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Use of Centchroman (Saheli) in conservative management of Menorrhagia: Our experience

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Abstract

Introduction: One of the commonest disorder encountered in gynecological practice is menorrhagia which accounts for about 12–23% of the outpatient department consultations and is also an indication for hysterectomy in about 21–36% of cases.
Objectives: To bring out the beneficial effects of a commonly used contraceptive Centchroman (Saheli) in the medical management of menorrhagia.
Materials and Method: 100 women between the ages of 25 - 50 years with complaints of menorrhagia were investigated and managed with centchroman and the results analysed in the form of decrease in amount of bleeding, pattern of bleeding, endometrial thickness.
Results: Out of the 100 patients 68 patients were in pre menopausal age group. Almost all the patients registered a rise in hemoglobin levels at the end of study after treatment with centchroman. The duration of the cycles increased in 80% of the patients and the amount of bleeding reduced significantly. 17% patients did not benefit from Centchroman, out of these 10 patients underwent hysterectomy and 07 patients were reverted back to Norethisterone for better control of bleeding during the cycle.
Conclusion: Centchroman (SERM), a non-steroidal, non-hormonal agent was found effective in reducing menstrual blood loss in patients with menorrhagia. It was found to be an excellent drug in controlling the systems of abnormal uterine bleeding without effecting normal endocrinal and physiological parameters.

Keywords: Menorrhagia, SERMs (Selective estrogen receptor modulators), Centchroman, Estrogen receptors, Norethisterone, PBAC (Pictorial Blood loss Assessment chart).

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Introduction

Menorrhagia is defined as an abnormally heavy or excessive cyclical uterine bleeding which lasts for more than seven days duration or with a total blood loss in excess of 80 ml. About 10-30% women are affected by menorrhagia at some stage or other during their reproductive period and approximately 12% of all gynecology referrals in women aged 30-49 yrs are accounted for by menorrhagia. [(1)]

Centchroman (Ormeloxifene), chemically 3, 4 trans-7- methoxy-2, 2-di-methyl-3-phenyl-4-[4-(2pyrrolidinoethoxy) phenyl] chromanhydrochloride, is a non steroidal, oral contraceptive agent belonging to a class of drugs known as SERMs (Selective estrogen receptor modulators), which act on estrogen receptors (ER) in the tissues.[(2)] They can produce both estrogenic as well as anti-estrogenic effects depending on their intrinsic activity and also on the specific tissue where they act. SERMs have been studied extensively and have been used effectively in the treatment of carcinoma breast, post-menopausal osteoporosis and management of infertility arising due to ovulatory dysfunction.[(3)] Centchroman is available as an oral contraceptive since early 90s and is marketed in India as "Saheli".[(4)] The dosage schedule is 30 mg weekly, however it is recommended that for the initial 12 weeks it is taken twice a week and subsequently the dose is reduced to once a week thereafter. Failure rate with its use has been found to be 1-2% which is slightly more as compared to that seen with the combined pills.[(5,6)]

Though centchroman is primarily used for contraception as once a week pill, it has also been found effective in the management of other gynecological problems such as menorrhagia, mastalgia and even fibro adenomas.[(5,6,7)] There are concerns about centchroman of having been associated with an increased risk of uterine prolapse and urinary incontinence. However, these have not been proved substantially, even in patients who have been on prolonged medication with Centchroman for more than 15 yrs.

Materials and Method

The present study was based on the hypotheses that, centchroman pill in usual dosage schedule will significantly reduce the amount & duration of bleeding in all patients of menorrhagia.

A prospective study was carried out comprising of a randomized sample of 100 women in the reproductive age group with a mean age of 35 ± 10 yrs, who presented to the out patient department of our hospital with complaints of frequent heavy cycles i.e. bleeding for more than 7 days, cycles occurring earlier than 21 days, giving history of passage of clots &/or flooding, PBAC score of 100 or more. Necessary clearance from the institutional ethical committee was obtained. A written informed consent was also taken from the

subjects at the time of their enrolment. The women were subjected to an elaborate history taking which included their parity and pattern of bleeding, followed by a complete clinical examination. Investigations such as complete hemogram, Coagulation profile, thyroid profile and pelvic ultrasonography were also performed. A gynecologist and a radiologist measured the endometrial thickness independently.

