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A Randomized Controlled Study of Vitamin D in the Treatment of Primary Dysmenorrhea

Primer Dismenore Tedavisinde Vitamin D ile Randomize Kontrollü Bir Çalışma

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ABSTRACT

Aim: The aim of this study was evaluating the effectiveness of vitamin D in the treatment of primary dysmenorrhea.

Material and Methods: A total of 142 patients between 16 and 35 years of age who were admitted to a university hospital and diagnosed with primary dysmenorrhea were included in the study in a randomized controlled manner. Cases were randomized into three groups of 667 IU vitamin D once a day, 200 IU vitamin E once a day and 400 mg ibuprofen twice a day. The treatment was given two days before the expected date of menstruation and the first three days of menstruation. Treatment was continued in two consecutive cycles. Severity of menstrual pain was measured with Visual Analogue Scale (VAS), as the primary outcome. Need for using nonsteroidal anti-inflammatory drugs (NSAIDs) during two-month study period was evaluated as the secondary outcome.

Results: There were no significant difference in age, body mass index and baseline VAS scores between groups. Pain severity of vitamin D group after treatment was found as low as in the ibuprofen group. Median VAS scores of vitamin D, vitamin E and ibuprofen groups were 5 (1-10), 7 (1-10) and 7 (2-10), respectively after treatment ($p<0.001$). Requirement of NSAIDs was significantly less in vitamin D group than the vitamin E group (27.3% vs 65.9%, $p<0.001$). There were no side effects in groups.

Conclusion: Both vitamin D and E are effective in alleviation the pain of primary dysmenorrhea, however the effect of vitamin D is clearer.

Keywords: Primary dysmenorrhea; vitamin D; menstrual pain.

ÖZ

Amaç: Bu çalışmanın amacı primer dismenore tedavisinde D vitamininin etkinliğini değerlendirmektir.

Gereç ve Yöntemler: Bir üniversite hastanesine başvurmuş ve primer dismenore tanısı alan 16-35 yaş arası 142 hasta randomize kontrollü bir şekilde çalışmaya dahil edilmiştir. Olgular günde bir kez 667 IU D vitamini, günde bir kez 200 IU E vitamini ve günde iki kez 400 mg İbuprofen alacak şekilde üç gruba randomize edildi. Beklenen adet tarihinden iki gün önce ve adetin ilk üç gününde tedavi verildi. Ardışık iki siklüsde tedaviye devam edildi. Birincil sonuç olarak Vizüel Analog Skala (VAS) ile menstrüel ağrının şiddeti değerlendirildi. İkincil sonuç olarak ise iki aylık araştırma süresince Nonsteroidal anti-inflamatuar ilaç (NSAIDs) kullanma ihtiyacı değerlendirildi.

Bulgular: Gruplar arasında yaş, beden kitle indeksi ve bazal VAS skorları açısından anlamlı bir farklılık saptanmadı. Vitamin D grubunda tedavi sonrası ağrı şiddeti, İbuprofen grubundaki kadar düşük bulundu. Tedavi sonrası median VAS skoru D vitamini grubunda 5 (1-10), E vitamini grubunda 7 (1-10) ve ibuprofen grubunda ise 7 (2-10) olarak saptandı ($p<0,001$). NSAIDs kullanma gereksinimi ise D vitamini grubunda, E vitamini grubuna kıyasla anlamlı şekilde daha düşük olarak saptandı (%27,3 vs %65,9, $p<0,001$). Grupların hiç birisinde yan etkiye rastlanmadı.

Sonuç: Primer dismenorede ağrı kontrolünde hem D vitamini hem de E vitamini etkili bulunmuştur, bununla birlikte D vitaminin etkinliği daha açık görülmektedir.

Anahtar kelimeler: Primer dismenore; D vitamini; menstrüel ağrı.

