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EFFICACY AND QUALITY OF LIFE IN THE MANAGEMENT OF MENORRHAGIA WITH TRANEXAMIC ACID OR MEFENAMIC ACID OR TRANEXAMIC ACID AND MEFENAMIC ACID: A PROSPECTIVE COMPARISON STUDY

1PRABAVATHI.P, 2SATHYAPRABHA .G

1M.Pharmacy, 2Assistant Professor

1The Tamil Nadu Dr. M.G.R. Medical university ,

2The Tamil Nadu Dr. M.G.R. Medical university

INTRODUCTION:

Heavy menstrual bleeding (HMB) significantly affects the lives of many women.[1] A woman may experience social, emotional, or sexual difficulties as a result of this blood loss and may also worry about a serious underlying disease (especially cancer) or risk diseases such as chronic iron deficiency anemia.[2] It is estimated that 30% of women experience menorrhagia globally.[3] HMB associated with heavy, prolonged, or regular uterine bleeding unrelated to pregnancy or any known pelvic or systemic disease. Women with HMB have menstruation lasting 21 to 32 days, while anovulatory periods involve heavy, often prolonged bleeding lasting 35 days or more.[4] Primary HMB is a disease that affects young women at the onset of menstruation, while secondary HMB is a very severe disease that occurs later years of a woman's reproductive age.[5] 90% of heavy uterine bleeding is ovulatory.[6,7] Women with heavy menstrual bleeding are unable to perform normal activities due to frequent changing of sanitary products and fear of staining of outer clothing. [8, 9] Menorrhagia is defined as prolonged (more than 7 days) or heavy (more than 80 ml) uterine bleeding occurring at regular intervals.[10] Adolescent girls often have irregular menstrual cycles due to frequent anovulatory cycles. Thus, the term heavy menstrual bleeding (HMB) better describes heavy menstrual blood loss, which is the most common menstrual problem among these young girls, regardless of their menstrual cycle.[11] Objective assessment of menstrual blood loss by alkaline haematin method is the best method available for menstrual blood loss. But it uses specialized and time-consuming techniques which are not available for routine clinical use. In an attempt to create a more accurate, yet simple method of assessment, a pictorial blood loss assessment chart (PBAC) was

devised by Higgham et al which corresponds well with objective measurement of blood loss which was easy to use and has a role in monitoring the treatment of menorrhagia. A pictorial score of 100 or more when used as a diagnostic test for menorrhagia was found to have a specificity and sensitivity of more than 80%.[12,13,14] Once a baseline score has been established, subsequent treatment cycles are assessed in the same way, and effectiveness is assessed by a decreasing score. Studies using PBAC scores for monitoring the treatment of menorrhagia has to behave reported.[15, 16]

According to laboratory studies, there are two main causes of heavy menstrual bleeding. Increased fibrinolysis and (ii) prostaglandin (PG) imbalance. Women with heavy menstrual bleeding have been shown to have lower levels of prostaglandin F2 (which causes vasoconstriction) and higher levels of prostaglandin E2 and prostacyclin, which induce vasodilation and prevent local aggregation of platelets.[17,18] Additionally, compared to women with lighter menstrual cycles, women with heavy menstrual bleeding had more prostaglandin E receptors in the uterus.[19] Nearly 28% of the female population consider their menstruation as excessive and plan their social activities according to their menstrual cycles, while nearly 10% of the employed women take time off work because of excessive menstrual loss.[20]

A good medical treatment will reduce hysterectomies and associated morbidity and mortality. Although conservative surgery (endometrial ablation) is an alternative to hysterectomy, its cost is a limiting factor in developing countries. This drug therapy should be the first line of treatment before recourse to surgery. Many drugs for DUB are available. Oral drugs used are NSAIDs, Antifibrinolytics, and Progestins, combined oral contraceptives (OCP), Danazol, and GnRH Analogue. It has been proved that fibrinolytic activity is increased in the menstrual fluid in menorrhagia and synthetic anti-fibrinolytic reduce menstrual blood loss. [21] Tranexamic acid, a synthetic derivative of the amino acid lysine, exerts its fibrinolytic activity through the reversible blockade of lysine binding sites on plasminogen molecules. It reduces menstrual blood loss by 45-60%. The side effects of Tranexamic acid therapy include nausea and leg cramps and rarely, deep vein thrombosis. NSAIDs or anti-prostaglandins act by reducing the elevated levels of prostaglandins which are seen in patients with excessive menstrual bleeding. Mefenamic acid, an NSAID and an anthranilic acid derivative is also known to reduce menstrual blood loss by 20%. Previous studies have evaluated the efficacy of various medical modalities (NSAIDs, hormones, anti-fibrinolytic, etc) and have established their role, but none has compared an anti-fibrinolytic with a combination of anti-fibrinolytic and NSAIDs in reducing menstrual blood loss in patients of HMB. This study was designed to compare the clinical efficacy of tranexamic acid alone and in combination with mefenamic acid in reducing blood loss in patients with heavy menstrual bleeding. The improvement in the clinical parameters which are associated with heavy menstrual bleeding, such as the degree of anemia and reduction in menstrual blood loss, were also evaluated as appropriate responses to therapy.