All patients were educated about pictoral blood loss assessment chart (PBAC) and were requested to maintain a record of the same.[8,9] Patients with more than 100 points on PBAC & with no known possible factors responsible for causing severe uterine bleeding were labelled as having menorrhagia.[8] They were subsequently admitted for undergoing dilatation and curettage. A pelvic ultrasound was done in the pre-menstrual phase to measure pre-treatment endometrial thickness. Patients were then started on treatment with Centchroman given initially in a dose of twice weekly for 12 wks and subsequently the dose was reduced to once a week for another 12 wks. Patients found to be anemic (Hb < 11gm/dl) during the clinical examination were also supplemented with hematinic in addition to Centchroman. Effects of therapy in the form of rise in hemoglobin levels, an increase in the duration of bleeding and a reduction in endometrial thickness were evaluated after 03 and 06 months of start of treatment.

Exclusion criteria: Women with acute heavy bleeding who were hemodynamically unstable, women with postmenopausal bleeding, recent history or clinical evidence of hepatic / renal disease, polycystic ovarian disease, chronic cervicitis or cervical hyperplasia, any organic pelvic pathology, chronic illness, such as tuberculosis, past / family history of thromboembolic diseases, known or suspected cancer of breast or other estrogen-dependent cancers and hypersensitivity to drugs.[8]

Results & Statistical analysis

All 100 women initially enrolled managed to complete the study. Age of the treated women ranged between 25 to 50 yrs with a mean age of ± 35 yrs. 68% of women were in the age group of 41 to 50 yrs. Acyclical bleeding was the most commonly observed finding. The Commonest pathology detected on HPE in these women was proliferative endometrium (53% women) suggestive of anovulatory cycles. Simple hyperplasia without atypia was seen in 15% and 24% women had secretory endometrium. 5% of the women were already on some form of hormonal treatment hence the reports showed similar picture (Table 1).

Majority of women (95%) were found to be anemic during initial investigations. A significant increase in Hb level was seen post-treatment with Centchroman and only 18 % were found to have mild anemia (Hb 8-11 mg/dl) at follow up. A mean increase in Hb level of 1.5 mg/dl was found and the result was statistically significant ($p<0.001$) (Table 2). A statistically significant ($p<0.001$) reduction in median PBAC score was seen at 25th week post start of therapy. 84% women recorded a mean PBAC score of less than 80 at the end of study period (Table 3). A significant reduction in endometrial thickness was also seen at the end of 6 months. The mean difference in ET was statistically significant ($p<0.001$) (Table 4).

There was a reduction in the number of days of active bleeding from 2–9 days to 2–4 days in 68 % of the women. The average duration of menstrual cycle increased from 20-26 days to 32–38 days. A total of 17 women achieved amenorrhea (Fig 5). 72% of women had significant relief from dysmenorrhea. 84% of women reported significant relief from passage of clots.

No major side effects were reported during the study. Few of the observed side effects were amenorrhea (16%), giddiness (6%), abdominal pain (3%) and headache (3%), which did not require termination of treatment. Women with amenorrhea were followed up with serial ultrasonography and those with an endometrial thickness of 10mm or more (6%) were offered a withdrawal bleeding with Norethisterone. 10% women underwent hysterectomy, as the control over the bleeding was inadequate. 7% women were shifted back to Norethisterone, as the decrease in amount of bleeding and the reduction in endometrial thickness was less than as expected.

