International Journal of
Reproductive Medicine & Gynecology

Research Article

# Vitamin D Supplements as Adjunctive Therapy with Analgesics for Primary Dysmenorrhea: A Randomized Clinical Trial -

**Alshaigi Lama[1], Alshamrani Najla[1], AlKhayrat Azzah[1], Algodair Areej[1], Elkattan Alaa[2], Alsuwaidan Salem[3]***

*[1]College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia*
*[2]Consultant Endocrinologist, Security Forces Hospital, Riyadh, Saudi Arabia*
*[3]Research consultant, Health Science Research Center, Princess Nourah bint Abdulrahman University, Riyadh, Kingdom of Saudi Arabia (KSA)*

***Address for Correspondence:** Alsuwaidan Salem, Health Science Research Center, Princess Nourah bint Abdulrahman University, Riyadh, Kingdom of Saudi Arabia (KSA), Tel: +966-545-566-722; E-mail: alraces@hotmail.com

**Submitted:** 03 April 2019; **Approved:** 08 May 2019; **Published:** 10 May 2019

**Cite this article:** Lama A, Najla A, Azah A, Areej A, Salem A, et al. Vitamin D Supplements as Adjunctive Therapy with Analgesics for Primary Dysmenorrhea: A Randomized Clinical Trial. Int J Reprod Med Gynecol. 2019;5(1): 004-014.



ISSN: 2640-0944

## ABSTRACT

**Objective and aim:** The primary aim of this study is to evaluate the effectiveness of vitamin D combined with analgesics versus analgesics alone in treating primary dysmenorrhea. Also to evaluate the effect of vitamin D supplement on pain length during menstruation.

**Methodology:** Pain severity was measured by visual analog scale (VAS), and serum vitamin D was measured by electrochemiluminescence method.

**Results:** Pain severity measured by VAS scale showed a significant decreased in the treatment group compared to baseline readings while in the control group remains with no change. It is found that (82%) of the treatment group reported a significant decrease in pain length compared with the control group.

**Conclusion:** The choice of analgesics in combination with vitamin D supplements, showed an additive effect in reducing pain severity. It is found that pain severity is negatively correlated with vitamin D level where the use of analgesics reduced considerably when vitamin D supplements were added. Also, a number of women in the control group reported that they stopped using analgesics by the end of the study. This result suggests that prescribing vitamin D supplements with or without analgesics will diminish pain severity in women with primary dysmenorrhea.


**Keywords:** Dysmenorrhea; Vitamin D; Visual analogue scale (VAS); Non-Steroidal Anti-Inflammatory Drugs (NSAIDs); Menstrual pain

## INTRODUCTION

Dysmenorrhea is the most common gynecologic problem in women, and it is divided into primary and secondary dysmenorrhea [1,2]. Primary dysmenorrhea is painful menstruation in the absence of any concomitant diseases in the pelvis unlike to the secondary, which is associated with an evident disease [2]. The duration of the painful menstruation is varied, however, it becomes less common as women age [3]. The pain severity varies from mildly irritating to incapacitating pain [4]. The pain is frequently accompanied by systemic symptoms such as nausea, vomiting, diarrhea, fatigue, and insomnia [5].

The prevalence of dysmenorrhea around the world is high ranging from 45% to 95% [2] compared to the prevalence of dysmenorrhea in Saudi women ranging from 54%-96.3% [6,7]. Moreover, one study found that 39.6% of Saudi women experienced pain occasionally [8].

There are some risk factors found to be associated with primary dysmenorrhea such as having a family history of dysmenorrhea, younger age, heavy menstrual flow [8,9], history of depression [10] and low body mass index [11].

Unbalanced diets such as low in dairy, vegetables and fruits or high intake of caffeine, and sugar were related to the increased risk of dysmenorrhea [11,12].

The diagnosis of dysmenorrhea is based on the medical history of the lady; an internal pelvic examination may be necessary for adolescent girls, using vaginal ultrasound to determine the exact condition [13]. Primary dysmenorrhea thought to be caused by excessive levels of uterine neuroactive peptides such as Prostaglandins (PGs), especially PGF2? [14].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are commonly the first-line therapy for dysmenorrhea, as it reduces the release of prostaglandins levels by the inhibition of cyclooxygenase-2. NSAIDs such as aspirin, naproxen, and ibuprofen are very effective in relieving dysmenorrhea [14]. However, NSAIDs have troubled side effects most commonly is the increased risk of gastrointestinal events [15]. The choice of using NSAIDs as the first line treatment should be based on effectiveness and tolerability of the individual patient since there is no NSAID that has been demonstrated more effective than others [16].