INTRODUCTION

Primary dysmenorrhea is one of the most common gynecologic problems, particularly among adolescent girls. The pain is most severe during the first and/or second day of bleeding and usually lasts up to 72 hours (1). Dysmenorrhoeic pain can spread to the thighs and back, and is usually accompanied by systemic symptoms including gastrointestinal symptoms such as diarrhea, vomiting, and nausea (2). It has been estimated that more than 55-80% of postmenarche women suffer from primary dysmenorrhoea. Thirteen to eighteen percent of them report severe dysmenorrhoea that limits workforce and daily activities (3-5). Primary dysmenorrhoea is the most important cause of recurrent school absenteeism in adolescent girls (6).

Menstrual pain is believed to be related to prostaglandins (7-9). The pathogenic trigger of dysmenorrhoea is associated with excessive uterine production of prostaglandins. Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications in the management of primary dysmenorrhea (10,11).

The presence of vitamin D receptors and synthesizing vitamin D in the human endometrium have been shown (12,13). Several studies have demonstrated an association between vitamin D insufficiency and painful clinical conditions. A pain reducing effect of vitamin D for the uterus is possible by suppressing the synthesis of prostaglandin E2 (14). The production of arachidonic acid and the conversion to prostaglandin, is suppressed by also vitamin E via an action on the enzymes cyclooxygenase and phospholipase A2 (15,16). In pharmacological doses, vitamin therapy has no side effects and is very well tolerated by patients. We investigated whether vitamin D would reduce the pain severity of primary dysmenorrhoea.

MATERIAL AND METHODS

Two hundred women aged between 16 and 35 years were recruited from outpatient clinics of the Department of Obstetrics and Gynecology at Bezmialem University, İstanbul between November 2012 and October 2013. This study was approved by the local Ethics Committee of the Bezmialem University (28.01.2013 and 31/16) and informed consent was obtained from each participant.

Eligible participants met the following inclusion criteria: 1) Women had normal menstrual periods lasting 21 to 35 days, with menstruation lasting 3 to 7 days; 2) Women had to be healthy and taking no medications including vitamin, magnesium, calcium and oral contraceptives. 3) Women who had no history of gynecological disease, and had a normal pelvic examination and 4) Current and previous use of intrauterine devices for contraception within 6 months to registrated were not allowed (17). Women whom had pelvic surgery history were excluded.

A total of 200 women were identified. Forty-six of them refused to participate and 154 were randomized. Participants were randomly assigned to the treatment groups. Six women were lost to up and six women discontinued the medication. Finally, the analysis was conducted with 142 women; 55 in vitamin D group, 44 in vitamin E group, and 43 in ibuprofen group (Figure 1).

Severity of dysmenorrhoeic pain was determined based on each women's self-perception of the pain. Women were asked to mark on a 10 cm visual analogue scale (VAS) anchored from "no pain at all" to "the worst pain I have ever felt" to indicate the severity of dysmenorrhoeic pain. Women who remarked their menstrual pain as >6 cm on the VAS were considered as severe dysmenorrhoeic pain (18). Use of NSAIDs was allowed and it had to be registrated.

Participants were randomized into 3 groups by simple randomization using random numbers table. Fifty-five women were given 667 UI of vitamin D once a day, 44 women were given 200 IU of vitamin E once a day, and 43 women were given 400 mg ibuprofen twice a day beginning from two days before the expected date of menstruation and continuing throughout the first three days of bleeding. Treatment was continued for two following menstrual cycles.

The primary outcome was the severity of menstrual pain measured by a VAS. The secondary outcome was use of NSAIDs during two-month study period of the investigation.

Statistical Analysis

Data were analyzed by IBM® SPSS 17 statistics software. Normality assumption of continuous data were examined using Kolmogornov-Smirnov test. Statistical comparisons between groups were determined using Kruskal-Wallis test. Wilcoxon signed rank test was used for determining the variation of VAS scores before and after drug regimen for each group. Categorical variables were analyzed using Pearson Chi-Square test. Statistical significance level was considered as 0.05.