Table 1: Endometrial tissue findings on Histopathology

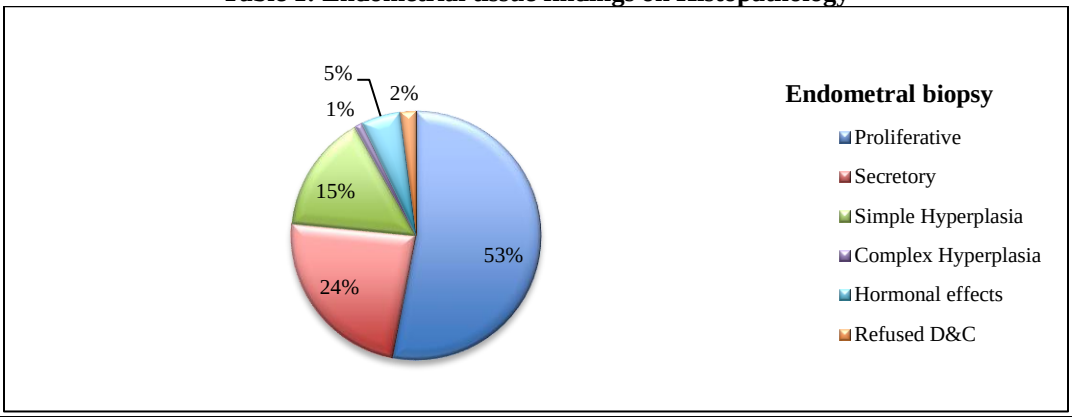


Table 2: Change in Hemoglobin levels pre and post treatment

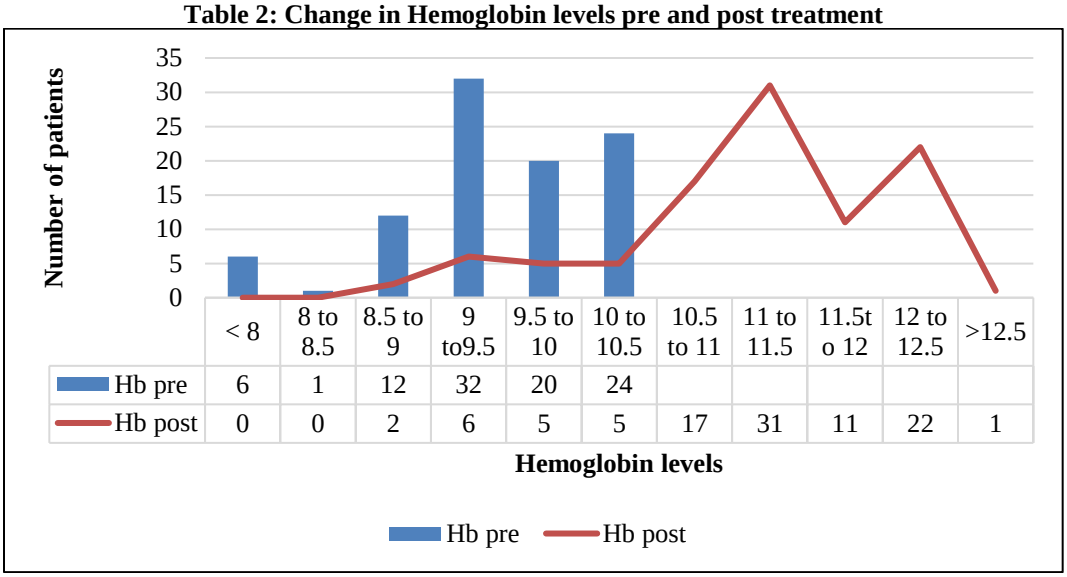


