (VAS) Score [Median (Range)]	6 (0-9)	5 (0-10)
Mean Baseline Bleeding±SD (mL)	855.74±77.38	837.35±549.13

Table 3: Laboratory investigations.

Parameter	Mefenamic acid Group (n=34)	Diclofenac Group (n=34)
TLC (Median)/mm ³	7330	7160
Platelet Count (Median) lacs/mm ³	2.42	2.64
Total Bilirubin (Mean±SD) mg/dL	0.38±0.14	0.39±0.10
SGOT (Mean±SD) IU/L	39.88±9.10	34.53±8.60
SGPT (Mean±SD) IU/L	41.5±7.12	34.27±7.97

Mefenamic acid versus diclofenac in control of menorrhagia

Control of menorrhagia in the Mefenamic Acid and Diclofenac groups using the modified intention-to-treat analysis for the entire period of observation is shown in Table 4.

The Diclofenac group showed a statistically significant decrease in the median bleeding volume (determined by

PBAC), median number of pads used and median number of days of bleeding compared to the Mefenamic Acid group.

Table 4: Control in menorrhagia: mefenamic acid versus diclofenac group.

Parameter	Mef. acid (n=25)	Diclofenac (n=30)	p-value
Bleeding Volume by PBAC - Median (Range) mL	450 (90-1125) (↓43.39% from baseline)	255 [#] (60-1840) (↓57.5% from baseline)	0.001
No. of pads used - Median (Range)	21 (3-50)	9.5 [#] (4-41)	0.008
No. of days of bleeding - Median (Range)	6 (3-12)	4 [#] (2-10)	0.0284
Haemoglobin (g/dL) - Median (Range)	10.9 (8.2-12.3)	10.55 ^{NS} (9.0-12.2)	0.4222

= p value <0.05 compared to Mefenamic Acid Group
NS = Not significant compared to Mefenamic Acid group

In the Mefenamic Acid Group, 21 out of 34 patients had dysmenorrhea along with menorrhagia and these patients provided data for subjective relief in dysmenorrhea over successive follow-ups with the use of this drug.

In the Diclofenac Group, 19 out of 34 patients had dysmenorrhea along with menorrhagia and these patients provided data for subjective relief in dysmenorrhea over successive follow-ups with the use of this drug.

Mefenamic acid versus diclofenac in control of dysmenorrhea

Control of dysmenorrhea (as reflected in VAS score) in the Mefenamic Acid and Diclofenac groups using the modified intention-to-treat analysis for the entire period of observation is shown in Table 5.

Table 5: Control in dysmenorrhea: mefenamic acid versus diclofenac group.

Parameter	Mef. acid (n=15)	Diclofenac (n=17)	p-value
Visual Analog Scale Score - Median (Range)	6 (0-8)	4 (0-8) ^{NS}	0.064

NS = Not significant compared to Mefenamic Acid

Adverse effects recorded with mefenamic acid and diclofenac

No serious adverse effect was seen in any patient. Adverse effects were mostly observed in first follow up. Adverse effects were reported in 12 out of the total 68 patients. The number of patients that reported adverse effects in

Mefenamic Acid group were 6 (= 5 in first follow up + 1 in second follow up) and in the Diclofenac group were also 6 (= 4 in first follow up + 2 in second follow up).

In the Mefenamic Acid group, headache was the most common adverse effect. In the first follow up 5 patients

reported adverse effects out of total of 34 patients (Table 6).

In the Diclofenac group, dyspepsia was the most common adverse effect. In the first follow up 4 patients reported adverse effects out of total 34 patients (Table 6).

Table 6: Comparison of adverse effects between the two treatment groups.

Adverse effects	Headache	Dyspepsia	Weakness of limbs	Pain abdomen	Increased urination with back pain	Nausea	Nervousness
Mefenamic Acid Group (n=34)	3	0	1	1	1	0	0
Diclofenac Group (n=34)	1	3	0	0	0	1	1

The adverse effects between the two groups were statistically not significant.

DISCUSSION

In the present study, it was observed that with Mefenamic Acid there was a significant improvement in menorrhagia for all the outcome parameters compared to baseline. The median reduction of menorrhagia with Mefenamic Acid was 43.39% (Range: 2.86% to 94.4%). Previous studies by van Eijkeren et al, and Cameron et al, show a reduction in bleeding to the extent of 40% and 34.1% respectively - similar to our study.^{15,20} In another study by Fraser et al, it is reported that the best response recorded was 80% reduction in menorrhagia.²¹ The highest response with Mefenamic Acid treatment observed in this study was 94.4% reduction of bleeding in a patient. Many studies in the past, however, have reported an average lower reduction in menorrhagia - in the range of 20% to 30%.²¹⁻²⁵ These studies recording lower improvement were done in Caucasian women and none of these were carried out in the South-East Asian population. Hence, this discrepancy might be due to ethnic or genetic variation in the Indian population.

