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Effects of boron supplementation on the severity and duration of pain in primary dysmenorrhea

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A B S T R A C T

Background: Primary dysmenorrhea refers to painful menstrual cramps without pelvic pathology. The condition is highly prevalent among women and exerts negative effects on their quality of life. Considering the evidence for anti-inflammatory properties of Boron, the present study aimed to determine the effects of Boron supplementation on the severity and duration of menstrual pain in female university students.

Methods: This triple-blind randomized clinical trial study recruited 113 university students. The participants were matched for the severity and duration of dysmenorrhea and randomly allocated into the case and control groups (n = 58 and 55, respectively). The case group consumed 10 mg/day Boron from two days before the menstrual flow until its third day. The control group received placebo capsules (similar to those distributed among the cases). All subjects were asked to take the capsules for two consecutive menstrual cycles. Pain severity (measured on a visual analog scale) and duration (in hours) were measured at baseline and during the two cycles.

Results: The two groups had no significant differences in the severity and duration of pain at baseline. After the intervention, however, the severity and duration of pain were significantly lower in the case group than in the control group ($P < 0.05$).

Conclusion: Based on our findings, Boron supplementation can reduce the severity and duration of menstrual pain through exerting anti-inflammatory effects. In order to clarify the effects of Boron on dysmenorrhea, future studies are required to measure the levels of hormones and inflammatory biomarkers.

1. Background

Dysmenorrhea is a common gynecological disorder in young women [1] characterized by painful menstrual cramps in the lower abdomen [2] without pelvic pathology. It starts a few hours before or immediately after the menstrual flow and lasts for 48–72 h. It is often accompanied by nausea, vomiting, diarrhea, headache, and rarely syncope [3]. While different definitions of pain make it difficult to determine the exact prevalence of dysmenorrhea [4], its overall prevalence among young girls has been estimated at 60%–90% [1]. An epidemiological study in Iran reported the prevalence of dysmenorrhea in adolescent girls as 91% [5]. The condition is generally caused by the increased levels of cytokines and thus production of prostaglandins by interleukins in response to dropped progesterone levels [1]. Decreased levels of progesterone at the end of the luteal phase can also lead to lytic enzymes and cyclooxygenase pathway activation and arachidonic acid production [3].

Dysmenorrhea interferes with daily activities of women and is recognized as a major cause of absence from school or work among young women [4]. Therefore, it exerts considerable negative effects on not only women's quality of life, personal health, and social life,

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but also the global economy [6,7]. As a result, women with primary dysmenorrhea may be afraid of menstruation [8]. A variety of treatments including non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives have been suggested for dysmenorrhea [1]. However, NSAIDs' gastrointestinal complications and failure of treatment in 20%–25% of the cases have increased the tendency toward other treatment methods [9]. Since some women are unable or unwilling to use medical and pharmaceutical treatments due to their side effects, alternative treatments, e.g. dietary and herbal methods, with minimal side effects have been attracting growing attention [10]. A number of studies have highlighted the benefits of micronutrients (such as Boron), vitamins, and minerals in the treatment of hormonal disorders and menstrual complications [11]. Boron, a metalloid element with atomic number 5 [12], is a useful and possibly essential element for human body [13]. Rather than a free element, Boron naturally occurs as various compounds. Boric acid [14] and calcium fructoborate have been the most common Boron-containing compound in different studies [15]. People constantly receive Boron from drinking water and food [16]. While maximum Boron intake recommended for all adults is 20 mg/day [17], one's daily Boron intake depends on his/her type of food (nuts and vegetables have higher concentrations of Boron than fruits and legume) and Boron content of drinking water [13].

