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Original Research Article

Comparison of safety and efficacy of Ormeloxifene and Norethisterone acetate in the treatment of heavy menstrual bleeding

Sunil Kumar Juneja, Pooja Tandon*, Gagandeep Kaur

Department of Obstetrics and Gynecology, DMCH, Ludhiana, Punjab, India

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***Correspondence:**
Dr. Pooja Tandon,
E-mail: drpoojatandon77@gmail.com

ABSTRACT

Background: Menorrhagia (menstrual blood loss more than 80% per cycle) affects 10-33% of women at some stage of their lives. Medical management is the first line of therapy for menorrhagia (heavy menstrual bleeding: HMB). Progestins have been found to be very effective in the management of heavy menstrual bleeding especially during acute episodes, norethisterone acetate being widely used for the same. Ormeloxifene is a new drug with promising results in managing HMB. The study was undertaken to compare the efficacy, safety and acceptability of Ormeloxifene /Norethisterone acetate in the medical management of heavy menstrual bleeding.
Methods: This was a retrospective study conducted from January 2016 till December 2018 in which 98 women of reproductive age group presented with abnormal uterine bleeding without any organic, systematic and iatrogenic causes. The patients were divided into 2 groups. Those wanting contraception along with control of HMB were assigned to Group O and given Ormeloxifene and others were given norethisterone (Group N). The primary outcomes measured were menstrual blood loss assessed subjectively by patients and ultrasonography for endometrial thickness. The secondary outcomes measured were acceptability and side effects of Ormeloxifene and norethisterone.
Results: There is a significant reduction in menstrual blood loss as evidenced by the history of patients recorded on follow up and there was a significant reduction in the endometrial thickness as evidenced on follow up scan at the end of 3-4 months. no major side effects were observed with both the drugs.
Conclusions: Ormeloxifene in comparison to norethisterone acetate with its effectiveness, significant results, convenient dosages schedule and no major side effects is an effective and safe alternative medical management of HMB.

Keywords: Heavy menstrual bleeding, Norethisterone, Medical therapy, Ormeloxifene

INTRODUCTION

Heavy menstrual bleeding is a prevalent condition affecting 20-30% women of reproductive age group.[1] Menorrhagia (menstrual blood loss more than 80% per cycle) affects 10-33% of women at some stage of their lives. Only half of women complaining of heavy menstrual bleeding fit the critical criteria of more than 80 ml blood loss per cycle.[2,3] After exclusion of anatomical disorders PALM (polyps, adenomyosis, leiomyoma, malignancy) and non-anatomical disorders COEIN (coagulopathies, ovulatory dysfunction, endometrial, iatrogenic, not otherwise classified) managing the symptom of HMB is a priority. A medical management is the first line of therapy for menorrhagia (heavy menstrual bleeding: HMB).[4] Many pharmacological agents have been used to treat HMB including iron, cyclooxygenase inhibitors, antifibrinolytics, combined oral contraceptives, gonadotropin-releasing hormone agonists, androgens and progestins. But ideal medical therapy is yet to be discovered. Progestins have been found to be very effective in the management of heavy menstrual

bleeding especially during acute episodes. Progestins can be administered systemically or locally and they may be given cyclically or continuously. With the increased use of effective medical therapies, the number of surgical procedures, such as endometrial ablation and hysterectomy has gone down.[5]

Ormeloxifene is a new modality and is found to be a better option in reducing menorrhagia with respect to a greater success rate, better compliance and cost effectiveness. We aimed to compare the safety, efficacy and acceptability of Ormeloxifene/Norethisterone acetate in the medical management of heavy menstrual bleeding.[6]

The study was undertaken to compare the efficacy, safety and acceptability of Ormeloxifene/Norethisterone acetate in the medical management of heavy menstrual bleeding.

METHODS

This is a comparative study conducted in the department of obstetrics and gynecology, Dayanand Medical College and hospital, Ludhiana from January 2016 till December 2018 in which 98 women of reproductive age group presenting with abnormal uterine bleeding without any organic, systematic and iatrogenic causes were enrolled.

Inclusion criteria

- Married women of reproductive age group presenting with heavy menstrual bleeding without any organic, systemic or iatrogenic cause attending gynae OPD.