In the interventional group the patients received Diclofenac. This group showed a significant improvement in menorrhagia for all the outcome parameters compared to baseline - which was similar to what was seen with the Mefenamic Acid treated group. The median reduction of menorrhagia with Diclofenac was to the extent of 57.5% (Range: 9.9% to 93.58%). There is a paucity of studies in menorrhagia with Diclofenac and we could find only two such previous studies by Riihiluoma P et al, and Ylikorkala O et al, that have shown a 13% and 24.4% reduction in bleeding respectively.^{13,14} The highest response with Diclofenac treatment observed in this study was 93.58% reduction in bleeding. (Similar to a highest reduction of 94.4% seen in a patient treated with Mefenamic Acid).

Patients with dysmenorrhea showed significant improvement in pain scores compared to baseline on treatment with Mefenamic Acid and this improvement was maintained in the subsequent cycles. This is consistent with previous studies showing significant relief with Mefenamic Acid in dysmenorrhea.^{24,26,27}

The Diclofenac treated group showed a significant relief in dysmenorrhea compared to baseline, which was maintained in the second follow up. However, there was no significant difference in the pain relief between the two treatment groups, suggesting that as far as dysmenorrhea is concerned, both these agents are equi-efficacious. This may be attributed to the same mechanism of action of prostaglandin synthesis inhibition. This is a similar finding to the one reported in a previous study by Roy S et al. In this study, the NSAIDs Mefenamic Acid and Ibuprofen were compared and no significant difference was reported in the pain scores - indicating thereby that control of dysmenorrhea may be similar across several NSAIDs.²⁷

The secondary objective was to observe the adverse effects of two study drugs. The incidence of adverse effects was similar in the two treatment groups. In the Mefenamic Acid group, headache was the most common adverse effect. Other adverse effects seen were: drowsiness, weakness of limbs, pain abdomen, and increased urination with back pain. This is in accordance with a Cochrane review which has reported that gastrointestinal adverse effects are less likely with Mefenamic Acid in the treatment of menorrhagia.⁹ In the Diclofenac group, dyspepsia was the most common adverse effect. The other adverse effects seen were: headache, nausea and nervousness. Adverse effects were mostly reported in first follow up.

The adverse effects were well-tolerated, and this may be due to the fact that the drug was given only for 5 days in each cycle.

Limitations of the study are mentioned below.

- Although ITT - LOCF has been used for the primary outcome, the study is still very much limited by the initial withdrawal from the trial. 13/68 represents an attrition rate of 19% which is very likely to cause bias in the findings, in particular because these withdrawals are different between randomised groups.
- The sample size was calculated using previous studies and the patients recruited in the study were in accordance with this calculated sample size. However, the observations show a non-normal distribution with this sample and therefore a larger sample size should be taken so that results can be effectively generalized.
- Non-standardization of the pads used by patients during menstruation is an important issue when using the Pictorial Blood Loss Assessment Chart (PBAC). There could be a variation in the absorbability characteristics with different pads, apart from subjective and psychological inter-individual and intra-individual variation over which we have no control.
- Menorrhagia is a subjective symptom and patient's perception of it may vary. Expressing a qualitative or subjective parameter in an objective form, as is done by the PBAC method, is a crude basis of estimating menorrhagia. Patients may require a training/ run-in period to report more accurately.
- Female patients may have apprehension while reporting to a male physician (the investigator in the present study was male) as menstruation is a sensitive issue among Indian females. This may have been one of the reasons for not giving the correct personal contact numbers which eventually resulted in difficulty in follow up of these patients.

Recommendations

It is recommended that personal bias towards Mefenamic acid should be discouraged and either of the two drugs- Mefenamic acid and diclofenac may be used to control excessive menstrual bleeding. Use of diclofenac should be advocated as it has better efficacy and it is present in the essential medicines list.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee of Maulana Azad Medical College, New Delhi, India (Identification code: F. No./11/IEC/MAMC/2015/317)

REFERENCES

1. Livingstone M, Fraser IS. Mechanisms of abnormal uterine bleeding. *Hum Reprod.* 2002;8(1):60-7.

2. Phillip CS, Dilley AS, Miller CH. Platelet functional defects in women with unexplained menorrhagia. *J Thromb Haemost.* 2003;1(3):477-84.

3. Menorrhagia. Chapter 24 In. Padubidri VG, Daftary SN, editors. *Howkins and Bourne Shaw's Textbook of Gynaecology.* 16th Edition. Elsevier; 2011:339.

