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Comparative Study of Effect of COCPs v/s Norethisterone for Management of Heavy Menstrual Bleeding

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Abstract

Background: To evaluate the efficacy and safety of COCPs v/s Norethisterone treatment in cases of heavy menstrual bleeding (HMB) by estimating the decrease in amount of blood loss during menses and improvement in quality of life of patients.

Methods: This is an observational study conducted at PDMC attached to RNT Medical College, Udaipur in 2018. The women who fulfill the inclusion criteria were studied with respect to reproductive age group females with Heavy Menstrual Bleeding. Administration of OCPs (Mala-N) for 21 days starting from day 5 of cycle for 3 consecutive cycles and administration of oral progesterone (norethisterone) 5 mg TDS from D5 to D26 of menstrual cycle for 3 cycles was done.

Results: Out of the total patients of heavy menstrual bleeding, majority were in the age group of 19-45 years i.e. 81.25%. Reduction in menstrual blood loss (MBL) is maximum with COCPs (70%). 55-60% patents improved haemoglobin with COCPs after 3 cycles of treatment. 71.4% of patients were relieved of dysmenorrhea, and 42.8% case of norethisterone. The side-effects reported were mainly epigastric pain, nausea, vomiting, headache and giddiness. COCPs improved QOL i.e. 75% and norethisterone (60%) which was almost equally effective. Reduction in menstrual blood loss was observed to be 36.7% ($p<0.001$) with norethisterone and 37.3% ($p<0.001$) with COCPs. There was improvement in mean haemoglobin levels after 3 treatment cycles with norethisterone ($p=0.022$) and COCPs ($p=0.001$).

Conclusion: Both COCPs and norethisterone, are effective in reducing the PBAC score with COCPs being the most effective drug. COCPs was the most effective drug in improving the quality of life parameters and in improving the mean haemoglobin. It improved efficacy and safety in the treatment of heavy menstrual bleeding.

Keywords: Menstrual Bleeding; COCP; Norethisterone; PBAC Score.

Introduction

Menstruation

It is defined as physiological shedding of endometrium associated with uterine bleeding that occurs at monthly intervals from menarche to menopause. It occurs approximately 400-500 times in an average woman.

During menstruation, functional superficial layer of endometrium is shed and is regenerated from the basalis layer which is also comprised of stem cells/progenitor cells that are present in niches within basalis layer. The regenerating property of endometrium is controlled by dynamic and interactive effect of endocrine and reproductive systems [1].

Endocrinology

The endometrium is an endocrine organ that

responds to circulating estrogen and progesterone. Estrogen and progesterone receptors are intranuclear.

There are two estrogen receptors- alpha and beta. Both receptors consist of two terminals- amino terminal binds to regulatory protein factors and carboxy terminal is hormone binding domain. It undergoes conformational change when hormone binds to it and allows DNA binding.

Steroid hormones have relatively low molecular weight and are transported to cells by passive diffusion.

Replenishment:

Induction of synthesis of its own and other steroid hormone receptors by estrogen is known as replenishment.

Estrogen receptors reach a maximum concentration in middle late proliferative phase. progesterone receptors are also induced and reach maximum concentration in late proliferative phase. Then, progesterone blocks estrogen replenishment mechanism by accelerating receptor turnover and inhibiting E2 induced gene transcription. However, enough progesterone receptors persist throughout the luteal phase to maintain endometrial responsiveness and induction of deciduation [1].

Histology and physiology

Postmenstrual endometrium consists of thin layer of basalis cells and dense irregular remnants of stromal cell derived stratum spongiosum. Glandular stromal cells are small spindle shaped with lesser cytoplasm. Protein synthesis and secretory activity are minimal.

Early proliferative phase

Estrogen induces the proliferative phase by inducing synthesis of mitogens- epidermal growth factors and IGF- I. Estrogen and growth factors induce the synthesis of endothelin-1 which plays a major role in proliferation and menstruation.