METHOD:

The outpatient Department of Obstetrics and Gynaecology at Kovai Medical Centre and Research in Coimbatore conducted this prospective comparison research over the course of six months. 65 patients with menorrhagia were enrolled in the research, after taking written/informed consent.

Inclusion criteria:

Patients in the age group of 18 to 45 years with complaints of menorrhagia were evaluated. Menstrual blood loss was assessed by a pictorial blood loss assessment chart (PBAC). Patients with PBAC scores of more than 100, normal pelvic examination, and normal abdominal examination were selected from the study.

Exclusion criteria:

Patients with organic pathology like fibroids, pelvic inflammation, and malignancy were excluded from the study, along with patients with renal impairment, thromboembolic conditions, peptic ulcers, and patients on hormone therapy within the past three months. Patients with irregular menstrual cycles, symptoms of intermenstrual bleeding, and spotting were also excluded from the study.

Patients with complaints of menorrhagia were completely evaluated by a complete medical history and systemic and pelvic examination. Menstrual blood loss was assessed by PBAC in one pre-treatment control cycle. Pre-treatment investigations included Hb%, PCV, platelet count, blood group and Rh typing, BT, CT, pelvic ultrasound, and Pap smear. Endometrial biopsy was considered in patients aged more than 40 yrs.

Any organic pathology detected by pelvic examination, ultrasound, Pap smear, and endometrial biopsy were excluded from the study. 76 patients qualified for the study after meeting inclusion and exclusion criteria. They were allocated to either of the three treatments tranexamic acid (Group A) or mefenamic acid (Group B) or tranexamic acid and mefenamic acid (Group C) by menstrual bleeding questionnaires (QOL). Patients allocated to Group A received tranexamic acid 500 mg, from day 1 to 5 days. Patients allocated to Group B received mefenamic acid 500 gm, from 1 to 5 days, similarly, Group C received tranexamic acid and mefenamic acid during the menstrual cycle for three consecutive cycles. PBAC score scale was used to assess the severity of bleeding. Quality of life questionnaires was used to compare the quality of life between groups. They were educated about the pictorial blood loss assessment chart (score 1 was given for lightly soiled pad, score 5 was given for moderately soiled pad and score 20 for heavily soiled pad, score 1 for 25p coin, and score 5 for 1re coin) and were instructed to note the number of pads, staining pattern, and the clots as per pictorial blood loss assessment chart. They were instructed to visit the outpatient department every month and PBAC scoring was done each month. Symptoms like dysmenorrhoea and any side effects of treatment were enquired. At the end of three treatment cycles, an average reduction in PBAC score was calculated. Women with dysmenorrhoea were asked for any improvement or worsening of dysmenorrhoea during the treatment cycles. Hb% was measured at the initial visit and the end of three cycles in the same lab and a difference in Hb% was recorded.

The incidence of side effects associated with the treatment cycles was evaluated, at each visit, and various side effects were recorded.

RESULTS:

In this prospective comparison study, we included 76 patients who were newly diagnosed with menorrhagia according to the inclusion and exclusion criteria. This study aims compare the efficacy and quality of life of patients treated with tranexamic acid or mefenamic acid or tranexamic acid and mefenamic acid. Quality of life was compared by using quality of life questionnaires whereas bleeding and clotting were estimated by PBAC score scale. For three groups. Number of subjects in each group - Group A (Tranexamic acid) – 29 Patients, Group B (Mefenamic acid) – 14 Patients, Group C (Tranexamic acid and mefenamic acid) – 33 Patients was undertaken to know the efficacy, acceptability, and safety of three drugs.

Statistical analysis:

1. For comparison of P value blood Hb level before and after treatment – Friedman the test
2. For comparison of mean PBAC score before and after treatment – the Kruskal Wallis Test
3. For comparison of quality of life questionnaires before and after treatment – Chi-square test.