4. Proctor M, Farquhar C. Diagnosis and management of dysmenorrhoea. *Br Med J.* 2006;332:1134-8.

5. Horne AW, Critchley HOD. Menstrual Problems: Heavy Menstrual Bleeding and Primary Dysmenorrhoea. Chapter-42 In. Edmonds DK, editor. *Dewhurst's Textbook of Obstetrics and Gynecology.* 8th Edition. Wiley-Blackwell Science; 2012:534-543.

6. Ylikorkala O. Prostaglandin Synthesis Inhibitors in Menorrhagia, Intrauterine Contraceptive Device-Induced Side Effects and Endometriosis. *Pharmacol Toxicol.* 1994; 75 Suppl 2:86-8.

7. Casablanca Y. Management of dysfunctional uterine bleeding. *Obstet Gynecol Clin North Am.* 2008;35(2):219-34.

8. National Institute for Health and Care Excellence (NICE). Clinical Guideline 44; Heavy menstrual bleeding; 2007. Available at: <http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf>. [accessed on 24 July 2016]

9. Lethaby A, Duckitt K, Farquhar C. Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2013. [cited 2017 Jan 24]. Available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000400.pub3/abstract;jsessionid=94F9FDAFF243FFBE504877A60517E86C.f02t02>

10. Protheroe J. Modern management of menorrhagia. *J Fam Plann Reprod Health Care.* 2004;30(2):118-22.

11. Maybin JA, Critchley HO. Medical management of heavy menstrual bleeding. *Women's Health.* 2016;12(1):27-34.

12. Hall P, Maclachlan N, Thorn N, Nudd MW, Taylor CG, Garrioch DB. Control of menorrhagia by the cyclo-oxygenase inhibitors naproxen sodium and mefenamic acid. *Br J Obstet Gynaecol.* 1987;94(6):554-8.

13. Riihiluoma P, Wuolijoki E, Pulkkinen MO. Treatment of Primary Dysmenorrhea with Diclofenac Sodium. *Europ J Obstet Gynec Reprod Biol.* 1981;12:189-94.

14. Ylikorkala O, Viinikka L. Comparison between antifibrinolytic and antiprostaglandin treatment in the reduction of increased menstrual blood loss in women with intrauterine contraceptive devices. *Br J Obstet Gynaecol.* 1983;90(1):78-83.

15. Cameron IT, Lumsden M, Smith SK. The Effects of Mefenamic Acid and Norethisterone on Measured Menstrual Blood Loss. *Obstet Gynaecol.* 1990;76(1):85-8.

16. Milsom I, Andersson K, Andersch B, Rybo G. A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. *Ame J Obstet Gynecol.* 1991 Mar 1;164(3):879-83.

17. Pringsheim T, Davenport WJ, Dodick D. Acute Treatment and Prevention of Menstrually Related Migraine Headache: Evidence-Based Review. *Neurology.* 2008;70(17):1555-63.
18. Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol.* 1990;97:734-9.
19. Hungund S, Thakkar R. Effect of pretreatment with ketorolac tromethamine on operative pain during periodontal surgery: A case-control study. *J Indian Soc Periodontol.* 2011;15(1):55-8.
20. van Eijkeren MA, Christiaens GC, Geuze HJ, Haspels AA, Sixma JJ. Effects of mefenamic acid on menstrual hemostasis in essential menorrhagia. *Am J Obstet Gynecol.* 1992;166(5):1419-28.
21. Fraser IS, Pearse C, Shearman RP, Elliott PM, McIlveen J, Markham R. Efficacy of mefenamic acid in patients with a complaint of menorrhagia. *Obstet Gynaecol.* 1981;58(5):543-51.
22. Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *Br Med J.* 1996;313(7057):579-82.
23. Coulter A, Kelland J, Peto V, Rees MC. Treating menorrhagia in primary care: an overview of drug trials and a survey of prescribing practice. *Int J Tech Assess Health Care.* 1995;11(3):456-71.
24. Dockeray CJ, Sheppard BL, Bonnar J. Comparison between mefenamic acid and danazol in the treatment of established menorrhagia. *Br J Obstet Gynaecol.* 1989;96(7):840-4.
25. Chamberlain G, Freeman R, Price F, Kennedy A, Green D, Eve L. A comparative study of ethamsylate and mefenamic acid in dysfunctional uterine bleeding. *Br J Obstet Gynaecol.* 1991;98(7):707-11.
26. Zhang WY, Po ALW. Efficacy of minor analgesics in primary dysmenorrhoea: a systematic review. *Br J Obstet Gynaecol.* 1998;105:780-9.
27. Roy S. A double-blind comparison of a propionic acid derivative (ibuprofen) and a fenamate (mefenamic acid) in the treatment of dysmenorrhoea. *Obstet Gynecol.* 1983;61(5):628-32.

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