VEGF plays an important role in angiogenesis. Torry and Torry [2] found that VEGF mRNA expression is induced by E2. VEGF is produced by the glandular epithelial cells, although some strong expression is evident in secretory phase. Kooy et al. [3] detected changes in VEGF in women with AUB, supporting a possible role in pathogenesis of menorrhagia.

Mitotic activity results in growth and pseudostratification of glandular epithelial cells. Arterioles grow into endometrium. The stromal cell proliferation and expression causes endometrium to grow upto thickness of 3–5 mm.

E2 also induces several enzymes i.e. alkaline phosphatase, 5-alpha reductase, phospholipase A2 as well as it stimulates cyclooxygenase synthesis of prostaglandin F2-alpha and PGE2, both of which have a role in menstrual function. PGF2-alpha has vasoconstrictive and muscle contraction effects and PGE2 is a vasodilator but causes contractions in uterine smooth muscle. Alterations in relative levels of PGF2-alpha and PGE2 can lead to change in menstrual bleeding patterns.

Late proliferative phase

Ovulation with corpus luteum formation and significant progesterone secretion leads to secretory transformation to late proliferative phase endometrium. Progesterone inhibits both estrogen and progesterone receptor synthesis as well as DNA synthesis and mitosis. It is accompanied by development of RNA filled channels between nucleoli and nuclear membrane that are responsible for progesterone induced active synthesis of cytoplasmic enzymes during secretory phase.

The secretory phase

Progesterone induces the cytoplasmic enzymes 17-beta and 20-alpha hydroxysteroid dehydrogenase (HSD). 17-beta HSD catalyses the conversion of estradiol to estrone, which, when sulfated by estrogen sulfotransferase, can no longer bind to estrogen receptors.

20-alpha HSD alters progesterone receptor binding and activity. Progesterone also induces acid phosphatase which is kept inactive within golgi derived lysosomes, the membrane of which are stabilized by progesterone.

Progesterone induces the activity of metalloendopeptidase which degrades the endothelin-1 peptide. Withdrawal of progesterone can lead to increased endothelin-1 activity with vasospasm and initiation of menstrual bleeding. Increased levels of protease inhibitors such as alpha-1 antitrypsin and antithrombin-lll are seen in secretory phase uterine fluid which may also be involved in mechanism of menstrual bleeding.

The luteal phase

Endometrium reaches its maximum thickness of 5–6 mm by the end of secretory phase and maintains this thickness throughout the luteal

phase. The subnuclear intracytoplasmic glycogen vacuoles in basal glandular cells transpose to the apex and are expelled into the glandular lumen. The stromal cells subsequently flatten into a low cuboidal form. Stromal cell differentiation from reticular spindle-shaped cells into plump peridecidual cells and phagocytic granulated cells defines two layers in the functional endometrium i.e. superficial compactum and deeper spongiosum. The predecidual stromal cells produce several metabolically active substances and are infiltrated by migratory leucocytes. The release of lysosomal enzymes from endometrial cells and possibly also from leucocytes may be involved in initiation of menstruation.

Menstruation

Menstruation results from progesterone withdrawal from estrogen primed endometrium. Markee described cyclical changes in endometrial vascularity and the development of coiled vessels supplying the superficial 2/3^{rds} of the endometrium [4].

If implantation does not occur, estrogen and progesterone levels fall, PG synthesis occurs and lysosomal membranes rupture, causing constriction of the spiral arterioles, ischaemic necrosis and sloughing of endometrium superficial to basalis layer. Lysosomal release and ischaemic necrosis was previously thought to be the main mechanism for normal menstrual bleeding. Current data supports the "metalloproteinase theory" as the mechanism leading to menstrual tissue breakdown and shedding. Matrix metalloproteinases (MMPs), lytic enzymes along with activated endometrial stromal granulocytes, macrophages and mast cells together are now thought to cause menstruation [4].

Estrogen and progesterone along with cytokines, appear to play a significant role in regulation and expression of MMPs. High levels of progesterone are believed to inhibit MMP production and activity. This explains endometrial tissue breakdown that occurs with decreasing progesterone levels from an involuting corpus luteum.