Vitamin D is a fat-soluble vitamin, synthesized in the skin in the presence of sunlight [17]. Vitamin D deficiency is common in healthy Saudi adults and it is more pronounced in females and in the younger age groups [18]. Recent studies showed efforts on the possibility of vitamin D in treating dysmenorrhea [19-21]. The possible mechanism for vitamin D in the treatment of dysmenorrhea is the anti-inflammatory effects mediated by reduced cytokines such as interleukin 6 and tumor necrosis factor and by decreasing the release of Prostaglandins [19].

The first study investigated the efficacy of vitamin D with a single dose of 300,000 IU/mL as a treatment for primary dysmenorrhea, shown by Lasco et al. 2012, this study showed a significant reduction of pain in vitamin D group compared to the placebo group [19]. The other clinical trial found that vitamin D supplementation with a weekly regimen of 50,000 IU for 8 weeks could improve dysmenorrhea and reduce the need for using NSAIDs in patients with dysmenorrhea and vitamin D deficiency [20].

## OBJECTIVE AND AIM

The primary aim of this study is to evaluate the effectiveness of vitamin D combined with analgesics versus analgesics alone in treating primary dysmenorrhea, among women with vitamin D deficiency.

Other objectives of this study were to evaluate the effect of vitamin D on pain length during menstruation and the use of analgesics in comparison to control group.

## MATERIALS AND METHODS

This is a randomized open-label clinical research; the physician and the participants were aware of the study groups, it was conducted after the approval of the ethics committee at security forces hospital. A written informed consent form was obtained from 26 women aged between 13-40 years complaining of primary dysmenorrhea. The inclusion criteria for this study include women with primary dysmenorrhea, using analgesics (either NSAIDs or acetaminophen) during menstrual cycles, and Vitamin D deficiency (Normal range 75 nmol - 250 nmol). The exclusion criteria were those using contraceptives within the past two months, previous and current intrauterine device within the past six months, and those ladies using supplements containing calcium or vitamin D within the past six months.

Eligible women included in this study were randomly allocated to either treatment or control group. Women in the treatment group (11 patients) received 50,000 IU vitamin D orally once weekly for

8 weeks, in addition to their usual analgesics regimen. The control group (11 patients) remained on the same analgesics regimen they were using. The analgesic regimen for both groups was either any type of NSAIDs or acetaminophen. A questionnaire in the Arabic language including demographic information was completed at baseline for all participants.

The menstrual pain severity and Vitamin D level were measured monthly prior, throughout and at the end of the trial during follow-up visits. Pain severity was measured by Visual Analog Scale (VAS). VAS is a 6-category pain scale ranged from (0-10) where 0 indicates no pain and 10 indicates very severe pain. Serum vitamin D was measured by electrochemiluminescence method.

Statistical analysis was performed by SPSS version 24.0 using independent sample t-test to compare means and descriptive frequencies to compare frequencies. A *P*-value of (< 0.05) was considered significant.

## RESULTS

Twenty-six women with primary dysmenorrhea aged 13-40 years were included in this study, four of them were excluded; two women did not continue using vitamin D properly, one woman was unwilling to continue follow-up visits and one woman became pregnant. Participants were randomly allocated into two arms namely treatment group (n = 11) and control group (n = 11). The characteristics (age, vitamin D level, pain severity, and duration of pain) were almost the same in both groups. Pain severity (measured by VAS) categorized as mild (1-3), moderate (4-6), severe (7-10) or no pain (0).

The treatment group showed a significant difference in pain severity after they received vitamin D supplements in comparison with the control group who remained on their usual analgesics regimen with no significant difference in pain severity. By using independent-sample t-test, at the end of the trial there was a significant increase in vitamin D level in the treatment group (80.2 ± 14.3 SD) compared to (30.1 ± 13.4 SD) at baseline, but not in control group (47.7 ± 11.3 SD) compared to their baseline (33.9 ± 11.9 SD) with ($P < 0.001$) (Figure 1). In addition, pain severity measured by VAS scale, found that decreased in the treatment group (3.6 ± 1.2 SD) compared to (7.8 ± 1 SD) at baseline while in the control group (6.4 ± 1.1 SD) and (6.9 ± 1.2 SD) at the end of the study and at baseline respectively with ($P < 0.002$) (Figure 2). Description of pain severity for the treatment group compared to the control group before treatment (as baseline) and after treatment (at the end of the trial) is shown in (Table 1).