About 85% of the consumed Boron is absorbed [18]. Since plasma levels of Boron are regulated through renal excretions, Boron toxicity in animals and humans is rare [19]. Boron is known to have a positive impact on bone growth and central nervous system function. It has also been shown to regulates hormone levels and reduce the risk of some cancers [20]. In a comparison between Boron-rich areas of Turkey and other parts of the country, Korkmaz et al. concluded that taking high levels of Boron in drinking water lowered the risk of cervical cancer [21]. Furthermore, due to its antioxidant properties, Boron can reduce inflammatory reactions by interfering with cytokines production [22]. According to previous research, calcium fructoborate may inhibit the synthesis of arachidonic acid, which is a class of proinflammatory prostaglandins [23]. While the consumption of less than 1 mg/day of Boron prevents its benefits, studies have shown that low-Boron diets are common [20]. Since Boron deficiency is harmful to the body [15], low Boron consumption should be considered as a health concern [13] and increased Boron intake through diets rich in fruits, vegetables, nuts, and seeds should be encouraged [20].

To the best of our knowledge, no previous study has investigated the relationship between Boron and dysmenorrhea. Considering the young population of Iran and high prevalence of dysmenorrhea in the country, the current research aimed to introduce a non-invasive treatment for the condition.

2. Trial objectives

The primary objective of the present study was to determine the effectiveness of Boron supplementation on primary dysmenorrhea in female residents of university dormitories in 2013–14. This was achieved by determining and comparing the severity and duration of pain in primary dysmenorrhea before and after the intervention in both Boron-supplemented and placebo groups.

3. Methods

This triple-blind clinical trial, in which the researchers, participants, and statistical analyzers were unaware of the grouping, was carried out from March 2013 to July 2014. It recruited single female students with dysmenorrhea who resided in dormitories of Shahid Beheshti University of Medical Sciences (Tehran, Iran). The inclusion criteria were aging 18–25 years, normal body mass index (19.8–25 kg/m^2), and regular menstrual periods with moderate to severe primary dysmenorrhea. Students who used any supplements or drugs, had chronic diseases or symptoms of genital tract infections, and experienced stressors such as separation of parents and death of first degree relatives in the past six months were not included. The exclusion criteria were unwillingness to continue participation at any stage of the research, development of pelvic pathology (myoma, pelvic tumors, endometriosis, and pelvic infection) during the study, improper use of the supplement/placebo, and taking any other supplements over the course of the study. Before their participation, all the students were asked to sign informed consent forms.

The eligible individuals were matched for the severity and duration of menstrual pain and placed in separate blocks (with either moderate or severe dysmenorrhea). They were then randomly allocated to the case and control groups to receive either a Boron supplement or placebo, respectively. According to similar studies [25], a confidence interval of 95%, and a test power of 80%, the sample size was calculated as 108 participants (two groups of 54). Considering the possible drop in the sample size, 59 patients were included in each group. The final sample size was 113 participants (58 cases and 55 controls). The randomization process, triple-blind design, and administration of valid and reliable tools could ensure unbiased data collection and analysis (see Fig 1).

At the beginning of the study, the participants' weight and height were measured and their demographic characteristics (age, Menarche age, Age of dysmenorrhea) were collected. The subjects were then asked to maintain their normal diet and physical activity during the study. The case group was provided with 300 mg capsules containing 88.5 mg sodium tetraborate (Sigma, St. Louis, USA), i.e. (containing 10 mg Boron), and 221.5 mg lactose powder (as a filling material). Placebo capsules contained 300 mg lactose powder. All capsules were nameless, coded, and similar in shape and packaging. All subjects were instructed to take one capsule a day from two days before the end of the cycle until the third day of menstrual flow (five capsules in total) for two consecutive cycles. A menstrual status questionnaire containing the severity and duration of menstrual pain was collected at baseline and at the end of each period. During the first three days of each menstrual flow, the subjects were asked to mark their daily maximum pain severity on a visual analogue scale (VAS) ranging from 1 to 10 (1–3: mild pain, 4–7: moderate pain, and 8–10: severe pain). If a painkiller was needed, maximum severity of pain before the medicine was marked on the VAS. The VAS was developed at McGill University and had approved validity and reliability [24]. The participants were also asked to record the duration of their menstrual pain (the number of hours they felt the pain during the first three days of menstrual bleeding). Content validity and test-retest were used to confirm the validity and reliability of the demographic and menstrual status questionnaires. Questions with correlation coefficients above 0.7 were considered acceptable.