In the second part of menstrual phase, mitotic activity resumes and epithelial regeneration begins. This occurs even while menstrual bleeding continues. Continuous proliferation of stem cells is ensured by higher telomerase activity. New blood capillaries are formed by the stimulating effect of VEGF and thymidine phosphorylase (TP) secreted by both epithelial and stromal cells. This process begins in the premenstrual phase of the cycle with cessation of synthesis and inspissation of ground substance and supporting tissues by lytic enzymes released from lysosomes, which causes loss of fluids and compression of endometrium, tonic contractions of spiral arterioles with reduction of blood flow to the tissues, loss of stromal edema and kinking of coiled spiral arterioles caused by reduction in endometrial thickness.

A generalised state of ischaemia develops in the superficial layer of endometrium and bleeding into the stroma begins. Acid phosphatase and PG released from autolyzed cells, together with increased endothelin-1 activity causes more intense vasoconstriction of spiral arterioles and devitalised tissues finally slough as small haemorrhages in stroma coalesce.

According to Beller [5], coagulation factors are decreased in normal menstrual discharge. Fibrinogen is absent, plasminogen is converted to plasminogen by released peptidases and the amount of plasminogen inhibitor is decreased. Menstrual blood generally does not clot, but it can form red blood cell aggregates with mucoid substances, mucoproteins and glycogen, as it collects in vagina. These red cell aggregates may appear to be blood clots, but they contain no fibrin. In presence of very heavy flow, however, clotting may occur [5].

Blood loss from the process of normal menstruation is limited by recovery of tone in myometrial and endometrial vasculature, cessation of cellular autolysis, eventual clotting over endometrial surface and eventual active regeneration of glands, stroma and vessels inbasalis layer in response to rising estrogen levels in new cycle. The retained basalis layer of endometrium is protected from destruction by lysosomal enzymes by a mucinous carbohydrate coat that covers the free surface of endometrial cells.

Endometrial regression during menstruation is described as a result of autophagia, heterophagia, extrusion of secretory products and elimination of fluids with some but not complete shedding of tissue.

Abnormal uterine bleeding (AUB)

Abnormal Uterine Bleeding [6] (AUB) is a common problem among women in reproductive age group. In pre-menopausal women abnormal uterine bleeding may be a result of observations in: Duration of bleeding; Frequency of bleeding; Regularity of menses, or Volume of menstrual blood loss.

In post-menopausal women, any vaginal

bleeding 1 year after cessation of menses is Abnormal Uterine Bleeding. Abnormal Uterine Bleeding may be accompanied by pain and discomfort, cause significant social embarrassment and have a substantial effect on health related quality of life. Abnormal Uterine Bleeding leads to loss of productivity and may result in surgical interventions including hysterectomy.

According to ACOG: AUB is bleeding from corpus that is abnormal in: Regularity, Volume, Frequency or Duration and Occurs in the absence of pregnancy [7].

Burden of HMB in India

Excessive bleeding has been reported in about 8–9% women from India and neighbouring countries. 42–53% of women aged <21 years complained of excessive bleeding. 15% of all gynaecology OPD visits and 25% of all gynaecological surgeries constitute HMB cases.

HMB has a major impact on a woman's quality of life. Over 60% of women diagnosed with HMB ended up having hysterectomy within 5 years from diagnosis. About 1/3rd of them result in removal of anatomically normal uterus [7].

Diagnosis

1. History & Examination

- History & physical examination
- History of concomitant use of any medications which may likely cause Abnormal Uterine Bleeding.
- Past history screening for coagulopathies –

a) History of heavy bleeding starting at menarche

b) Atleast one of the following-

- PPH
- Surgery – related bleeding
- Bleeding associated with dental work.

c) At least two of the following

- At least one episode of bruising per month
- At least one episode of epistaxis per month
- Frequent gum bleeding
- Family history of bleeding symptoms
- Examination: including assessment of weight, pallor, thyroid, breast, acne, hirsutism, abdominal examination P/S and P/V examination.

