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Review Article

Investigating the Effect of Boron Supplements on the Severity of Systemic Symptoms associated with Primary Dysmenorrhea, the Need for Painkillers, and Disruption of Daily Activities: A Clinical Trial Study -

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ABSTRACT

Background: Primary dysmenorrhea is one of the most common problems of women, that treatment is non-steroidal anti-inflammatory drugs. The Boron supplement has anti-inflammatory effects.

Objectives: Due to the lack of such study in Iran, this study was to determine the effects of boron supplement on systemic symptoms associated with primary dysmenorrhea, need to analgesic and disruption in daily activity.

Methods: A triple blind clinical trial was conducted on 113 students. Samples after matching the intensity of dysmenorrhea were randomly divided into two groups. For boron group ($n = 58$) was administered one capsules containing 10 mg of boron for a period of 2 days prior to the third day of bleeding and placebo group ($n = 55$) treated with similar capsules containing lactose with the same instruction. Systemic symptoms were compared and follow-up with verbal multidimensional questionnaires. Data obtained were analyzed by using Friedman test, Mann-Whitney, Wilcoxon and Fisher.

Results: In both groups, the systemic symptoms of dysmenorrhea, need for analgesics, disruption in daily activities decreased after the intervention than before the intervention, except in cases of diarrhea this decrease was statistically significant in after intervention between the two groups ($p < 0.05$).

Conclusions: According to the results, boron supplement were effective in reducing systemic symptoms associated with dysmenorrhea, work dysfunction and need for analgesic. Further studies are recommended with boron supplement to find more applications in obstetrics and gynecology.

Keywords: Systemic symptoms of dysmenorrhea; Boron supplement analgesic

BACKGROUND

Dysmenorrhea is one of the most common problems among women [1] referring to the pain of menstruation which is divided into two types: primary and secondary. Primary Dysmenorrhea occurs as the result of ovulatory cycles with the absence of detectable pelvic diseases, while secondary Dysmenorrhea is associated with pelvic pathological problems [2]. Primary dysmenorrhea is usually accompanied by nausea, vomiting, sweating, tachycardia, diarrhea, lethargy, dizziness and breast tenderness [3]. Mental tensions also happen in addition to physical problems, so that fatigue, depression, and inability to concentrate at work have been reported as three common symptoms that appear the day before and at the first day of menstruation. Headache and loss of appetite are among the eighth common symptoms [4]. The prevalence of dysmenorrhea is about 30-90 percent [3]. According to an epidemiological study in Iran, the prevalence of dysmenorrhea among teen girls is reported to be 91% [5]. Severity of dysmenorrhea in 10% of young women is such that it leads to their disability to participate in the activities at school, work, home, and social interaction during the first 3 to 4 days of menstrual [6].

Increase of Prostaglandins is one of the main causes of dysmenorrhea [7]. Increase of Prostaglandins and cytokines occurs in response to the drop in progesterone at the end of luteal phase, however cytokines themselves stimulate the production of prostaglandins [2].

Levels of Nitric oxide and interleukin-6 are higher in women with primary dysmenorrhea than healthy ones [8]. Furthermore, the expression of proinflammatory cytokines gene such as interleukin-1 beta, 6 and 8 increases in women with primary dysmenorrhea [9].

Regarding the pathophysiology of dysmenorrhea, NSAIDs are effective in the treatment of dysmenorrhea, although these drugs are contraindicated in some patients and have side effects [7].

In recent researches, special attention have been paid on CAM (Complementary and Alternative Medicine) in the treatment of primary dysmenorrhea [10]. Various supplements are effective in reducing menstrual pain [11] such as Boron which is approved

by Food and Drug Administration (FDA) of the USA [12]. Daily consumption of boron for most adults is about 1-3mg [13] and the maximum recommended dose for adults older than 19 years is about 20mg per day. Since boron is an essential component in the structure of plant cell walls, all the products of plant origin contain boron. Nuts and vegetables are richer than crops and fruits in terms of boron concentration [12]. Boron consumption can positively affect human health such as its role in calcium metabolism and bone growth [14-16], increasing brain function, preventing various types of cancer [12,17,18], setting the steroid hormones [19], kidney stone repulsion with a minor pain [20-22], and reduce the severity and pain duration of the primary dysmenorrhea [23]. Boron also leads to anti-inflammatory and antioxidants effects by reducing cytokines [24-26]. Calcium Fructoborate is a boron-based nutritional supplement with a chemical structure similar to natural compounds of boron [27] and can restrain the synthesis of arachidonic acid which is a class of pro-inflammatory prostaglandins [28]. The toxicity resulted by consumption of boron rarely appear in animals and humans [29]. According to our research, boron supplement is consumed by women in other countries to prevent cancer of cervix, lung, breast, and osteoporosis, but there is no research conducted in Iran or abroad regarding this issue.