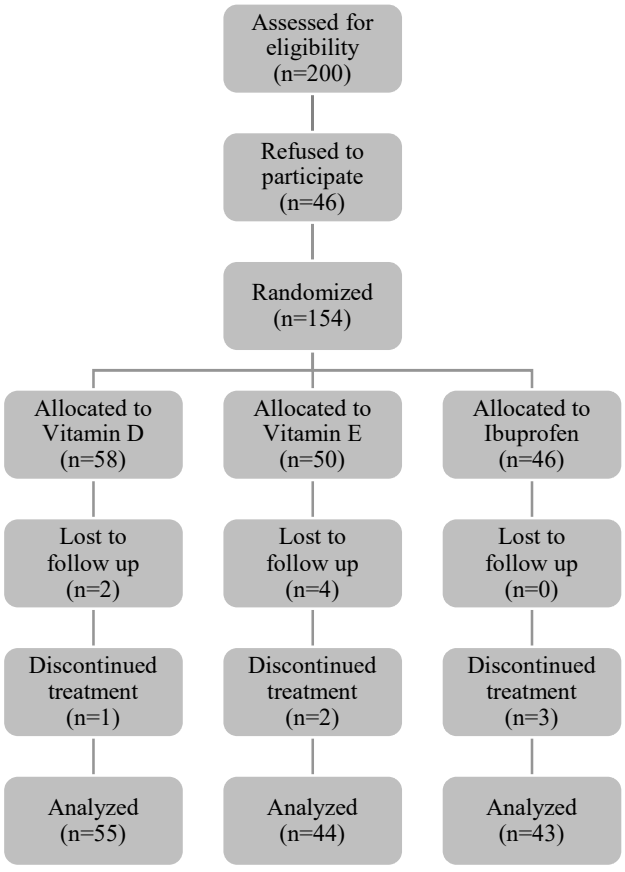

Figure 1. Flow diagram

RESULTS

The median age were 22 (16-33) in vitamin D group, 21 (17-27) in vitamin E group and 20 (16-35) in ibuprofen group. The median body mass index (BMI) was detected as 20.7 (16.1-33.5) in vitamin D group, while 21.4 (16.6-28.6) in vitamin E group, and 20.7 (18.2-27.2) in ibuprofen group. The median baseline VAS score were 9 (6-10) in vitamin D group, 8 (6-10) in vitamin E group, and 8 (6-10) in ibuprofen group. There were no significant difference in terms of age, BMI and baseline VAS scores between the three groups (Table 1).

Requirement of NSAIDs was significantly lower in vitamin D group than the vitamin E group (n=15, 27.3% vs n=29, 65.9%, p<0.001). We found significant decrease of pain severity both in the vitamin D and vitamin E groups but the reduction was greater in the vitamin D group. The median VAS scores after treatment were 5 (1-10) in vitamin D group, 7 (1-10) in vitamin E group, and 7 (2-10) in ibuprofen group (p<0.001; Table 2).

DISCUSSION

Primary dysmenorrhoea is among the most common menstrual disorders, occurring in at least 50% of reproductive-age women (11). It is also among the most common reason for work discontinuity in young women.

Dysmenorrhoeic pain derives from prostaglandins, which control vasoconstriction and myometrial contraction. Oral contraceptives and NSAIDs are effective at reducing pain in many women, but these drugs have some side effects (19). Women may need alternative treatment choices with fewer adverse effects. Use of vitamin D in these patients may allow for a reduced usage of NSAIDs.

Vitamin D receptor is present in many tissues including parathyroid glands, skeleton, and the reproductive tissues. This nuclear receptor activates transcription of over 900 genes (20,21). The reduction in the pain could be attributed to the action of vitamin D on the endometrium with a decrease in prostaglandin synthesis and an increase in prostaglandin inactivation by suppression of cyclo-oxygenase 2 and up-regulation of 15-hydroxyprostaglandin dehydrogenease, respectively. Vitamin D has also different anti-inflammatory effects, such as increasing mitogen activated protein kinase phosphatase 5 activity and inhibiting nuclear factor-β signaling, thus blocking cytokine production via p38 activation (22).