Exclusion criteria

- Fibroid uterus, adenomyosis, atypical endometrial hyperplasia, pregnancy, bleeding disorders, medical disorders like liver dysfunction, heart disease, migraine, stroke, renal disease and thyroid function and patients after abortion.

A detailed history and clinical examination were done. As AUB is a diagnosis of exclusion, investigations were done to rule out any other possible cause for abnormal uterine bleeding. These included complete blood cell count, including Hb levels, TSH, prolactin, coagulation profile, pap smear, pelvic ultrasound to measure size of uterus, size of ovaries and endometrial thickness and rule out any pelvic pathology.

The patients were divided into 2 groups. Those wanting contraception along with control of HMB were assigned to Ormeloxifene group (Group O) and those who did not want contraception were given norethisterone acetate (Group N).

In Group N, there were 46 patients who received norethisterone acetate in the dosage of 5 mg twice daily for 21 cycles for 6 cycles.

In Group O, patients received 60 mg of Ormeloxifene twice a week for 12 weeks, followed by 30 mg dose of Ormeloxifene twice a week for next 3 months followed by 30 mg dose weekly for next 3 months.

The primary outcomes measured were menstrual blood loss assessed subjectively by patients by pictorial blood loss assessment chart (PBAC), amount of bleeding, days of bleeding, and with history on follow up in terms of dysmenorrhea, heaviness in lower abdomen. Also follow up was done after 3-4 months with repeat ultrasonography for endometrial thickness. The secondary outcomes measured were acceptability and side effects of Ormeloxifene and norethisterone.

Data were described in terms of range frequencies (number of cases) and relative frequencies (percentages) as appropriate. For comparing categorical data, Chi square ($\chi 2$) test was performed and exact test was used when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. Patients from both the groups were followed for 3 months after completion of therapy for recurring symptoms.

Statistical analysis

All statistical calculations were done using SPSS (Statistical Package for the Social Science) SPSS 17 version statistical program for Microsoft Windows.

RESULTS

There was a significant reduction in menstrual blood loss as evidenced by the history of patients recorded on follow up in both the groups. More than 90% of patients reported symptomatic relief at the end of one month of treatment. Also, there was a significant reduction in the endometrial thickness as evidenced on follow up scan at the end of 3-4 months. There were no major side effects with only one patient reporting hypersensitivity reaction at the end of second week of treatment and only 2 patients were non-compliant and on reassurance resumed the treatment.

Table 1: Distribution of patients in two groups according to parity.

Parity	Group O	Group N
P0A0	12	11
P1	26	22
P2	14	13
Total	**52**	**46**

Chi-square value 0.046, p value 0.976.

Distribution of patients in both the groups according to the parity has been shown in Table 1 (p value 0.976). Majority of the patients in both the groups were parous women.

Table 2: Distribution of patients in two groups according to age.

Age group (years)	Group O	Group N
20-25	4	2
26-30	24	21
31-35	20	19
36-40	4	4
Total	**52**	**46**

Chi-square value 0.527, p value 0.913.

Out of 52 total patients in Group O, four patients belonged to the age group 20-25 years, 24 patients belonged to the age group 26-30 years, 20 belonged to the age group 31-35 years and four belonged to the age group 36-40 years. Out of 46 total patients in Group N, two patients belonged to the age group 20-25 years, twenty-one patients belonged to the age group 26-30 years, nineteen belonged to the age group 31-35 years and four belonged to the age group 36-40 years (Table 2) (p value 0.913).

Table 3: Distribution of patients into the two groups based on endometrial thickness.

Endometrial thickness on USG	Group O total number = 52	Group N total number = 46
< 10 mm	10	12
10-12 mm	16	14
12-15 mm	26	20

Chi-square value 0.733, p value 0.693.

Prior to the therapy, 42 patients had post menstrual endometrial thickness more than 10 mm in Group O and 34 patients had post menstrual endometrial thickness more than 10 mm in Group N and both the groups were comparable in this regard (Table 3) (p value 0.693).

Post menstrual endometrial thickness evaluated after 3 months and 6 months of therapy is shown in Table 4 (p value 1.657) and Table 5 (p value 0.822) respectively showing that there was no significant difference regarding the same in the two groups.

