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Intravaginal danazol effectiveness on menstrual periodes and bleeding volume in heavy menstrual bleeding patients in Medan-Indonesia, graded on a pictorial blood loss assessment chart

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Introduction

Menstrual disorders are common problem of women. Clinical features of menstrual disorders were menorrhagia, metrorrhagia, menometrorrhagia and oligomenorrhagia. Menorrhagia is often associated with hormonal imbalance or it was due to organic disorders such as submucous fibroids. Menorrhagia is defined as menstrual bleeding exceeding normal limits (more than 8 days). This disorder is caused by intrauterine conditions, such as uterine myoma with a broad endometrium surface and with disturbed contractility, endometrium polyps, disturbance in the form irregular endometrium shedding, and other factors. During these events of irregular endometrium shedding observed with endometrium growth disturbance, endometrium growth followed by shedding disturbances during menstrual periods are usually present (3-5). Nearly all women have experienced menstrual disturbance during their life and it is frequently observed in perimenarche and perimenopause aged women (1, 2). Several hormonal and non hormonal treatment of menstrual disorders, especially in the case menorrhagia has advantages and disadvantages. Using danazol can reduced the amount of menstrual bleeding significantly in cases of unexplained menorrhagia. In many studies showed that danazol is more effective to reduce bleeding compared with placebo, mefenamic acid or norethindrone (1, 2). Which is why, Danazol is the first choice in reducing heavy menstrual bleeding, although its use is limited due to certain side effects such as hot flushes, increased body weight, serum glutamic oxaloacetic transaminase and myalgia. Intravaginal Danazol use may reduce these certain side effects. Vaginal administered Danazol is effective in women with menorrhagia, endometrium hyperplasia or endometrial polyp. Oral Danazol use is observed with certain side effects and is significantly androgenic in nature. Most women can not tolerate these side effects (1, 2).

Danazol is an isoxazole derivative of testosterone or a derivative of 17α ethinyl testosterone without estrogen or progestational effects that produce hypoestrogenic or hyperandrogenic as detrimental effect on growth, development and functional endometrial tissue (1, 3). In this recent study, we aimed to use intravaginal danazol administration as an alternative treatment for menorrhagia that prior treatment for menorrhagia conventionally has been treated by oral administered (3, 4).

The efficacy of intravaginal danazol as treatment for menorrhagia was evaluated in order to reduce the number of menstrual days and the amount of menstrual bleeding. The results of this study was expected to show the efficacy of intravaginal danazol as a treatment for women with menorrhagia, in order to consider intravaginal danazol as an alternative treatment for menorrhagia. Therefore, danazol can be an effective treatment for heavy menstrual bleeding. Although in several studies, it still might be limited to use because of the adverse effects, such as hot flashes, weight gain, increase in
serum glutamic-oxalo acetic transaminase, and myalgia. But, the use of danazol by vaginal route can reduce the adverse effects (5).

The two most effective drugs in this category are mefenamic acid and tranexamic acid. Both of these drugs are first-line drugs to treat menorrhagia (3, 5, 6, 8). Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase enzyme system responsible for the conversion of acid into prostaglandins and leukotriena arachidonat. The study conducted since the early 1980s suggested that prostaglandins were involved in the pathogenesis of the number of menstrual blood loss (3, 5, 6). During normal menstrual cycle, active local hemo-stasis occurs in endometrial vascular. Endometrial hemo-stasis was impaired in women with dysfunctional bleeding (3, 5, 6). It was showed by increased of concentrations of fibrinolytic enzymes in the menstrual blood of women with dysfunctional bleeding. Tranexamic acid is used as antifibrinoli-pitic agent for women with menorrhagia. It is a syn-thetic derivative of the amino acid lysine. The comparative studies showed that tranexamic acid is better for reducing menstrual blood loss than NSAIDs, with decreased total menstrual blood loss up to 56% versus 44% and 21% and 24% respectively for flurbiprofen and diclofenac (3, 5, 6). Although endometrial hemo-stasis was impaired in women with dysfunctional bleeding, Ethamsylate, a drug which is believed to reduce capillary fragility and inhibit the prostaglandin pathway is still doubtful efficacy. Therefore, Ethamsylate was no longer recommended as an effective treatment for menorrhagia (3, 5, 6).