Most of the women in this study were using NSAIDs (n = 18) in both groups and four women were using acetaminophen to overcome the pain. It has been found from the treatment group that 45.5% of women stopped analgesics in the follow-up visit and 64% of women stopped analgesics at the end of the study. On the other hand, it has been found that 36.4% and 45.5% from the control group stopped using analgesics by the follow-up visit and at the end of the study respectively.

Regarding pain length during menstruation, which is measured by days. It was found that 9 women (82%) out of 11 women from the treatment group reported pain length of more than two days at baseline while at the end of the study the number decreased to only 2 women (18.2%). In the control group, 6 (54.5%) women remained suffering from pain for more than two days in comparison to 8 (73%) at baseline.

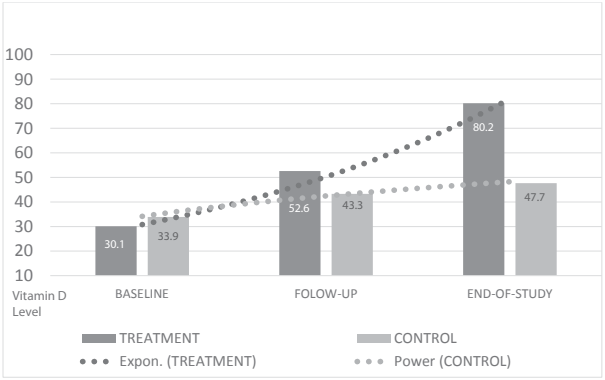


**Figure 1:** Average of Vitamin D level of treatment and control groups throughout the study.

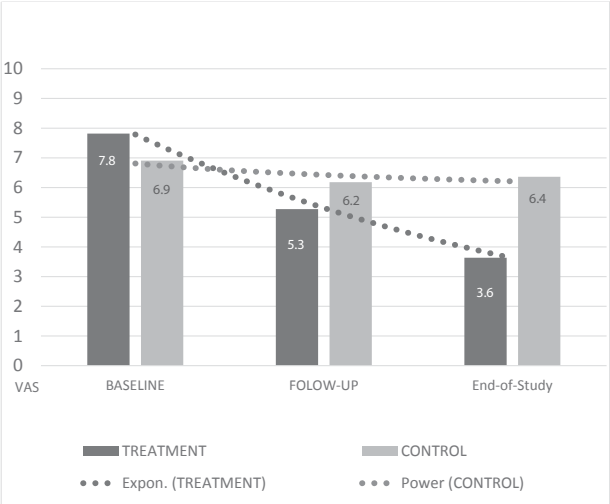


**Figure 2:** Average of Pain severity (0-10) for both groups (control and treatment) throughout the study.

## DISCUSSION

In this study, the authors found that vitamin D in combination with analgesics is superior to the use of analgesics alone as a therapy for primary dysmenorrhea in women with vitamin D deficiency.

Pain severity indicated by VAS was reduced from almost 8 at baseline to about 3.5 at the end of the study in the treatment group. While in the control group pain severity remained the same throughout the study (Figure 1).

The standard care treatment of vitamin D deficiency is to prescribe 50,000 IU vitamin D orally once weekly for 2 to 3 months [22]. Considering all patients participated in this study that they have had a low level of vitamin D at the baseline, we kept the treatment group on 50,000 IU vitamin D orally once weekly during the length of the study. The results in (Figure 1) shows that vitamin D level in the treatment group is increasing toward normal levels after 2 months of treatment while this is not the case in the control group with a slight or no increment on vitamin D level.

The association between pain severity and vitamin D level is inversely correlated. In comparison between (Figure 1 and 2), which show that at baseline when vitamin D level was low the pain severity

**Table1:** Description of pain severity at baseline and at the end of trial in both study groups.

| | Treatment group | | Control group | |
|---|---|---|---|---|
| **Pain severity** | **Baseline** | **End of trial** | **Baseline** | **End of trial** |
| Severe | 7 women (63.6%) | 3 women (27.3%) | 6 women (54.5%) | 5 women (45.5%) |
| Moderate | 4 women (36.4%) | 2 women (18.2%) | 4 women (36.4%) | 4 women (36.4%) |
| Mild | None | 4 women (36.4%) | 1 woman (9%) | 1 woman (9%) |
| No pain | None | 2 women (18.2%) | none | 1 woman (9%) |

was the highest in contrast with what we found at the end of the study. This relationship between Vitamin D level and dysmenorrheal pain severity has been found in previous studies which support our finding [20,21].

