

Comparison of Efficacy of Norethisterone (Primolut-N) Between Twice or Thrice Daily Dose to Avoid Menstrual Bleeding During Hajj and Umrah

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Abstract

Objective: To compare the efficacy between twice and thrice dosage of norethisterone to avoid menstrual bleeding during Hajj and Umrah.

Study Setting: Gynaecology OPD (Pakistan Air Force Hospital Mushaf Sargodha).

Duration of Study: The study was conducted for a period of two years from 01.1.2015 to 31.12.2016.

Study Design: This was an Interventional comparative study.

Methodology: One hundred and seventy-eight women, going to perform Hajj or Umrah were selected for this study purpose. A detailed history was taken and the women were examined with the help of Cusco's speculum, bimanual pelvic examination and one step diagnosis by transvaginal ultrasound. The women were given different doses of norethisterone and were divided in three groups. Group I was given 5 mg BD dosage. Group II was given norethisterone 5 mg in TDS dose and group III used 10 mg BD dose. They were also advised to start the medicine ten or fifteen days before menstruation and to continue it throughout their stay at Saudi Arabia. They were advised to come for follow up after their arrival in Pakistan. There were 178 women among whom 150 women came for follow up. On arriving in Pakistan, the problems of bleeding were noted.

Results: The best response was seen with 10mg dose BD when it was started 10-15 days before the menstruation. While 5 mg BD dose of Norethisterone was not effective in about 50% of women. Similarly, 5 mg TDS dose was equally effective if started 10-15 days before next menstruation

Conclusion: Norethisterone is an effective for prolongation of menstrual bleeding in special events like Hajj and Umrah. Best results are achieved when it is started 15 to 10 days before next menstrual cycle and given in 15mg to 20 mg daily dosage.

Keywords: Menstrual bleeding, Norethisterone, Dysfunctional Uterine Bleeding, Progestogen.

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Introduction

Hajj and Umrah are two very important occasions for the Muslims all over the world. The pilgrims visit the country of Saudi Arabia to perform Hajj and Umrah for a specified time period. Not only do they visit

Masjid-e-Haram at Mecca and Rozai Rasool (PBUH) at Madina but they also go to other Holy places over there for the purpose of Ziarat. It is necessary for the women and girls during this time period to avoid

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menstruation. For this purpose, they need medication to shift the timing of menstruation. The medicines help them to prolong or shorten menstrual cycle according to the wish and circumstances of the ladies. A large number of women and girls come before going to Hajj and Umrah in the day to day practice of gynecologists to get advice about this matter and the gynecologist has to provide such medicine that should be safe, effective, cheap, and easily available in Pakistan and Saudi Arabia.

A number of drugs are in use to alter or shift timing of menstrual cycle. It can also be used to postpone the start of period for special circumstances as for Hajj and Umrah, during travel or taking part in sports events. All over the world Norethisterone is most commonly used medicine for this purpose. Its chemical name is 19-nor-17 α -ethynyltestosterone, molecular formula is C₂₂H₂₆O₂ and molecular weight is 298.4 and contains 5mg dosage in one tablet. It can be taken as 2, 3 or 4 tablets in different doses.

It is a first-generation progestogen and is a potent Gonadotrophin inhibitor and suppressor of ovarian function.² It was synthesized for the first time by chemists Luis Miramontes, Carl Djerassi, and George Rosenkranz at Syntex in Mexico City in 1951.³ Norethisterone was first introduced, as Norlutin, in 1957.⁴ Norethisterone mimics the effects of natural progesterone and so can help to regulate the healthy growth and normal shedding of the endometrial lining. Its recommended dosage leads to complete transformation of endometrium from a proliferative phase to secretory phase and shedding of endometrium will occur when the drug is stopped as per requirement. Its serum levels follow typical biphasic pattern with half-lives of 1-2 and 5-13 hours in the two phases.^{1, 4} It is considered to be an effective progestogen with minimal androgenic effects that can be neglected. It is safe for most of the patients and dosage is easy to be adjusted according to the requirements. It is not an expensive medicine and is easily available in both countries.

