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Running title: Prevention of menstrual migraine

**Prevention of menstrual migraine with perimenstrual transdermal
17- β -estradiol -a randomized, placebo-controlled, double-blind
cross-over study**

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Capsule

In a double-blind, placebo-controlled randomized cross-over trial estradiol treatment was not shown to be superior to placebo in the prevention of menstrual migraine attacks

Abstract

The effect of treatment with percutaneous estradiol (100µg estradiol/24h) during two weeks perimenstrually on the number and severity of menstrual migraine attacks was studied in 27 women in a randomized, placebo-controlled double blind cross over trial. We were not able to demonstrate any difference between estradiol supplementation and placebo on the number or severity of migraine attacks but both regimens showed significant effects compared to pre-treatment.

This study was registered in Clinical Trials.gov: Identification number NCT00204074

Key words: menstrual migraine, estradiol, RCT

After puberty migraine is approximately three times more common in women than in men and approximately 18% of all women of fertile ages suffer from migraine(1).The gender difference of migraine and the nature of menstrual migraine suggest a hormonal trigger. Pure menstrual migraine is defined by the International Headache Society (IHS) as migraine attacks that occur two days before to three days after the onset of bleeding and at no other times of the menstrual cycle. Attacks should be without aura and present in two out of three menstrual cycles (2).

Sommerville concluded that the rapid decrease in serum concentrations of estradiol triggered migraine attacks in certain women. The estradiol drop also requires a preceding high serum concentration of more than a few days to be able to trigger a migraine attack, explaining why estradiol drops after ovulation seldomly are associated with migraine attacks (3, 4). In women with menstrual migraine the stability rather than the concentrations of estradiol might be crucial to avoid and prevent attacks. Treatment may cause stability at low estrogen concentrations either by use of GnRH analogues or danazole (5, 6) or at higher concentrations using combined oral contraceptives or estrogen supplementation perimenstrually (7, 8, 9, 10). There seems to be a dose-response pattern as better results have been reported with use of a higher estradiol dose with also suggest a critical concentration (11).

The aim of this study was to test the hypothesis that a high dose estradiol administered perimenstrually would reduce the number, duration and severity of migraine attacks in women with pure menstrual migraine.

Pure menstrual migraine was defined according to IHS (2). There were two study centers (University Hospital, Linköping Sweden and the County Hospital, Jönköping, Sweden). The women had to be 18-45 years old, otherwise healthy and have regular menstrual cycles (26-30

days). No hormonal contraception was allowed and adequate wash-out periods were demanded if the women had used contraceptive injectables, implants or intrauterine progestin

At the screening visit and end of trial, a thorough general medical examination and a gynecological examination including ultrasound was conducted. Each woman was informed in both writing and orally and thereafter she gave her written informed consent

After screening, the woman filled in a diary prospectively in order to confirm regular menstrual periods and the diagnosis of pure menstrual migraine. An experienced neurologist (AML) confirmed the diagnosis.

The treatment was administered transdermally as two patches with 50µg estradiol/24h (Climara[®], Schering Nordiska AB, Stockholm) or placebo in seven-day patches. Seven days before the estimated onset of the menstrual bleeding the woman started treatment. Two new patches replaced these patches after seven days and were then followed by two weeks without treatment, i.e. two weeks of treatment each menstrual cycle.

This procedure was repeated three times (i.e. during three consecutive menstrual cycles). After one month of wash-out, women crossed-over to the treatment they had not received the first three consecutive cycles (Supplemental material - Flow chart).. The research nurse delivered the patches before the start of each treatment period.

The women recorded menstrual data, use of patches, the number of migraine attacks and severity of the attacks (mild-moderate-severe) (12). A severe attack was defined as an attack that prevented the patient from work or other scheduled activities.

Compliance to treatment was evaluated from unused patch count and the number of migraine attacks each cycle as well as the average number of attacks was calculated.

Statistical evaluation was performed using Wilcoxon's signed-rank test. To be able to detect a difference between treatments of one attack each cycle or one step decrease in severity at a 5% significance level, with a 90% power, 29 patients had to fulfill the treatment. Estimating a 20% dropout rate, 36 patients were planned to be included.

The Regional Ethical review Board in Linköping and the Swedish Medical Products Agency approved the study, which was conducted according to Good Clinical Practice.