2. Investigation

a) Laboratory investigations

- CBC
- UPT if pregnancy suspected
- Platelet count, BT, PT, aPTT recommended in all adolescent and in adults with the screen for coagulopathy
- testing for VW disease, histocetin co-factory activity, factory VIII activity.

b) Imaging

c) Endometrial Histopathology

Recommended in Abnormal Uterine Bleeding:

- In more than 40 years
- In less than 40 years with high risk factors for Ca endometrium i.e. irregular bleeding, obesity along with HTN, PCOS, DM, ET>12 mm, family history of carcinoma of ovary/breast/endometrium/colon, use of tamoxifen for HRT or Ca breast, late menopause, HNPCC, Abnormal Uterine Bleeding unresponsive to medical treatment.

Treatment

Non-Hormonal Treatment

1. Anti fibrinolytics: women with heavy menstrual bleeding may have over activation of fibrinolytic system during menstrual phase.
2. NSAIDS: Increased local inflammation may lead to increased BPV. TNF-alpha is significantly elevated in menstrual effluent of women with heavy bleeding versus those with normal blood loss.

Hormonal Treatment

a) Combined OCPs – contain estrogen and progesterone –

- given for 3 weeks followed by a pill free week in which woman experiences a hormone withdrawal bleed.
- COCPs cause approx. 50% reduction in blood loss.
- It is particularly used for women with frequent or irregular heavy bleeding, once pathology has been excluded.
- COCPs can be used for 3 consecutive cycles.

b) Progesterone Only Pills (POPs) – they are a safer alternative to COCPs.

Some POPs like desogestrel containing POPs induce amenorrhea in upto 20% of users [7].

Aims and Objectives

To evaluate the efficacy and safety of COCPs v/s Norethisterone treatment in cases of heavy menstrual bleeding (HMB) by estimating the decrease in amount of blood loss during menses and improvement in quality of life of patients.

Materials and Methods

Centre and Study Design

This is a randomized controlled trial study conducted on 40 patients with Heavy Menstrual Bleeding at Panna Dhay Zanana Hospital, Udaipur during year 2018.

Detailed history of patient was taken and investigations were done i.e. CBC, USG to rule out PCOS and anatomical causes, BT, CT, PT-INR, S.TSH, before starting the treatment.

Inclusion Criteria

- Reproductive age group females with Heavy Menstrual Bleeding.

Exclusion Criteria

- Perimenopausal patients with amenorrhea of >6 months.

- Known Bleeding disorders

- Hormonal disorders

- Bleeding due to intra uterine devices

- Bleeding due to polyp or atypical endometrial hyperplasia

Intervention

a) Administration of OCPs (Mala-N) for 21 days starting from day 5 of cycle for 3 consecutive cycles.

b) Administration of oral progesterone (norethisterone) 5 mg TDS from D5 to D26 of menstrual cycle for 3 cycles.

Assessment

All patients were assessed in terms of decrease in blood loss and improvement in quality of life according to following parameters:

- Amount of blood loss (no. Of pads soaked per day) - PBAC score (Fig. 1)
- Duration of blood loss
- Improvement in Hb
- Relief in dysmenorrhea
- Improvement in work productivity
- Impact on relationship with partner.

PBAC SCORING

Name of patient	Days							Score	
Sanitary Pads	1	2	3	4	5	6	7		
									1= Lightly stained
									5=Moderately stained
									20= Completely stained
Tampons									
									1= Lightly stained
									5=Moderately stained
									10= Completely stained
Clots/Flooding									
1 Point	For each small clot (Australian 5 cent coin)								
5 Points	For each largel clot (Australian 50 cent coin)								
5 Points	For each episode of flooding								

Fig. 1:

Results and Discussion

Out of the total patients of heavy menstrual bleeding, majority were in the age group of 19–45 years i.e. 81.25% and 18.75% were in age group of 11–18 years (Graph 1).