It is indicated for use in other conditions as well such as dysfunctional uterine bleeding (DUB), primary dysmenorrhoea, endometriosis, premenstrual syndrome and progesterone challenge test for secondary amenorrhoea. Norethisterone has also been formulated in some preparations as a contraceptive. It produces secretory effects on

estrogen-primed genital tissue, has a sedative effect on uterine muscle and a styptic effect on uterine hemorrhage^{3, 4}.

Methodology

Inclusion Criteria: All women reporting to Gynecology Out Patient Department who were ready to participate in data collection before going to perform Hajj or Umrah during 2015 to 2016 with no gynecological pathology were included in the study.

Exclusion Criteria: Women with history of irregular bleeding P/V and menorrhagia due to structural pathology like fibroid uterus, endometriosis, ovarian cysts and adenomyosis were excluded from study. Women who lost follow up after Hajj or Umrah were also excluded.

Patients coming at OPD were motivated to volunteer for study with the help of leaflets and counseling. One hundred and seventy-eight women, going to perform Hajj or Umrah were selected for this study purpose. All these patients reported to gynae OPD at one, two or three weeks before going to Hajj or Umrah. A detailed history was taken in OPD by postgraduate trainee doctors. The women were examined thoroughly to exclude pelvic pathology. Those women who had intrauterine contraceptive device (Copper- T, Multiload) placed in utero and wanted it to be removed, the device was removed. Further evaluation was done by classified gynecologist with the help of per speculum examination, bimanual pelvic examination and one step diagnosis by transvaginal ultrasound. The women were told about the study and those who volunteered for study were noted in a register. The women were given different doses of norethisterone and were divided in three groups. Group I were those women who wanted minimal dosage of the drug so were given 5mg BD dosage. However, they were advised to reschedule and increase the dosage when they had menstrual problem. Group II were the women who were advised norethisterone 5mg in TDS dose and group III were those who used 10mg BD dose. The women were counseled about the drug norethisterone in detail and were advised about its dosage and side effects. They were also advised to start the medicine ten or fifteen days before the menstruation and to continue throughout their stay at Saudi Arabia. They were also advised to report to

Pakistan House Medical Squadron at Saudi Arabia both at Macca and Madina in case of any problem like side effects or noncompliance. They were also told to reschedule the dosage in case of occurrence of bleeding P/V and were advised about rescheduled dosage. They were advised to come for follow up after arrival at Pakistan or inform on telephone about the questions as required in study. There were 178 women among whom 150 women came for follow up while 28 women did not report back so were excluded from study. On arriving in Pakistan, the problems faced by patients during stay at Saudi Arabia were noted. The data was calculated and analyzed in figures and percentages. Study was presented in tabulated form and means and frequencies were calculated.

Statistical Analysis: Data was analyzed using Statistical Package of Social Sciences (SPSS) version 19 and ratio scale was used to measure the efficacy of drug with different parameters. Further inferential statistical test independent sample T-Test was used to compare the means of three groups (twice a day dose/thrice a day dose) on basis of P-value. The results are shown in tables in comparative form and serial wise.

Results

Out of 10 women who started Norethisterone 15 or 12 days before their menstrual period, 5 (50%) had no bleeding problems and responded well while half had bleeding problems and had to adjust the medicine as was required. Out of the 10 women who started medicating 10 or 7 days before their menstrual period, 4 (40%) achieved full benefits of the drug. Women who started the drug 2 days before their period, none (0%) showed positive outcomes

and no required effect of drug could be achieved. (Table I)

Out of 10 women 9 (90%) achieved the expected results when they took the drug 15 days before their menstrual period. Almost same results were observed in women who started norethisterone 12 or 10 days before their period, 8 (80%) got the desired results and had no menstrual problems as was expected. Those who started medicating 7 days before their menstrual period, 3 (30%) out of 10 achieved the desired results. Women who started the drug 2 days before their next menstrual cycle, only 2(20%) were able to achieve the expected effects. (Table II)