A total of 83 patients were screened for inclusion and totally 38 patients were included. Eleven patients were excluded from the study. Three women didn't fulfill the criteria for inclusion and one woman used the patch incorrectly. Six women didn't complete the study because of adverse events (Supplemental material - Flow chart). The women were on average 39,6 years (+/- 4,3) Both estradiol and placebo treatment reduced the number of migraine attacks as compared to pre-treatment. There were, however, no significant differences between estradiol and placebo on the number of migraine attacks or the severity of migraine attacks (table 1). Neither were there any differences in the number of days of sick leave from work between the treatment period and the placebo period.

Patch count yielded a result slightly above 100% due to the fact that some patients used an extra patch because the originally placed patch was lost.

Six women discontinued due to adverse events. Two of these women reported increased headache, two women discontinued because of local skin reactions, one due to nausea and one because of increased blood pressure. One woman became pregnant and was therefore excluded. Two women reported minor disturbances of the menstrual cycle but both these women continued. No serious adverse events occurred.

Table 1. Number of migraine attacks, severity of headache, intensity of attack and sick-leave. Values are presented as median and range. Wilcoxon signed-rank test. Intensity means the patients' subjective rating of the attack including not only headache but also related symptoms such as nausea, vomiting, etc.

	Pre-treatment		Estradiol				
	vs	vs	Pre-treatment	Estradiol	Placebo	Estradiol	
Placebo	Placebo						
Number of menstrual migraine attacks/cycle		1.5 (1-3)	1.0 (0-2)	1.0 (0-2,5)	p=0.0001	p=0.0004	p=0.92
Average severity of headache in migraine attacks/cycle	1.75 (1-3) p=0.96	1.67 (0-3)	1.67 (0-2,5)		p=0.13	p=0.12	
Average intensity of the migraine attacks/cycle		1.5 (1-2,5) p=0.82	1.5 (0-3)	1.6 (0-2,5)	p=0.15		p=0.40

In the present study we were not able to demonstrate any difference between treatment with 100µg transdermal 17β-estradiol or placebo on the number, duration or severity of menstrual migraine attacks.

Both treatments had significant effect on migraine attacks compared to pre-treatment.

The strict inclusion criteria made it difficult to recruit patients. Therefore, we decided to break the code and stop the study when only 27 patients had fulfilled the study. As a consequence, we did not reach the planned sample size and statistical power. However, when estimating two more patients with maximum effect of active treatment, the lack of difference between estradiol and placebo would have remained.

Previous placebo controlled studies have shown conflicting results. Studies of treatment with 25 to 50µg estradiol/24h have failed to demonstrate any effect compared to placebo (9,10, 11). whereas 100µg estradiol/24h have been reported to be effective (11). Also studies using 1,5mg estradiol transdermal gel have reported good effects (7, 8, 13). The serum concentrations of estradiol in women using patches with 100µg estradiol may produce even higher serum concentrations of estradiol (14, 15, 16) than 1,5mg estradiol gel and the lack of difference in results between estradiol and placebo could most probably not be explained by an insufficient dose of estradiol.

MacGregor et al (13) used a fertility monitor to establish the time of ovulation for timing of the treatment. Such a regimen is more reliable concerning the timing but is difficult to use in everyday life. We relied on the women's self reported menstrual data and the pre-treatment

diaries confirmed regular cycles.

The women in our study were treated during a prolonged time (14 days, starting seven days before estimated start of the menstrual bleeding) in order to maintain a higher serum concentration of estradiol and to avoid influence of a variation in cycle length, whereas other studies generally treated women for seven days totally (7, 8, 13). The aim of this regimen was to make sure that serum concentrations of estradiol would be stable at the time of the anticipated start of the bleeding and migraine attacks. This regimen minimizes the risk of insufficient timing of the treatment due to variable menstrual cycle length.

According to IHS-guidelines for controlled clinical trials of drugs in migraine (17) at least 48 hours of freedom from symptoms should have occurred if the headache should be identified as a new migraine attack. Otherwise it should be considered as relapse. In the present study, the exact hour of the onset of the attack was not recorded, only the day and the duration of the attack.

Therefore we have included both new attacks and attacks that maybe could be classified as a relapse. We consider it unlikely that this slight modification should have had any impact on the interpretation of the results as we used the same classification during all cycles and consequently the same method was used for both active and placebo treatment.

In conclusion we found no benefit in treating women with menstrual migraine with transdermal estradiol 100µg/24h versus placebo, however, both treatments improved migraine headache in the group of women studied. The results are in contrast to previous studies.

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Supplemental material. Participant flow-chart.