Table 4: Effect of Ormeloxifene and Norethisterone on endometrial thickness post 3 months of therapy.

Post menstrual endometrial thickness post 3 months of therapy (day 5 - day 10)	Group O	Group N
< 10 mm	42	32
> 10 mm	10	14
Total	**52**	**46**

Chi-square value 1.657, p value 0.198.

Pre therapy and post therapy 6 months endometrial thickness showed significant reduction in both the groups with p value being 0.115 and 0.148 respectively.

Table 5: Effect of Ormeloxifene and norethisterone on endometrial thickness post 6 months of therapy.

Post menstrual endometrial thickness post 6 months of therapy (day 5-day 10)	Group O	Group N
< 10 mm	48	43
> 10 mm	4	3
Total	**52**	**46**

Chi-square value 0.050, p value 0.822.

Table 6: Distribution of patients into the two groups based on pre-therapy haemoglobin.

Pre-therapy haemoglobin (gm%)	Group O Total number = 52	Group N Total number = 46
< 7	1	3
7.1-9.9	40	37
> 10	11	6

Chi-square value 2.228, p value 0.328.

Pre-therapy and post 3 and 6 months of therapy haemoglobin estimations showed improvement with p value 0.198, 0.822, 0.328 respectively (Table 6-8). Pre therapy and post therapy 6 months, there was statistically significant improvement in haemoglobin levels in both the Ormeloxifene (p value 0.022) and Norethisterone acetate group (p value 0.001).

Table 7: Effect of Ormeloxifene and Norethisterone on haemoglobin post 3 months of therapy.

Post 3-month therapy haemoglobin (gm%)	Group O	Group N
< 7	0	1
7.1-9.9	18	19
> 10	34	26
Total	**52**	**46**

Chi-square value 0.813, p value 0.666.

Table 8: Effect of Ormeloxifene and Norethisterone on haemoglobin post 6 months of therapy.

Post 6-month therapy haemoglobin (gm%)	Group O	Group N
< 7	0	0
7.1-9.9	08	9
> 10	44	37
Total	**52**	**46**

Chi-square value 0.297, p value 0.585.

Dose related side effects such as gastritis, headache, abdominal discomfort were seen in both the groups with majority being in Group N. Gastritis and headache were significantly less in Ormeloxifene group (p value 0.007 and 0.010 respectively). Distribution of patients in both the groups with respect to side effects is being shown in Table 9. Amenorrhoea was observed in 16 patients in

Group O while it was not present in Group N (p value 0.000). Four patients in Group O and three patients in Group N did not show any improved results. However, five patients in Group N had recurrence whereas only two patients in Group O had recurrence after two months of completion of therapy.

Table 9: Distribution of patients in two groups according to side effects and complications with Ormeloxifene and Norethisterone.

Side effects and complications	Group O	Group N	Chi-square value	p value
Gastritis	2	10	7.272	0.007
Headache	3	11	6.562	0.010
Abdominal discomfort	4	6	0.763	0.382
Ovarian cyst	4	1	1.535	0.215
Amenorrhoea	16	0	16.916	0.000
Failure	4	3	0.050	0.822
Recurrence	2	5	1.815	0.177

DISCUSSION

Abnormal uterine bleeding (AUB) bleeding is a common condition which affects the quality of life of many women.[7] It accounts for most of the referrals to the gynecological clinics. Various modes of medical and surgical treatment options are available to treat this condition. The present study was a comparative study to assess the efficacy of Ormeloxifene and norethisterone in treating heavy menstrual bleeding in patients without any organic, systematic and iatrogenic causes.