The choice of analgesics for relieving dysmenorrhea depends on the preference of each woman and the majority of them were using NSAIDs. In combination with vitamin D supplements, which believed to have an anti-inflammatory effect, together they showed an additive effect in reducing pain severity [19]. Since analgesics are considered the predominant therapy used for dysmenorrhea, we compared the use of vitamin D supplements and analgesics versus analgesics alone. Unlike the previous studies, which compared vitamin D supplement versus placebo [19,20].

Pain length was reduced greatly in the treatment group at the end of the study compared with pain length at baseline; it has been also noticed a slight reduction in the control group at the end of the study. There were few studies investigating the relationship between vitamin D and the menstrual cycle. In one study, increasing vitamin D level was associated with half the odds of having long menstrual cycles [23]. While another study found that lower levels of vitamin D may influence menstrual cycle irregularity [24].

It is suggested that any improvement found in the control group might be due to the effect of season changes while the study was conducted [25]. Other suggestions are that some of the women in this study were affected by the implementation of a healthy lifestyle such as diet and exercise [5].

By the end of the study, it has been found that the use of analgesics in the treatment group reduced considerably when vitamin D supplements were added. Number of women in the treatment group reported that they stopped using analgesics by the end of the study. This study confirmed the results of previous studies to change the trend of treatment for dysmenorrhea. Prescribing Vitamin D 50,000 IU vitamin D orally once weekly along with analgesic for three months should be the trend of treatment. This is the same recommendations from previous studies that vitamin D or without analgesic therapy could have a significant decrease in pain and symptoms [26-28].

## CONCLUSION

Based on this study, we found that pain severity is negatively correlated with vitamin D level. This result suggests that prescribing vitamin D supplements with or without analgesics will diminish pain severity in women with primary dysmenorrhea and vitamin D deficiency.

## ACKNOWLEDGMENTS

We would like to express our deep gratitude to Prof. Eitedal M. Fouda who inspired us and for her encouragement. The completion of this study could not have been possible without the assistance of Dr. Amal Al Najar. Also, we would like to thank our Research Center at Princess Nora University especially Dr. Ashraf El Metwally who assisted us in data analysis. Finally, we owe a great thanks to our colleagues who helped at the beginning and was very generous with us Basmah Al Qahtani and Eman Mahnashi.

## REFERENCES

1. Osayande AS, Mehulic S. Diagnosis and initial management of dysmenorrhea. Am Fam Physician. 2014; 89: 341-346. https://bit.ly/2FWCKfX
2. Proctor M, Farquhar C. Diagnosis and management of dysmenorrhea. Bmj. 2006; 332: 1134-1138. https://bit.ly/2DVctQy
3. Patel V, Tanksale V, Sahasrabhojanee M, Gupte S, Nevrekar P. The burden and determinants of dysmenorrhea: a population-based survey of 2262 women in Goa, India. BJOG. 2006; 113: 453-463. https://bit.ly/2DYP6pc
4. Nasir L, Bope ET. Management of pelvic pain from dysmenorrhea or endometriosis. J Am Board Fam Pract. 2004; 17: 43-47. https://bit.ly/2vI98j6
5. Iacovides S, Avidon I, Baker FC. What we know about primary dysmenorrhea today: a critical review. Hum Reprod Update. 2015; 21: 762-778. https://bit.ly/2JkeDfY
6. Shaji JCH. Severity of primary dysmenorrhea and menstrual distress among university students in kingdom of Saudi Arabia. Int J Health Sci Res. 2014; 4: 209-215. https://bit.ly/2JoFirR
7. Karout N. Prevalence and pattern of menstrual problems and relationship with some factors among Saudi nursing students. Journal of Nursing Education and Practice. 2015; 5. https://bit.ly/2Jmccte
8. Aldayel A, Alshaigi L, Alsuwandi M, Alshamrani N, Alkhayrat A, Alsuwaidan S. Prevalence of Dysmenorrhea in Saudi Arabia: A cross-sectional study. Under process.
9. Hailemeskel S, Demissie A, Assefa N. Primary dysmenorrhea magnitude, associated risk factors, and its effect on academic performance: evidence from female university students in Ethiopia. Int J Womens Health. 2016; 8: 489-496. https://bit.ly/2H7Zuww
10. Sahin N, Kasap B, Kirli U, Yeniceri N, Topal Y. Assessment of anxiety-depression levels and perceptions of quality of life in adolescents with dysmenorrhea. Reprod Health. 2018; 15: 13. https://bit.ly/2H4Pa7A
11. Ozerdogan N, Sayiner D, Ayranci U, Unsal A, Giray S. Prevalence and predictors of dysmenorrhea among students at a university in Turkey. Int J Gynaecol Obstet. 2009; 107: 39-43. https://bit.ly/2YgKqmd
12. Abdul-Razzak KK, Ayoub NM, Abu Taleb AA, Obeidat BA. The influence of dietary intake of dairy products on dysmenorrhea. J Obstet Gynaecol Res. 2010; 36: 377-383. https://bit.ly/2Va4y7E
13. Wilson CA, Keye WR. A survey of adolescent dysmenorrhea and premenstrual symptom frequency. J Adolesc Health Care. 1989; 10: 317-322. https://bit.ly/2WxjCO3
14. Bernardi M, Lazzeri L, Perelli F, Reis FM, Petraglia F. Dysmenorrhea and related disorders. F1000Research. 2017; 6: 1645. https://bit.ly/2VPS61c
15. Arroyo M, Lanas A. NSAIDs-induced gastrointestinal damage. Review. Minerva gastroenterologica e dietologica. 2006; 52: 249-59. https://bit.ly/2VksBpk
16. Marjoribanks J, Ayeleke RO, Farquhar C, Proctor M. Nonsteroidal anti-inflammatory drugs for dysmenorrhea. Cochrane Database Syst Rev. 2015; 7: 1751. https://bit.ly/2VLqHxv
17. Helde Frankling M, Bjorkhem Bergman L. Vitamin D in Pain Management. Int J Mol Sci. 2017; 18: 2170. https://bit.ly/2PS6b8L