OBJECTIVES

According to the high prevalence of dysmenorrhea and non-invasive treatment method, a study was conducted to determine the effect of boron supplement on severity of systemic symptoms associated with primary dysmenorrhea, the need for painkiller drugs, and disruption of daily activities in order to propose a more effective treatment to deal with this common disorder among women.

METHODS AND MATERIALS

The research is a triple blind clinical trial. All single female students staying in dormitories of Shahid Beheshti University of Medical Sciences, who had the features of the research, were examined from March 2015 to July 2016. Regarding the same studies, the sample size was estimated 108 people with 80% of test validity and 95% level of confidence. Data collection tool was a questionnaire. Single students with primary dysmenorrhea that were willing to participate in the

study filled the required data including age, education, major of study, body mass index, education level and occupation of parents, exercise, health and nutrition status, existence of stressors in last six months, and order and menstrual period. The validity and reliability of the questionnaire were determined through Content validity and test-retest methods, respectively. Furthermore, only the questions with correlation higher than 0.7 were accepted. To determine the severity of symptoms accompanied by dysmenorrhea before and during two consecutive cycles after the intervention in three first days of menstruation, multidimensional verbal system was used in which its reliability and validity have been proved [30].

Single girls in the range age of 18-25 years had normal BMI from 8.19 to 25 who had regular menstrual periods with moderate to severe level of primary dysmenorrheal based on McGill pain ruler (According to this ruler, the pain score is from zero to ten, and consists of three parts: mild (0-3), moderate (7-4) and severe (10-8) [30]. and they did not take any special drug or supplement, suffer from any known chronic disease and symptoms of genital infection or they did not have any stressor during last six months such as parents 'divorce, death of close relative, etc; were selected to participate in the study after filling the written consent.

Those participants who declared their dissatisfaction to continue to participate in every stage of the research, showing any pelvic pathology diagnosis such as (myoma, pelvic tumors, endometriosis, of pelvic infection) during the study, misusing the supplement or placebos, or consuming any other supplement during the study, were excluded from the rest of the research.

First, eligible people were divided into separate blocks (moderate and sever dysmenorrheal) and then, they were equally and randomly separated into two groups of boron and placebo consumers. 54 samples were considered for each group. However, sample size was determined to be 59 people in each group due to the probability of the drop of samples and finally, the study was conducted onto a total number of 118 people. Supplement capsules (Sigma St. Louis) were prescribed for one group. Each capsule contained 5.88mg of sodium tetra borate (containing 10mg of boron) and the rest of its capacity was filled with 300 mg of lactose powder known as a filler and ineffective material in the pharmacy.

On the other hand, capsules containing 300 mg of lactose powder as a filler and ineffective material were used for the placebo group. The capsules were provided for both groups in similar packages, without name, and with specific code. Samples took one capsule daily while fasting from the last two days of their cycle up to the third day of bleeding (total $n = 5$ days) during two consecutive cycles.

Finally, the sample size reduced to 113 (58 in the boron supplement group and 55 in the placebo group), since one sample of the placebo group and four samples of boron supplement group were no longer willing to participate in the study at the end of first cycle and were excluded from the study (Figure 1). During the research, the researcher was available in dormitories or on the phone answering the samples' probable questions related to the study. Furthermore, the results of the research were informed to samples on the phone. To analyze the data, SPSS software version 17 and Friedman, Mann-Whitney, Wilcoxon and Fisher statistical tests were used. Significant level of Tests was equal to 0.05. The present study was registered in Ethics Committee of Shahid Beheshti University of Medical Sciences and in the Clinical Trial Center of Iran with ethic code 400.7554 and IRCT 201207153226N5 code, respectively.