All the 10 (100%) women who used the drug 15, 12 or 10 days before their menstrual period had similar results. They had no bleeding problems during their stay and had the desired outcome. Out of the 10 women who started the drug 7 days before their next cycle, 7 (70%) were able to achieve cessation of menstruation whereas who started the drug 2 days before their periods only 2(20%) were able to achieve the desired results. (Table III)

Table IV shows an overall view of the effects of norethisterone to postpone menstruation. It was observed that among the patients who were taking a 5 mg BD dose of Primolut-N, 18 (36%) out of 50 achieved a cessation of their period while 32 (64%) could not achieve the goal. Among women who were taking a 5 mg TDS dose, 30 (60%) out of 50 achieved positive results and 20(40%) could not get it. Whereas best results were obtained among the patients who were taking two tablets 5 mg BD, 39 (78%) out of 50 depicted the desired results and only 11(12%) were unable to prolong the menstrual cycle.

Table I: Effects on prolongation of menstrual cycle with use of drug in 5mg BD dose in Group I

Timing of starting of medicine as advised	Effect on prolonging menstrual cycle 5mg BD) (Total dose 10mg daily n=50		Percentage
	Number of Patients	Patients Who Responded	
15 days before next menstrual period	10	05	50.00%
12 days before next menstrual period	10	05	50.00%
10 days before next menstrual period	10	04	40.00%
7 days before next menstrual period	10	04	40.00%
2 days before next menstrual period	10	00	0.00%

Table II: Effects on prolongation of menstrual cycle with use of drug in 5mg TDS dose in Group II

Timing of starting of medicine as advised	Effect on prolonging menstrual cycle 5mg (Total dose 15mg daily) (TDS)n=50		Percentage
	Number of Patients	Patients Who Responded	
15 days before next menstrual period	10	09	90.00%
12 days before next menstrual period	10	08	80.00%
10 days before next menstrual period	10	08	80.00%
7 days before next menstrual period	10	03	30.00%
2 days before next menstrual period	10	02	20.00%

Table III: Effects on prolongation of menstrual cycle with use of drug in 5mg 2 X BD dose in Group III

Timing of starting of medicine as advised	Effect on prolonging menstrual cycle 5mg(Total dose 20mg daily) (2 BD) n=50		Percentage
	Number of Patients	Patients Who Responded	
15 days before next menstrual period	10	10	100.00%
12 days before next menstrual period	10	10	100.00%
10 days before next menstrual period	10	10	100.00%
7 days before next menstrual period	10	07	70.00%
2 days before next menstrual period	10	02	20.00%

Table IV: Bird's Eye View with different dosage of norethisterone in Group I, II & III

Overall response with different doses	Total no. of patients	Achieved postponement of menstrual cycle	Not achieved postponement of menstrual cycle	P-Value
Response with 5 mg BD dose (10 mg total)	50	18 (36%)	32(64%)	0.14
Response with 5 mg TDS dose (15 mg total)	50	30 (60%)	20(40%)	0.08
Response with two tablets 5 mg BD dose (20 mg total)	50	39 (78%)	11(12%)	0.04

Discussion

The drug norethisterone has been in use since a long time for delaying menstrual blood flow all over the world in events like sports, camping, vacations and overseas travel and for Hajj and Umrah. It can also be used to treat irregular or heavy menstrual bleeding. The study was carried out to demonstrate the effect of different doses of norethisterone on menstrual bleeding during Hajj and Umrah. The women were given norethisterone in different regimens in three groups and minimal to enhancing dosage was given. The high percentage of efficacy of norethisterone tablets demonstrates that response of this drug is better when used two tablets twice a day.