Data were analyzed using two-sided significance tests at a 5% level of significance. All analyses were performed in SPSS for Windows 17.0 (SPSS Inc., Chicago, IL, USA). The statistician was unaware of the grouping until after data analysis. The researchers remained blind until the final stage. Independent t-tests were applied to identify the demographic differences between the two groups. Repeated measures analysis of variance (ANOVA) was conducted to investigate the therapeutic effects of Boron supplementation and time along with their interaction effects on menstrual pain.

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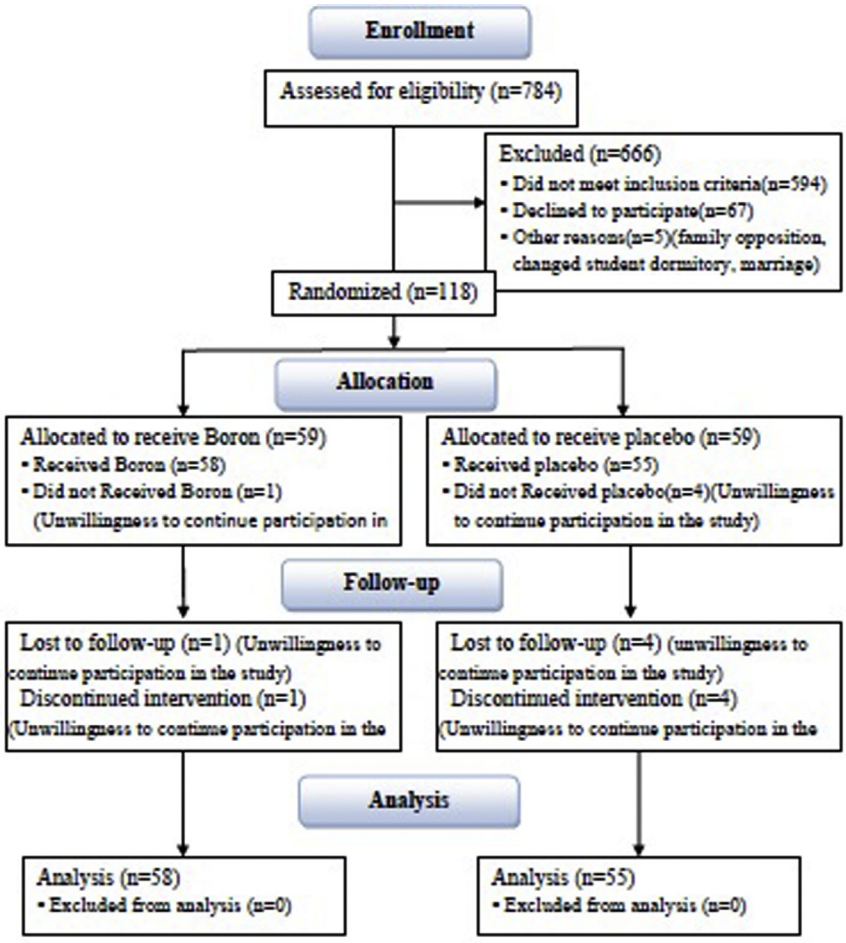

Fig. 1. Flow of participants through the study.

4. Results

Table 1 summarizes the demographic characteristics of the cases (n = 58) and the controls (n = 55). The two groups had no significant differences in terms of age, age at menarche, age at onset of dysmenorrhea, and body mass index.

The mean severity of pain in the case group was reduced from 5.90 ± 1.89 before the intervention to 4.35 ± 2.23 during the second cycle. The mean values in the control group were 6.44 ± 1.76 before the intervention and 5.87 ± 2.30 in the second cycle. Before the intervention, the mean duration of pain was 4.15 ± 2.42 and 4.46 ± 2.85 h in the case and control groups, respectively. The corresponding values were 2.74 ± 2.14 and 4.08 ± 2.67 h over the second cycle (Table 2). The two groups were not significantly different in the mean severity and duration of pain before the intervention. During the first and second menstrual cycles, however, the mean severity and duration of pain were significantly lower in the case group than in the control group.