TABLE 1: COMPARISON OF SOCIODEMOGRAPHIC FACTORS WITH QOL DOMAINS

Characteristics	variables	Group A		Group B		Group C		P value
		F (N)	P (%)	F (N)	P (%)	F (N)	P (%)	
Age (yrs.)	18-25	5	17.12	3	21.4	2	6.1	0.743
	26-30	0	0	0	0	0	0	0
	31-35	2	6.9	1	7.1	1	3.0	0.671
	36-40	5	17.2	2	14.3	10	30.3	0.701
	41-45	17	58.6	8	57.1	20	60.6	0.863
BMI ($kg/m^{2)}$	Underweight	3	10.3	1	7.1	0	0	0.278
	Normal	10	34.5	1	7.1	5	15.2	0.180
	Overweight	12	41.4	10	71.4	18	54.5	0.139
	Obese	4	13.8	2	14.3	10	30.3	0.123
Location	Urban	18	62.1	9	64.3	9	57.6	0.680
	Rural	5	35.7	5	35.7	14	42.4	0.672
Occupation	Homemakers	18	62.1	9	64.3	19	57.6	0.804
	Working women	3	10.3	2	14.3	4	12.1	0.671
	Students	4	(13.8	2	14.3	1	3.0	0.872
History	Hypertension	2	6.9	2	10.7	6	18.2	0.449
	Diabetes mellitus	-		1	7.1	1	3.0	0.356
	Hyperlipidemia	-	-	-	-	2	6.1	
	Thyroid	4	13.8	3	21.5	3	9.1	0.253
Family history	Hypertension	1	3.4	2	10.7	6	18.2	0.671
	Diabetes mellitus	-	7.1	1		1	3.0	0.580
	Menorrhagia	1	3.4	-	-	-	-	

	Thyroid	4	13.9	3	21.5	2	6.1	0.623
Abdominal examination	No	19	65.5	9	64.3	19	57.6	0.692
	Yes	10	34.5	5	35.7	14	42.4	0.692
Pelvic examination	No	26	89.7	13	92.9	23	69.7	0..908
	Yes	3	10.3	1	7.1	10	30.3	0.812

Out of 76 cases, 62 patients were in the age group of 36-45 years, followed by 14 cases in 18-35 yrs. Age group. The majority of cases were in the category of moderate anemia (Hb=7.1-10.0) and the duration of menorrhagia was 4-6 months.

TABLE 2:

Hemoglobin (g/dl)	Pre-treatment %	Post-treatment %	P value
Group A (%)	24 (82.75)	5 (17.25)	0.069
Group B (%)	9 (60.55)	5 (32.05)	0.052
Group C (%)	23 (69.7)	10 (30.3)	0.086

The average Hb concentration of the pre-treatment cycle was 82.75% in Tranexamic acid (Group A), 60.55% in Mefenamic acid (Group B), and 69.7% in Tranexamic acid and Mefenamic acid (Group C). At the end of the three treatment cycles, the average Hb% was 17.25%, 32.05%, and 30.03%. In group A, group B and group C. Hb% improved in 5 patients in group A, 5 patients in group B and 10 patients in group C. Thus, Hb% was not significant in groups with a p-value of 0.069 for group A and 0.052 for group B and 0.086 for group C.

TABLE 3: DISTRIBUTION OF NAPKIN UASGE, BLEEDING, AND CLOTS IN THE STUDY POPULATION USING PBAC SCORE (N=76)

GROUPS	Pre-treatment (baseline)	Post-treatment (3 months)	MEAN ± SD	P value
GROUP A (N=29)	52.91	30.80	6.53 ± 6.087	0.000
GROUP B (N=14)	40.93	41.09	3.15 ± 3.552	0.019
GROUP C (N=33)	45.59	35.82	11.51 ± 7.481	0.024

The mean PBAC score of group A was 6.53 ± 6.087 (P = 0.000), group B 3.15 ± 3.552 (P = 0.019), and group C 11.51 ± 7.81 (P = 0.024). The pre-treatment mean for group A was 52.91%, group B 40.93%, and group C 45.59%. The post-treatment mean of group A was 30.80%, group B 41.09%, and group C 35.82%. A significant difference between the groups was revealed in the intergroup comparison.