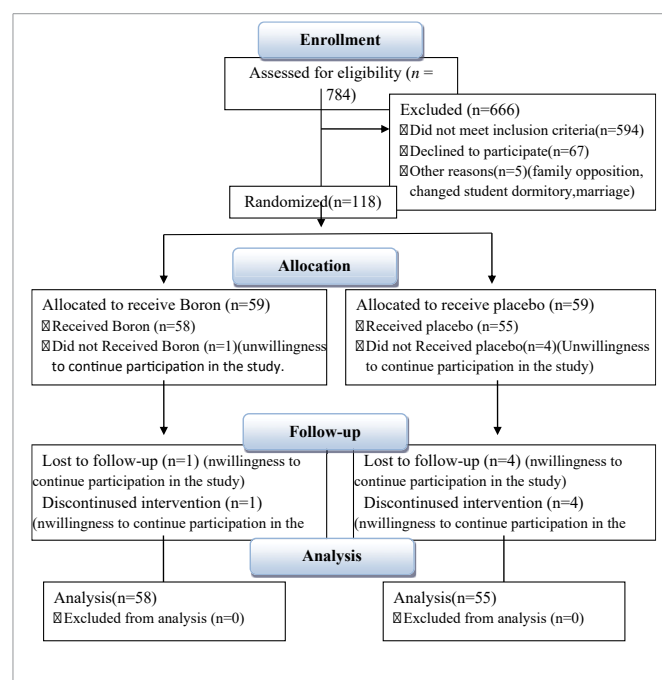


Figure 1: Flow of participants through the study.

RESULTS

Demographic characteristics are presented in table 1 that show the samples of both group were homogeneous and were not statistically different in terms of age, age of menarche, age of the onset of dysmenorrheal, and BMI (Table 1).

After intervention, the severity of systemic symptoms associated with dysmenorrheal was decreased in both groups compared to pre-intervention. This reduction was significant in the boron supplement group in all symptoms except nausea and vomiting ($p > 0.05$), while the reduction was not significant in the placebo group in all symptoms except in the severity of change in the nervous state ($p < 0.05$). All the systemic symptoms except diarrhea were significantly different between two groups after the intervention ($p < 0.05$) (Table 2).

After the intervention, disruption of daily activities and the need to take painkiller drugs reduced in both groups; however, this reduction was just significant in boron supplement group ($p < 0.001$) which led to the significant statistical differences between two groups after the intervention ($p < 0.05$) (Table 2).

In the boron supplement group, 52 subjects (89.7%) did not report any complications after the intervention and only 6 subjects (10.3%) had problems. In the placebo group, 47 samples (85.4%) did not have any problems, while 8 samples (14.6%) reported complications. Fisher test did not showed any significant differences between the two groups in terms of complications ($p = 0.059$) (Figure 2).

DISCUSSION

In the present study, boron supplement reduced the amount of disruption in daily activities and the need for taking painkillers. Reviewing the related literature, no similar study on taking boron supplement for this purpose was found. However, researchers in other studies have examined the usage of compounds containing boron supplement to reduce inflammation factors and severity of pain in different diseases.

Table 1: Demographic characteristics of the participants^a

Characteristics	Boron group (n = 58)	Placebo group (n = 55)	P-value ^b
Age, y	22.04 ± 1.94	21.53 ± 1.79	0.159
Menarche age	13.41 ± 1.36	13.34 ± 1.53	0.802
Age of dysmenorrhea	15.46 ± 1.93	15.44 ± 1.94	0.936
Body mass index ^c	21.39 ± 1.28	21.75 ± 1.62	0.199

^aValues are given as mean ± SD

^bIndependent t test

^cCalculated as weight in kilograms divided by the square of height in meters.

Table 2: Comparison of systemic symptoms of primary dysmenorrhea and the need for analgesic and disruption in daily activity between Boron supplementation and placebo groups.