Use of hormone therapy did not improve the primary disease, but only leads to control the normal menstrual cycle. The mechanism is influencing the hormonal level limited to the endometrium or mechanism negative feedback to hypothalamic-pitu-tary-ovarian axis (3). Oral contraceptive pills are also effective as treatments for women with menorrhagia. It reduces menstrual blood loss about 50%. Even, only 11% of 518 clinicians who prescribe the COCs in cases of menorrhagia as primary health care medicine (3, 5, 6). Hormone Replacement Therapy (HRT) can be helpful for women in the perimenopausal period to regulate the menstrual cycle and also reduces the effects of hot flush. However, incidence of menorrhagia in women who received HRT is similar with the incidence of women who did not received it. The adverse effects are common, so it also associated with cyclic HRT with additional progestogen agent. The adverse effects included mastalgia, abdominal bloating, headaches and mood swing that may be severe, therefore HRT was limited to use (3, 5, 6). Cyclic progestogen can be used with two different treatment rules. First, low-dose progestogen for 5-10 days in the luteal phase, and second, during the 10-14 days. The use of cyclic progestogen was no significant to reduce the menstrual blood loss (3, 5, 6).

Danazol that is administered by vaginal route is absorbed through:
1. Transcellular, the diffusion depends on the concentration of which can pass through the cells.
2. Paracellular mediated by tight junction.
3. Vesicu-larly or mediated by transport receptors.

More effects of danazol, it can increased the levels of blood clotting factors: prothrombin, plasminogen, antithrombin III, factor VIII and factor IX, resulting in lower rates of bleeding episodes. This study was therefore conducted to determine the effect of Intra Vaginal Danazol use in menorrhagia patients towards menstrual period and the amount of menstrual bleeding.

Methods

Research design

A clinical trials with pre-post test design was conducted to evaluate the efficacy how do you measure efficacy of intravaginal danazol for women with menorrhagia, in order to reduce the number of menstrual days and the amount of menstrual bleeding. The study was conducted at the outpatient gynecology clinics of H. Adam Malik Medan Centre General Hospital; Dr. Pirngadi General Hospital; Halim Fertility Centre and North Sumatera University Teaching Hospitals, all over Medan city began January 2011 to June 2011.

Research subjects

Inclusion criteria were women aged 20-55 years with a menstrual period every month, women with menorrhagia, women with a minimum education level of high school or equivalent, women with high levels of examination hemoglobin ≥ 10 g / dl, women have never smoked, women who do not use drugs: hormonal and tranexamic acid, or at least
has stopped 3 months prior to the study, have no history of: coagulopathy, thromboembolism, hypertension, cerebrovascular disease, heart disease, liver function disorders, endocrine disorders, women who have no history of hormone-dependent malignancies. Exclusion criteria were the woman who for two consecutive days does not consume intravaginal danazol because of intentional or unintentional.
The applied coupled Numeric Variable sample analysis formula is as follows:

\[
N1=N2 = \left[ \frac{(Za + ZB) \cdot SD}{X_1-X_2} \right]^2
\]

Where:
- \( N \) : The similar respondent/coupled sample size
- \( Za \) : One way hypthesis, type 1 error plotted at 5%, resulting \( Za = 1.64 \)
- \( ZB \) : One way hypthesis, type 2 error plotted at 5%, resulting \( ZB = 0.84 \)
- \( SD \) : Standard deviation = ± 1 (literature)
- \( (X_1-X_2) \) : Minimal significant difference (40%=0.4) (literature)

\[
N = \left[ \frac{(Za + ZB) \cdot SD}{X_1-X_2} \right]^2
\]

\[
= \left[ \frac{(1.64) + (0.84) \cdot (1)}{X_1-X_2} \right]^2
\]

\[
= \left( \frac{2.48}{0.4} \right)^2
\]

\[
= (6.2)^2
\]

\[
= 38.44
\]

\[
N = 40 \text{ subjects}
\]

The required study samples is up to 40 samples.

**Intervention**

Pretreatment in the first month, subjects were patients diagnosed as menorrhagia was observed about the number of menstrual days and the amount of menstrual bleeding. After completion of the first menstrual cycle, all subjects are given intervention with intravaginal danazol treatment with dose 200 mg/day for 10 days in each menstrual cycle for two menstrual cycles. Assessment of the number of menstrual days and the amount of menstrual bleeding was measured by the Pictorial Blood Loss Assessment Chart (PBAC). It was recorded by the patient herself. Data was processed by a computerized statistical analysis and presented in the form of a frequency distribution table.