Table 4: COMPARISON OF QUALITY OF LIFE COMPONENTS

QOL	Group A (n=29)		Group B (n=14)		GROUP C (n=33)		P value
	F (N)	P (%)	F(N)	P (%)	F(N)	P (%)	
Physical	19	65.5	6	42.9	14	64.24	0.000
Social	13	44.8	7	50.0	18	54.5	0.000
Emotional	13	44.8	9	64.3	15	45.5	0.000
Bleeding	10	34.5	9	64.3	23	69.7	0.135

Based on the quality of life of Patients were classified into physical, social, emotional, and bleeding. Tranexamic acid (Group A): 19 (65.5%) patients were physically improved, 13 (44.8%) patients improved with QOL socially, 13 (44.8%) patients were their QOL emotionally, and 10 (34.5%) patients were bleeding. In the comparison between regions, it was analyzed that there was a significant difference (P=0.000) between the regions in the quality of life. Mefenamic acid (Group B): 6 (42.9%) patients were physically improved, 7 (50.0%) patients were socially improved, 9 (64.3%) patients were emotionally improved, and 9 (64.3%) patients have less bleeding. Comparing regions, a significant difference was found between physical, social, and emotional domains (P=0.000) and bleeding regions (P = 0.122). Tranexamic acid and Mefenamic acid (Group C): 14 (64.24%) patients were physically improved, 18 (15.4%) patients were social, 15 (45.5%) patients were emotional, and 23 (69.7%) patients were bleeding women. In the interregional comparison, it was analyzed that there was a significant difference in the quality of life between the regions. (P=0.000).

DISCUSSION:

This study compares the use of two non-hormonal drugs used in the treatment of menorrhagia in terms of reduction of menstrual blood loss, painful dysmenorrhea (menstrual cycle) or menstrual cramps, improvement of Hb%, and improvement. Quality of life reflects treatment acceptance. Abnormal uterine bleeding is defined as excessive or prolonged and regular or irregular menstrual cycles without organic uterine pathology, or endocrine or hematological disorders. Of women, 40– 45 years old, 32% of women experience heavy menstrual bleeding. In our study, 51.31% of cases (n=45) belong to the age group of 41 -45 years, with experience in menorrhagia. This was similar to the finding observed by **T.S. Karlsson et al.** [22] where the average age of the cases was 43.5 years. The diagnosis of menorrhagia and blood loss can be detected by various methods, such as the women's statements, the duration of menstruation, the number of sanitary napkins used in each menstrual cycle, the weight of sanitary napkins in each menstrual cycle, laboratory analysis of blood content of used hygiene products. Products and image blood loss assessment charts (PBAC) **J.L. Engstrom et al**. [23, 24] The number of days of

menstruation is not important in the diagnosis of menorrhagia, we found that women started menstruation with short intervals. This study shows that both tranexamic acid and mefenamic acid significantly reduce menstrual blood loss, but tranexamic acid was more effective. The PBAC score was reduced by 44.6% in the mefenamic acid group and 52.6% in the tranexamic acid group. This was consistent with previous studies, by **Cameron et al.** [25] Compared mefenamic acid with norethisterone in 32 patients with ovarian menorrhagia and found that

menstrual blood loss was reduced by 24% in the mefenamic acid group and 20% in the norethisterone group. **Peterson et al.** [26] compared the efficacy of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia, 25 patients received tranexamic acid and 21 patients received norethisterone. They found that tranexamic acid reduced menstrual blood loss by 45% and norethisterone by 20%. **Bonnar et al.** [27] compared the effectiveness of ethamsylate, mefenamic acid, and tranexamic acid in the treatment of menorrhagia in a randomized trial and found that menstrual blood loss was reduced by 20% in the ethamsylate group and 31% in the mefenamic acid group, 54% reduction in the tranexamic acid group. **Lee et al.** [28] compared the efficacy of tranexamic acid in essential menorrhagia. Most previous studies used basic haematin methods to estimate menstrual blood loss, but this is a laborious and time-consuming procedure and is not applicable in clinical practice in most situations. Therefore, the study used a simple but more accurate method to create an image blood loss assessment with a sensitivity and specificity of more than 80%. Few previous studies have used pictorial charts of blood loss. In terms of improvement in menstrual pain, this study showed an improvement rate of 86.2% in the mefenamic acid group and 79.48% in the tranexamic acid group. **Dockeray et al.** [29] compared mefenamic acid with danazol in 40 patients with menorrhagia and reported a 77% improvement in patients treated with mefenamic acid. In a study comparing ethamsylate, tranexamic acid, and mefenamic acid, **Bonnar et al.** [27] showed improvement in dysmenorrhea in 4%, 9%, and 13% of patients treated with ethamsylate, tranexamic acid, and mefenamic acid, respectively. This study showed an average increase in Hb% of 8.6% in the tranexamic acid group and 9% in the mefenamic acid group. **Lee et al.** [28] reported a mean Hb% increase of 7.7% when tranexamic acid was used in menorrhagia. **Gleeson et al.** [30] reported a mean increase in Hb% I of 9.1% in patients treated with tranexamic acid for menorrhagia. In our study, mean hemoglobin concentration increased in both groups, but at a 3-month follow-up, the percentage increase was greater in the Tranexamic acid and mefenamic acid (Group C) (17.25 vs. 30.3%).