Table 1: Improvement in PBAC

Drug given	Total number of patients	Number of patients with improved PBAC	% of patients with improved PBAC
Norethisterone	20	13	65
COCPs	20	14	70

p>0.05 (NS)

The above table 1 shows that reduction in menstrual blood loss (MBL) is maximum with COCPs (70%). However, there was no statistically significant difference between the drugs. This is in consonance with the studies of Lethaby et al. [8] conducted a Cochrane database review which concluded that norethisterone had a similar effect on MBL. Srivaths LV *et al.* [9] concluded that COCPs significantly reduce the MBL.

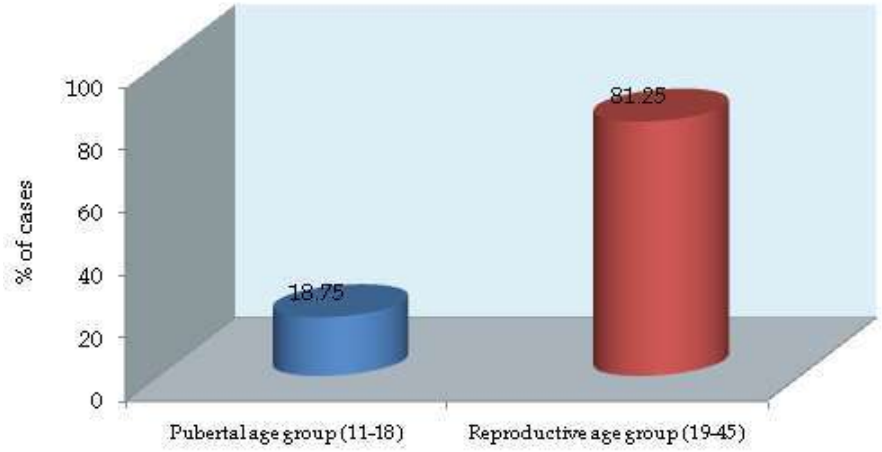
Table 2: Improvement in haemoglobin

Drug given	Total patients	No. of patients with improved Hb	% of patients with improved Hb
Norethisterone	20	11	55
COCPs	20	12	60

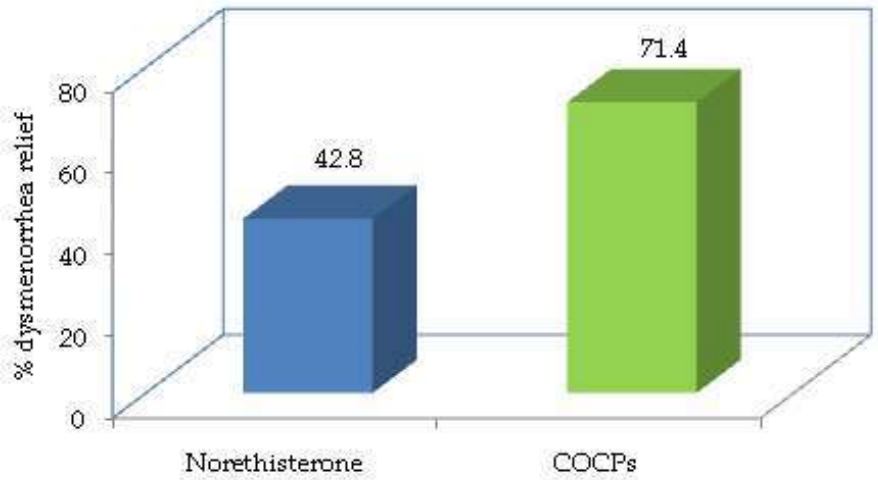
p>0.05 (NS)

55-60% patents improved haemoglobin with both norethisterone, and COCPs after 3 cycles of treatment (Table 2).

The present study observed that COCPs was more effective for relief of dysmenorrhea i.e. 71.4% of patients were relieved of dysmenorrhea, followed by 42.8% case of norethisterone (Graph 2).