In group I norethisterone was given in 5mg on tablet in twice daily dose. These were the women who opted for minimal dose and they were also advised to increase the drug if they had bleeding problems. There were eighteen out of fifty women who responded with this dose of medicine and thirty two had menstrual problems during their stay. The reason behind this that norethisterone is more effective in high dose and we have given minimal dose to group I.

In group II norethisterone was given in 5mg one tablets in thrice daily dose. There were thirty out of fifty women who responded with this dose of medicine and twenty had menstrual problems. There

were certain reasons for this that they missed medicine due to different problems during the stay.

Group III was the one who took norethisterone 5mg two tablets in twice daily dose. There were thirty nine out of fifty women who responded with this dose of medicine and only eleven had menstrual problems during their stay. This group responded maximum of all the women and had minimal problems with the drug usage. The compliance was better in this group and they admitted that it twice daily dose was a very comfortable dose regime.

Multiple factors were responsible for decreasing the compliance of norethisterone. The compliance was decreased in those patients who missed the medicine and depends upon the number of doses not taken. The morbidities like gastroenteritis and upper respiratory tract infection occur more often during Hajj and Umrah time due to overcrowding of people leading to cross infection by common usage things and can cause noncompliance as these women did not took medicine due to cough, fever, loose motions or vomiting. These morbidities were most common factors observed for poor control of menstrual bleeding. Similarly, sometimes non-availability of drugs or loss of medicine can be responsible for noncompliance.

The study predicted that compliance of drug is increased when it is given in high and twice daily dosage. Not only this dosage schedule is comfortable for the patient but also it has minimal menstrual problems. The women who used thrice daily dose found the dosage to be difficult for them due to busy schedule of the chain of the events of Hajj and Umrah. Minimal compliance was observed in group I due to small quantity of the drug. There were certain reasons as well in all the women who had menstrual problems over there in all the three groups. These were that they forgot to take the drug due to busy schedule. There were few who lost medicine and had non-availability of the drug. There were many who left medicine due to co morbidities of gastroenteritis, upper respiratory tract infection, dehydration or vomiting.

A study was carried by Robert B to delay menstruation with norethisterone. He reported that norethisterone was effective in females to prolong menstruation. He used 20-40 mg of norethisterone orally from the 5th to the 25th day of the menstrual

cycle and studied its effects by calculating basal body temperature, disappearance of cervical fern, and induction of a secretory endometrium. He calculated that 10-20 mg daily of norethisterone for five days given to women induced a prompt temperature rise and withdrawal bleeding 24-72 hours after medication is stopped. The study has come to conclusion that administration of 20-40 mg. of norethisterone daily will delay the onset of menstruation effectively.⁵

In the study done by Opare-Addo and Henry S at Ghana the use of Primolut N tablet was done for contraceptive purpose. The study not only demonstrated the effects on contraception but also showed that it was effective for delaying menstruation in women with menstrual irregularities⁶.

The study conducted by J. G. Azzopardi on the synthetic progestogen-oestrogen therapy and uterine changes to prolong menstruation showed that continuous therapy with synthetic progestogen-oestrogen produces marked atrophy of endometrial glands and massive pseudodecidual stromal transformation leading to prolongation of periods. On the other hand cyclical therapy produces poorly developed glands. A possible inductive role of the glands on the stromal response to progestogens is postulated.⁷

Bishop P and his coworkers conducted the study of use of norethisterone for functional menstrual disorders by using its different regimes. This study is comparable to our study as he used dosage of 5 to 25 mg daily in different days of menstrual cycle. He concluded that effects were better when high dosage was used. Similarly, it was also observed that the drug was effective for prolonging to menstrual cycle when it was started 15 to 25 days before next menstrual cycle.⁸

Conclusion

Norethisterone is an effective and easily available drug that can be used for prolongation of menstrual. It can be given to women in different doses and at different days of cycle. However, effects are best when it is started 15 to 10 days before next menstrual cycle and compliance is increased with 10 mg BD dosage.

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