Najam R and Agrawal D et al. [31] conducted a comparative study of tranexamic acid with a combination of tranexamic acid and mefenamic acid in heavy menstrual bleeding. Baseline Hb was 9.5% in the Tranexamic acid group and 8.6% in the Tranexamic acid and mefenamic acid group. After three months of therapy, the mean Hb was 11.4% in the T group and 11.8% in the TM group. In their study, **Glutekein M et al.** [32] reported the role of tranexamic acid in the treatment of DUB and found that it reduced menstrual bleeding by 66%. In their study, the initial hemoglobin concentration was 10.6 g/dL, which increased to 12.1 g/dL after three courses of tranexamic acid. This was comparable to the results of our study, where tranexamic acid improved the PBAC score by 56.2%, while the combination of tranexamic acid and mefenamic acid improved the PBAC score by 47 or 3 months. **Kriplani et al.** [33] found that in patients treated with tranexamic acid for three cycles, the PBAC score significantly decreased from 356.9 to 141.6, or 60.3%. **Sukanya S et al.** [34] conducted a study on the role of tranexamic acid in idiopathic menorrhagia and found that the PBAC score improved by 46.1% at the end of three treatment cycles. In our study, tranexamic acid (group A) improved the mean hemoglobin concentration by 17.25 after 3 months of treatment, and mefenamic acid (group B) had a mean improvement of 32.05 after 3 months of treatment. Tranexamic acid and mefenamic acid (group C) improved the mean hemoglobin concentration by 30.3%, which was not significantly higher than tranexamic acid (group A) and mefenamic acid (group B).

SUMMARY AND CONCLUSION:

One of the most prevalent medical conditions affecting women is heavy menstrual bleeding. HMB's negative effects on a woman's physical, social, emotional, and/or material quality of life have an impact on many aspects of her daily activities and are frequently the cause of a woman's contact with the physician, who is frequently a general practitioner. Mefenamic acid and tranexamic acid, used alone or in combination, were successful in treating menorrhagia. Benefit from only being used during menstruation. HMB can be effectively treated with tranexamic acid 500 mg for 1-5 days. 500 mg for 1-5 days is the recommended dosage of mefenamic acid for effectiveness. Similar to mefenamic acid and tranexamic acid 500 mg is a successful menorrhagia treatment. HMB primarily affects female patients between the ages of 18 - 45 in the current study. Combination therapy of tranexamic acid and mefenamic acid significantly reduces menstrual blood loss, as does monotherapy of tranexamic acid and mefenamic acid, although combination therapy of tranexamic acid and mefenamic acid was found to be more effective. When compared to the groups receiving tranexamic acid and mefenamic acid monotherapy, it was seen that the Hb level in the tranexamic acid group had slightly increased. Patients taking tranexamic acid and mefenamic acid combination therapy had endometrium thickness within the normal range. Improved health-related quality of life by the use of tranexamic acid and mefenamic acid in combination therapy and monotherapy. Tranexamic acid and mefenamic acid combination therapy quality of life more than tranexamic acid and mefenamic acid monotherapy. A non-hormonal, non-surgical therapeutic option may be an important alternative for medical procedures and surgical procedures for women who experience heavy menstrual bleeding.

So, this study suggests that tranexamic acid and mefenamic acid monotherapy and combination therapy were both successful in controlling heavy menstrual bleeding. Tranexamic acid and mefenamic acid combination therapy was more effective, reduced blood loss, and improved quality of life than tranexamic acid and mefenamic acid monotherapy.

LIMITATION:

The major limitation of this study was, the distribution of patients in three groups was not even. Women with HMB in each of these studies were treated with Tranexamic acid (group A), Mefenamic acid (Group B), Tranexamic acid, and mefenamic acid (Group C) thus results may not be generalized to other women with HMB treated with other medications, or procedures. Furthermore, to assess daily MBL in women with HMB and examine any relationships between objective measures of daily MBL and subjective measures regarding patient efficacy and its subsequent impact on quality of life. Future studies specifically designed to assess the statistical significance of these relationships would be beneficial.

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