Graph 1: Age distribution of heavy menstrual bleeding



Graph 2: Relief of Dysmenorrhea

Table 3: Side-effects

Drug given	Total number of patients	Number of patients who experienced side-effects	% of patients who experienced side-effects
Norethisterone	20	8	40
COCPs	20	7	35

Side-effects were reported in 40%, 35% of patients taking treatment with norethisterone and COCPs. The side-effects reported were mainly epigastric pain, nausea, vomiting, headache and giddiness. The difference between the drugs was not significant (p>0.05). This is in consonance with the study by Lethaby A *et al.* [8] who reported that there were no significant differences in the side effects. Srivaths LV *et al.* [9] observed that more patients experienced side-effects with COCPs (64%) (Table 3).

The present study observed that majority of patients taking COCPs improved QOL i.e. 75%, whereas norethisterone (60%) was almost equally effective in improving quality of life. This is in consonance with the study conducted by Srivaths LV *et al.* [9], who concluded that OCPs are almost equally effective in improving quality of life (p value >0.05).

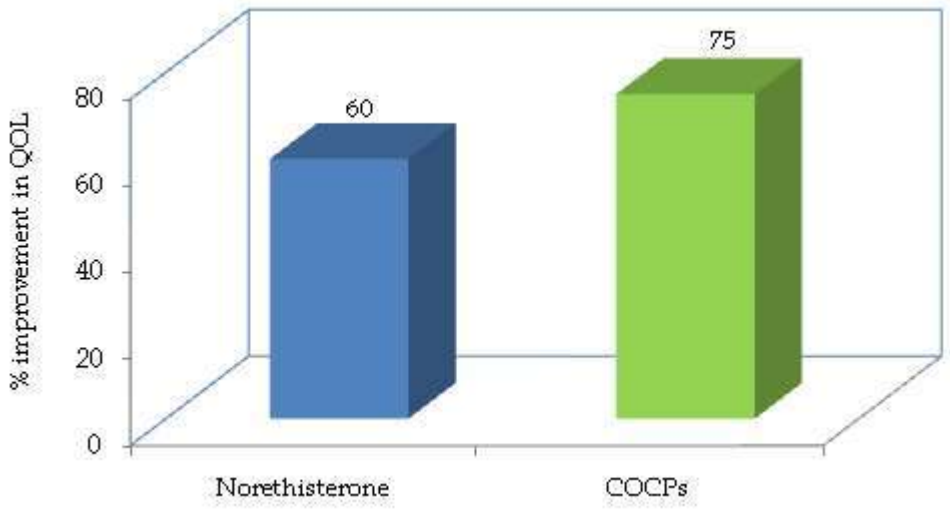
The reduction in menstrual blood loss was observed to be 36.7% (p<0.001) with norethisterone and 37.3% (p<0.001) with COCPs. However, there was no significant difference between the two drugs (Table 4).

Srivaths LV *et al.* [9] proved that significant improvement (p <0.05) was demonstrated by TA and COC in MBL (mean Pictorial Blood Assessment Chart score decrease: TA, 536.4; COC, 430.6) [9].

Table 5: Mean haemoglobin Before and After treatment

Drug	Mean haemoglobin Before Treatment	Mean haemoglobin After Treatment	P value
Norethisterone	9.9 ± 0.94	10.8 ± 1.4	0.022 (S)
COCPs	9.2 ± 0.77	10.5 ± 1.36	0.001 (HS)

There was improvement in mean haemoglobin levels after 3 treatment cycles with norethisterone (p=0.022) and COCPs (p=0.001). P value was highly significant in case of COCPs proving it to be superior than the other drug (Table 5).



Graph 3: Improvement in quality of life

Table 4: Mean PBAC scores

Drug given	Mean PBAC score before treatment	Mean PBAC score after treatment	% reduction in PBAC	P value
Norethisterone	212.85 ± 55.50	134.7 ± 58.23	36.7	<0.001
COCPs	217.8 ± 59.84	136.85 ± 84.32	37.3	<0.001

p>0.05 (NS)

Conclusion

Both COCPs and norethisterone, are effective in reducing the PBAC score with COCPs being the most effective drug. COCPs was the most effective drug in improving the quality of life parameters and in improving the mean haemoglobin. It improved efficacy and safety in the treatment of heavy menstrual bleeding.

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