Ormeloxifene is a selective estrogen receptor modulator (SERM) used primarily as a contraceptive. In some parts of the body, its action is estrogenic (e.g., bones), in other parts of the body, its action is antiestrogenic (e.g., uterus, breasts). It causes an asynchrony in the menstrual cycle between ovulation and the development of the uterine lining, although its exact mode of action is not well defined. Ormeloxifene was also found to be effective for dysfunctional uterine bleeding and advanced breast cancer.[8]

Norethisterone acetate is a synthetic progestogen and is used to treat heavy menstrual bleeding. It is an agonist of the progesterone receptor, the biological target of progestogens like progesterone.[9] It has weak androgenic and estrogenic activity and no other important hormonal activity.[10]

In our study Ormeloxifene was found to be more effective in reducing menstrual blood loss and controlling AUB compared to cyclical progesterone. Shravage et al compared Ormeloxifene to another progesterone, medroxyprogesterone acetate. They found an 85.7% reduction in menstrual blood loss with Ormeloxifene as compared to 54.76% with medroxyprogesterone acetate.[11]

At the end of the treatment Ormeloxifene was found to cause significant reduction in endometrial thickness. Reduction in endometrial thickness is a definitive objective evidence showing reduction in menstrual blood loss. While both Ormeloxifene and norethisterone exhibit antiestrogenic activity in the endometrium preventing endometrial proliferation, Ormeloxifene is more efficacious as it directly blocks the oestrogen receptors and thereby prevents mitogenic activity exhibited by oestrogen. A study conducted by Jacob et al using similar drugs showed reduction in endometrial thickness by both the drugs although the reduction was greater with Ormeloxifene compared to norethisterone.[12] Failure rate was higher with norethisterone compared to Ormeloxifene.

Amenorrhea being a major side effect with Ormeloxifene is due to hypoestrogenic effects causing delay in ovulation which leads to lengthening of the follicular phase. In majority of the subjects menstrual cyclicity returned to normal after 3-6 months.

Ormeloxifene has been associated with a number of advantages. It can be started at any time during the cycle unlike the progesterone's. It is an effective endometrial hemostat controlling bleeding within 48 hours. It is economical compared to any drug. While preventing HMB it also offers perimenopausal bone and cardiovascular protection which is not seen with other drugs.

CONCLUSION

Ormeloxifene in comparison to norethisterone acetate with its effectiveness, significant results, convenient dosages schedule and no major side effects is an effective and safe alternative medical management of HMB.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Marsh EE, Brocks ME, Ghant MS, Recht HS, Simon M. Prevalence and knowledge of heavy menstrual

bleeding among African American women. Int J Gynecol Obstet. 2014;125(1):56-9.
2. Vilos GA, Lefebvre G, Graves GR. Guidelines for the management of abnormal uterine bleeding. SOGC clinical practice guidelines. J Obstet Gynaecol Canada. 2001;106:1-6.
3. Harlow SD, Campbell OMR. Menstrual dysfunction: a missed opportunity for improving reproductive health in developing countries. Reprod Health Matters. 2000;8(15):142-7.
4. Hartz AJ, Barboriak PN, Wong A, Katayama KP, Rimm AA. The association of obesity with infertility and related menstural abnormalities in women. Int J Obes. 1979;3(1):57-73.
5. Amezcua CA, Lu JJ, Felix JC, Stanczyk FZ, Zheng W. Apoptosis may be an early event of progestin therapy for endometrial hyperplasia. Gynecol Oncol. 2000;79:169-17.
6. Bhargava VL. Textbook of Gynaecology ANE Books. 2nd ed; 2009:109.
7. Livingstone M, Fraser IS. Mechanisms of abnormal uterine bleeding. Hum Reprod Update. 2002;8(1):60-7.
8. Shelly W, Draper MW, Krishnan V, Wong M, Jaffe RB. Selective estrogen receptor modulators: an update on recent clinical findings. Obstet Gynecol Surv. 2008;63(3):163-81.
9. Doshi HU, Kriplani A. Clinical cases in Obstetrics and Gynaecology, 1st ed; 2003:250-251.
10. Samuel NC, Clark TJ. Future research into abnormal uterine bleeding. Best Pract Res Clin Obstet Gynaecol. 2007;21(6):1023-40.
11. Shravage J, Mekhala D, Bellad MB, Ganachari MS, Dhumale HA. Ormeloxifene versus medroxyprogesterone Acetate (MPA) in the treatment of dysfunctional uterine bleeding: a double- blind randomized controlled trial. JSAFOG 2011;3(1):21-24.
12. Jacob KJ, Mini, Deepak AV. A comparative study on the effectiveness of ormeloxifene versus norethisterone in the management of perimenopausal dysfunctional uterine bleeding. JS Asian Fed Obstet Gynecol. 2015;2(7):87-92.

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