Table 3: Observed PBAC score pre & post treatment

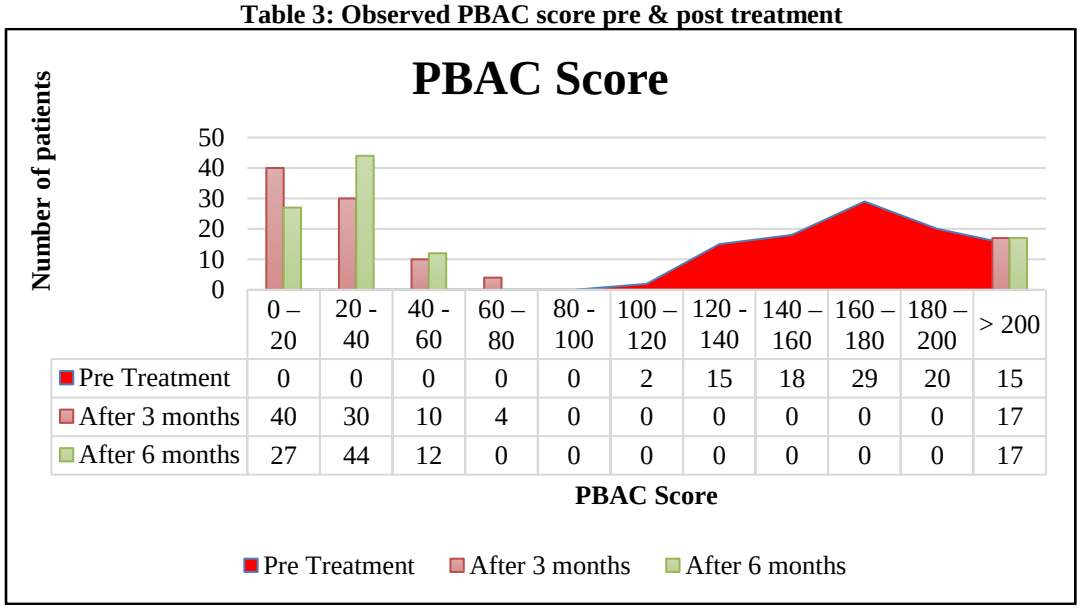


Table 4: Depiction of change in Endometrial Thickness pre & post treatment

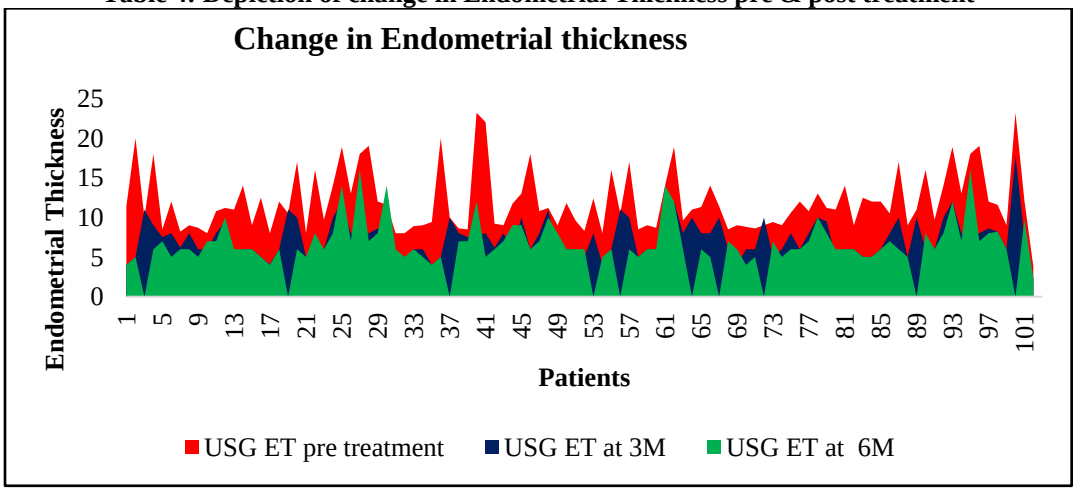
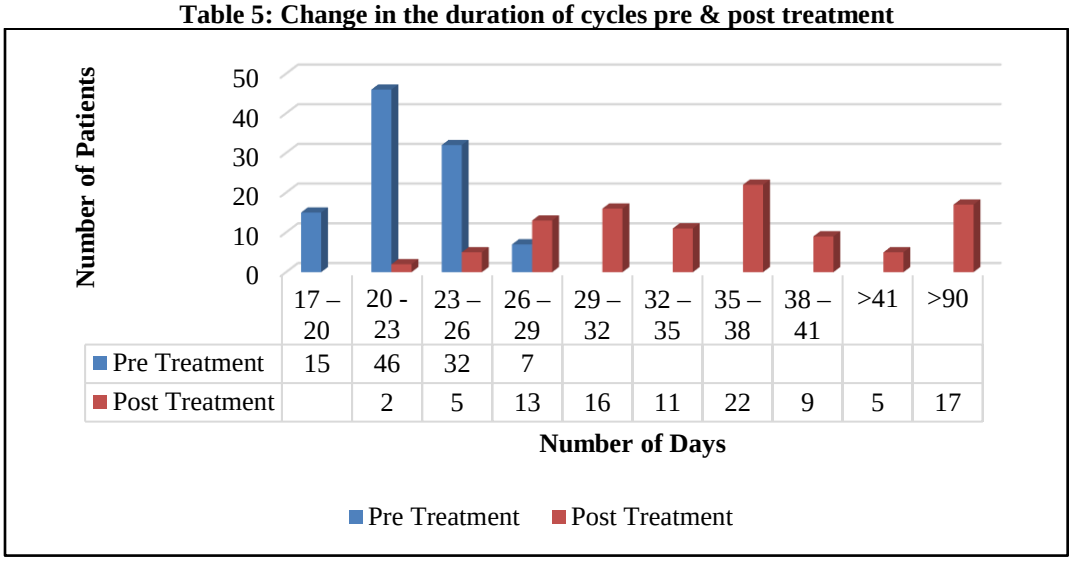