**Statistical analysis**

Statistical significance was \( p\)-value < 0.05 with confidence interval 95%.

**Ethical clearance**

The research is an intervention study / clinical trials with pre-postest design and was approved by the ethical committee of the Faculty of Medicine, University of Sumatera Utara.

**Results**

We obtained menorrhagia cases from 40 women. There were 6 women who dropped out. Four women did not control to the clinic and 2 women are not willing to continue treatment. The oldest ages who fulfill the criteria of study was the age group of 31-35 years and 46-50 years age (20%), whereas the group age of 20-25 years was the youngest age group (5%). Women with age over 50 years was found at 10% cases of menorrhagia were known as perimenopausal disfunctional uterine bleeding. Fohury women with menstrual period data were obtained. Both before and after the treatment was carried out. Before treatment, the longest menstrual period is 10 days (15 women) and the shortest 7 days. The mean of number of menstrual days is 8.83 days. After treatment, either in first or second month, turned out of the 15 women who has 10 days menstrual period reduced to only one respondent. As for the shortest menstrual period in the first month is 4 days and 3 days in the second month. In the first month after the first treatment, the mean of number of menstrual days was decreased from 8.83 days to 6.63 days. In the second month, the mean of number of menstrual days was decreased from 8.83 days to 5.95 days (Fig. 1).
Forty women with menstrual period data were obtained. Both before and after the treatment carried out by PBAC scoring. Before treatment, the average score of PBAC was 201.4. After treatment in the first months, turns out an average score of 103.1 which means the PBAC to be reduced by 98.3 points from before treatment. The average score of PBAC after intravaginal Danazol administration in the second month amounted to 73.7, which mean decreased by 29.4 points from the first month PBAC scores (Fig. 2).

The mean of PBAC score before treatment was $201.4 \pm 57.7$. After intravaginal danazol treatment in the first month was $103.1 \pm 33.23$ and in the second month was $73.7 \pm 34.34$.

There were 6 women (15%) who had weight gain; only 3 women of six women had symptoms i.e. nausea and abdominal bloating, one of them had symptoms i.e. headache and body weakness. On the other side, there was only one of 40 women was exposed with pubic area skin irritation. Three women (7.5%) of 40 women who experienced gastrointestinal disturbances i.e. nausea. The number of subjects who have oily skin and acne were 2 women (5%) (Fig. 3).

**Discussion**

Forty women with menstrual period data were obtained. Both before and after the treatment carried out by PBAC scoring. Before treatment, the average score of PBAC was 201.4. After treatment in the first months, turns out an average score of...
103,1 which means the PBAC to be reduced by 98.3 points from before treatment. The average score of PBAC after intravaginal Danazol administration in the second month amounted to 73.7, which mean decreased by 29.4 points from the first month PBAC scores (Fig. 2).

A clinical trial study showed that the daily intravaginal administration of danazol tablet is efficacious and safe for reducing heavy menstrual bleeding in women with menorrhagia. In addition, this study showed that the use of intravaginal danazol does not affect the hormonal changes and duration of the menstrual cycle. The safety and high compliance of vaginal-administered danazol agree with previous reports of vaginal administration in women with menorrhagia (10, 12).

This is probably due to the elevated uterine pelvic efficacy with limited systemic absorption leading to undetectable serum levels (6). The low dose of vaginal danazol does not affect the pituitary-ovarian axis and dose not modify the endometrial thickness induced by estrogens and progestosterone. In particular, daily administration of a suppository containing 200 mg danazol produces high ovarian and uterine concentrations but low serum concentrations, and no effect was detected on the hypothalamic-pituitary-ovarian axis (15).

Intravaginal danazol resulted efficacy as medical treatment in women with menorrhagia, and because of the lack of significant adverse effects it may be proposed as an alternative medical treatment.

Study limitation

The limitation of this study is the limited time available to conduct this study (from January to June 2011).

Conclusion

Intravaginal danazol can be used as an alternative treatment in women with menorrhagia to reduce the number of menstrual days and the amount of menstrual bleeding with less adverse effects.

References

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