We have shown that vitamin D has a role in reducing the intensity of menstrual pain like vitamin E and ibuprofen. Intake of vitamin D significantly reduced the requirement for NSAIDs.

The effect of vitamin D on dysmenorrhoea and in other menstruation related conditions including premenstrual syndrome, endometriosis and fibromyalgia has been evaluated previously (22,23). The association and effects of vitamin D on endometriosis have been investigated recently because endometriosis often behaves like a malignant disease and carries several characteristics of an autoimmune disease. A recent study with 104 endometriosis cases (61.7% of cases have severe dysmenorrhea) showed that women with endometriosis have lower vitamin 25-OH D levels than healthy women in reproductive age. Furthermore, inadequate vitamin D levels were significantly correlated with the presence of pelvic pain in various degrees (24).

Bahrami et al (25) evaluated the effect of 50,000 IU/week vita-min D supplementation on premenstrual syndrome and dysmenorrhoea subjects. They found significantly reduction in the incidence and severity of symptoms. Karacin et al (26) demonstrated in their study that the positive correlation between VAS scores and vitamin D levels and the reduction in serum vitamin D levels of the dysmenorrhoea patients were statistically significant. Therefore, they claimed the possible role of vitamin D deficiency in the primary dysmenorrhoea.

Table 1. Baseline characteristics of the women with primary dysmenorrhoea

	Vitamin D n=55		Vitamin E n=44		Ibuprofen n=43		p
	Median (Min-Max)	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	Mean±SD	
Age	22 (16-33)	23.4±5.6	21 (17-27)	21.2±2.8	20 (16-35)	20.4±4.8	0.357
BMI	20.7 (16.1-33.5)	21.4±3.7	21.4 (16.6-28.6)	21.8±2.8	20.7 (18.2-27.2)	21.4±2.7	0.546
VAS	9 (6-10)	8.5±1.2	8 (6-10)	8.2±1.3	8 (6-10)	8.1±1.3	0.470

Min: Minimum, Max: Maximum, SD: Standard Deviation, BMI: Body Mass Index, VAS: Visual Analogue Scale

Table 2. VAS scores after drug regimen for each group

	Vitamin D n=55		Vitamin E n=44		Ibuprofen n=43		p
	Median (Min-Max)	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	Mean±SD	
VAS-1	9 (6-10)	8.5±1.2	8 (6-10)	8.2±1.3	8 (6-10)	8.1±1.3	0.470
VAS-2	5 (1-10)	4.9±2.4	7 (1-10)	6.5±2.1	7 (2-10)	4.0±1.1	0.641
p	<0.001		<0.001		<0.001		

Min: Minimum, Max: Maximum, SD: Standard Deviation, VAS-1: Visual Analogue Scale before treatment, VAS-2: Visual Analogue Scale after treatment

Lasco et al (17) and Ziaei et al (27,28) observed the effects of vitamin E and vitamin D versus placebo on dysmenorrhoea. They reported lower pain scores in the vitamin arms than the placebo arms. We used ibuprofen and identified that vitamin D and E could reduce menstrual pain almost as much as ibuprofen.

Strengths and Limitations

The main strength of this study is that we did not use a single high dose (300.000 IU) of vitamin D therapy for two months compared to Lasco et al. (17). If we administered their suggested dose, the average daily vitamin D intake would remain above the tolerable upper intake level set by the Institute of Medicine of 4000 IU/d. There are a few limitations of our study. First; the small number of our study population sample means our results should be considered with caution. Since this study was conducted in only one university hospital, results cannot be extended to other countries or other regions of Turkey. Second; vitamin D levels in our study population could not be measured before and after treatment due to the health insurance company not funding this endeavor.

CONCLUSIONS

We demonstrated that vitamin D can be a treatment option with fewer adverse effects for primary dysmenorrhoea. Further investigation should determine the functionality of vitamin D on primary dysmenorrhoea.

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