18. Alsuwadia AO, Farag YM, Al Sayyari AA, Mousa DH, Alhejaili FF, Al Harbi AS, et al. Prevalence of vitamin D deficiency in Saudi adults. Saudi Med J. 2013; 34: 814-818. https://bit.ly/2PVzJlZ

19. Lasco A, Catalano A, Benvenga S. Improvement of primary dysmenorrhea caused by a single oral dose of vitamin D: results of a randomized, double-blind, placebo-controlled study. Arch Intern Med. 2012; 172: 366-367. https://bit.ly/2H9LoLs

20. Moini A, Ebrahimi T, Shirzad N, Hosseini R, Radfar M, Bandarian F, et al. The effect of vitamin D on primary dysmenorrhea with vitamin D deficiency: a randomized double-blind controlled clinical trial. Gynecol Endocrinol. 2016; 32: 502-505. https://bit.ly/2H8nXAF

21. Karacin O, Mutlu I, Kose M, Celik F, Kanat Pektas M, Yilmazer M. Serum vitamin D concentrations in young Turkish women with primary dysmenorrhea: A randomized controlled study. Taiwan J Obstet Gynecol. 2018; 57: 58-63. https://bit.ly/2VMgPDF

22. Pepper K, Judd S, Nanes M, Tangpricha V. Evaluation of Vitamin D Repletion Regimens to Correct Vitamin D Status in Adults. Endocr Pract. 2009; 15: 95-103. https://bit.ly/2Yjpuet

23. Jukic AMZ, Upson K, Harmon QE, Baird DD. Increasing serum 25-hydroxyvitamin D is associated with reduced odds of long menstrual cycles in a cross-sectional study of African American women. Fertil Steril. 2016; 106: 172-179. https://bit.ly/2PTeKAv

24. Jukic AM, Steiner AZ, Baird DD. Lower plasma 25-hydroxyvitamin D is associated with irregular menstrual cycles in a cross-sectional study. Reprod Biol Endocrinol. 2015; 13: 20. https://bit.ly/2H8o9zT

25. Praschak Rieder N, Willeit W, Neumeister A, Hilger E, Stastny J, Thierry N, et al. Prevalence of premenstrual dysphoric disorder in female patients with seasonal affective disorder. J Affect Disord. 2001. 63; 239-242. https://bit.ly/2Wtr3pq

26. Zeynali M, Haghighian HK. Is there a relationship between serum vitamin D with dysmenorrhea pain in young women. J Gynecol Obstet Hum Reprod. 2019: 2468-7847: 30434-30443. https://bit.ly/2JpZAkI

27. Kucukceran H, Ozdemir O, Kiral S, Berker DS, Kahveci R, Ozkara A, et al. The impact of circulating 25-hydroxyvitamin and oral cholecalciferol treatment on menstrual pain in dysmenorrheic patients. Gynecol Endocrinol. 2019; 35: 53-57. https://bit.ly/2DYRiNs

28. Bahrami A, Avan A, Sadeghnia HR, Esmaeili H, Tayefi M, Ghasemi F, et al. High dose vitamin D supplementation can improve menstrual problems, dysmenorrhea, and premenstrual syndrome in adolescents. Gynecol Endocrinol. 2018; 34: 659-663. https://bit.ly/2VQSlcf