Table 5: Change in the duration of cycles pre & post treatment



Discussion

Abnormal uterine bleeding (AUB) is defined as irregular uterine bleeding occurring in the absence of any recognizable medical disease, pelvic pathology or pregnancy. Menorrhagia is abnormally heavy or excessive cyclical uterine bleeding which lasts for more than seven days duration or with a total blood loss in excess of 80 ml. Bleeding in such cases is usually due to hormonal imbalance and is associated with absence of ovulation in 80-85% cases. The cause of AUB is usually related to one of the three conditions associated with hormone imbalance i.e. estrogen breakthrough bleeding, estrogen withdrawal bleeding and progesterone breakthrough bleeding.[1]

Wide ranges of treatment modalities are available for AUB, which include medical management as well as surgical interventions. Abnormal uterine bleeding is a significant cause of morbidity in peri-menopausal women, but it can occur at any age. For women in reproductive age group who are desirous of preserving their fertility, many pharmacological options are currently available. These include NSAIDs like mefenamic acid, progestins like Norethisterone or Medroxy progesterone, anti fibrinolytics, Danazol, GnRH agonists and SERMs.[10,11]

Centchroman (Ormeloxifene), is a non-hormonal, non-steroidal oral contraceptive (marketed as Saheli, Centron, Novex-DS and Sevista). It is a selective oestrogen receptor modulator (SERM), a class of drugs that produces its effect by acting on the oestrogen receptors. SERMs were developed with an aim to reap the benefits of '*Estrogen*' while avoiding its potential side effects. Centchroman is a benzopyran, which blocks cytosol estrogen receptors by its competitive binding over estradiol. Though it is a potent estrogen antagonist, it also has a weak agonist activity on selective tissues and it exerts an effective contraceptive effect. It normalizes the bleeding during the menstrual cycle by regularizing the expression of estrogen receptors on the endometrial tissue. Though primary use of Centchroman is as a contraceptive agent, it is increasingly being used in the management of menorrhagia, mastalgia & even breast cancers. It is cheap and easily available drug used for the management of menorrhagia.[4,11]

The present study confirmed a significant rise in hemoglobin level in women with amenorrhea after treatment with centchroman, which was also reported in other studies.[4,8,9,10] A significant reduction in post treatment values of endometrial thickness as compared to baseline measurements was seen. The amount of bleeding also decreased significantly which was seen as a significant decrease in PBAC score. The duration of menstrual cycle increased. In fact, few of our patients developed amenorrhea, which was a welcome side effect in these patients. These results are similar as demonstrated in other studies.[4,8,9,10,11,12]

In a few patients who had severe menorrhagia, tab Norethisterone 5mg twice a day along with twice a week dose of tab centchroman from day 5 to day 25 was given for one (01) month. Thereafter dose of Norethisterone was tapered to 5mg twice daily from day 15 to day 25 i.e. for 11 days per cycle for next two (02) months before withdrawing it completely. This combination resulted in faster and more effective control of bleeding before centchroman took full effect. These patients were then continued on once a week tab centchroman from the 13th week onwards.

The patients, who were benefitted, were advised to continue with Centchroman at once a week dose till they were free of periods for at least 1 year and an endometrial thickness of less than 5mm i.e. indicative of menopause. As a contraceptive Saheli has been used by the patients for many years without any serious side effects. People who have benefitted from Centchroman prefer it over any other mode of treatment because of ease of dosage and relative absence of side effects.

Conclusion

Centchroman is a non-steroidal, non-hormonal oral contraceptive drug with good therapeutic efficacy and a favorable side effect profile. The compliance rates of therapy with this drug are also good due to convenient dosage schedule. Though the sample size in our study was small, yet the results with centchroman show a significant reduction in the menstrual blood loss and passage of clots, an increase in the duration of menstrual cycle, a reduction in endometrial thickness and an increase in the hemoglobin levels in women with menorrhagia that makes it a suitable pharmacologic agent in in the management of AUB. However, studies with large sample size may help to further determine the efficacy and safety profile of this agent in women with AUB.

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