Systemic symptoms	P. Baseline ^a	P. 1st Cycle	P. 2nd Cycle	P. Boron ^b	P. Placebo
Tiredness	0.865	0.019	0.007	0.001	0.732
Nausea	0.213	0.011	0.009	0.337	0.982
Lethargy	0.125	0.001	0.001	0.001	0.098
Diarrhea	0.327	0.161	0.157	0.036	0.236
Neural states	0.112	0.001	0.001	0.001	0.034
Fainting	0.840	0.008	0.001	0.001	0.074
Headache	0.966	0.001	0.001	0.001	0.763
Need for analgesic& disruption in daily activity	0.665	0.004	0.003	0.001	0.069

^aP. value of Mann-Whitney test

^bP. value of Friedman test

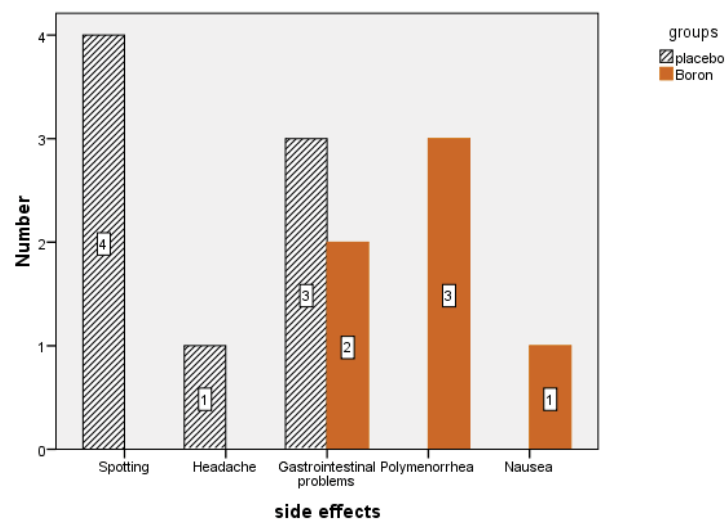


Figure 2: Chart of side effect.

Prostaglandins are the main factor causing dysmenorrhea [2,7]. On the other hand, nitric oxide and cytokines stimulate the production of prostaglandins in the luteal phase [2]. Therefore, taking a drug that can reduce the level of nitric oxide and cytokines would be beneficial for reducing the pain and subsequently the need for taking painkillers, disruption in daily activities, and systemic symptoms associated with dysmenorrhea. Scori, et al. [31] reported that the calcium borate fructo decreases the level of cytokines and nitric oxide *In vitro*. In another survey conducted by Nikkhah, et al.

[23] on girls who suffered primary dysmenorrhea, consumption of Boron supplementation significantly decreased severity and duration pain. Anti-inflammatory property of salicylic acid existing in Aloe vera also reduces inflammation and relieves pain. Regarding this property, Khozaei, et al. [32] designed a study using aloe vera and placebo. After intervention, the need for taking painkillers reduced during the first and second cycles in both groups (aloe vera and placebo); however, this reduction in the amount of taking painkillers was statistically significant. It seems that boron supplement being

used in the present study is more successful in reducing the need for painkillers comparing to aloe vera.

According to some evidences indicated the anti-inflammatory and analgesic properties of fenugreek, Yunesi, et al. [33] examined the effect of fenugreek on systemic symptoms associated with dysmenorrhea. The results showed that all the symptoms in the fenugreek group reduced significantly after intervention. However, boron supplement has been as effective as fenugreek.

Although the severity of nausea and vomiting reduced after intervention in boron supplement group, this reduction was not significant. Therefore, it seems that fenugreek was more effective than boron supplement in reducing the severity of nausea and vomiting. For adults, the dose of 20mg of boron per day has no side effects [34]. In this study, a normal dose of boron (10mg) was prescribed. However, the most common effects of boron, in case of gastrointestinal side effects, include vomiting, diarrhea, and abdominal pain [35] which not only did not exacerbate nausea and vomiting in the current study by taking boron supplement, but also decreased it comparing to placebo.

Therefore, it can be concluded that boron supplement is effective in reducing the severity of systemic symptoms associated with dysmenorrhea, the amount of need for taking painkillers, and disruption of daily activities. In this study, the reported complications by participants were not so severe to leave the research.

CONCLUSION

The results of the current study indicated that taking boron supplement for two months significantly reduced the severity of systemic symptoms associated with dysmenorrhea, the need for painkillers, and disruption at work compared to placebo. Regarding the effect of boron supplement on reduction of mentioned cases and lack of special report from participants about significant complications, it seems that boron supplement can be used for treatment of primary dysmenorrhea and thereby improve the quality of life of women and teen girls. It is recommended to conduct other studies in order to evaluate the effect of boron supplement on menstrual disorders in women who have primary dysmenorrhea.

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