According to repeated measures ANOVA, the group−time interaction was not significant for pain severity (P = 0.074). In contrast, this interaction was statistically significant for the duration of pain (P = 0.020), i.e. over time, supplementation with Boron was effective in decreasing the mean duration of pain. Furthermore, time had significant effects on the severity and duration of pain (P < 0.001). In other words, the severity and duration of pain significantly decreased during the three cycles. Additionally, ANOVA showed a significant difference between the two groups. In fact, the mean severity and duration of pain were significantly lower in the case group than in the control group (Table 2).

Independent t-test did not show a significant difference in the mean pain severity before and after the first cycle between the two groups (P = 0.074). Nevertheless, the difference between the two

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

[a] Values are given as mean ± SD.
[b] Independent t test.
[c] Calculated as weight in kilograms divided by the square of height in meters.

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Table 2
Pain severity measured on a 0–10 cm visual analog scale[a] and pain duration (hours).

Group	Baseline	1st Cycle	2nd Cycle	P value[b]
Pain severity:				
Placebo	6.44 ± 1.76	6.01 ± 2.06	5.87 ± 2.30	
Boron	5.90 ± 1.89	4.78 ± 2.19	4.35 ± 2.32	
P value[c]	0.126	0.003	0.001	0.001
Pain duration:				
Placebo	4.46 ± 2.85	4.33 ± 2.65	4.08 ± 2.67	
Boron	4.15 ± 2.42	3.15 ± 2.34	2.74 ± 2.14	
P value[c]	0.530	0.014	0.004	0.032

[a] Values are given as mean ± SD.
[b] Repeated measures ANOVA.
[c] Independent T-test.

groups was statistically significant for the mean duration of pain ($P = 0.011$). The mean differences for severity and duration of pain before the intervention and in the first cycle after the intervention between two groups and before the intervention and in the second cycle after intervention between two groups was statistically significant. However, this difference in the first and second cycle after intervention between two groups showed no significant difference for severity and duration of pain.

Finally, no major side effects were observed in either group.

5. Discussion

In this study, Boron supplementation reduced the severity of moderate and severe dysmenorrhea. This appears to be the first research study to investigate the relationship between Boron and dysmenorrhea in female students. Previous research has confirmed the role of Boron in alleviating inflammatory factors and pain severity in different conditions. Studies in Iran have also underscored the efficiency of valerian and wheat germ in decreasing the severity of menstrual pain [8,25].

Increased uterine contractions stimulated by prostaglandins [1] is considered to be responsible for dysmenorrhea [3]. Since nitric oxide and cytokines facilitate the production of prostaglandins in the luteal phase [1], higher levels of nitric oxide and interleukin 6 have been found in women with primary dysmenorrhea [26]. Furthermore, the same group of women have been reported to have up-regulations in gene expression of proinflammatory cytokines (e.g. interleukins 1, 6, and 8 and tumor necrosis factor-alpha) during the proliferative, secretory, and menstrual phases of the uterine cycle [27]. Therefore, the administration of compounds capable of decreasing nitric oxide and cytokines levels will be effective in the management of dysmenorrhea. Boron has been suggested to reduce inflammatory reactions by interfering in the production of cytokines [23]. Calcium fructoborate has also been proved to play its anti-inflammatory role by inhibiting interleukin 1 and 6 and nitric oxide release [28].

In a study on patients suffering from angina, Militaru et al. indicated significant relations between calcium fructoborate intake and not only reduced inflammatory factors and number of angina attacks, but also improved quality of life among the patients [29]. Reyes-Izquierdo et al. administered the same tool as we used to measure pain severity in patients with osteoarthritis of the knee. They reported a significant reduction in pain severity on days seven and 14 after taking a short course of calcium fructoborate [30]. Likewise, in a study by Naghii et al., one week of supplementation with Boron (10 mg/day) was associated with lower cytokine levels (a significant reduction in tumor necrosis factor-alpha levels and non-significant reductions in interleukin 6 and C-reactive protein levels) in men. Moreover, hormonal levels also changed within a week [31]. Scorei et al. evaluated the effects of calcium fructoborate on the production of inflammatory mediators in vitro. They showed that in macrophages irritated by lipopolysaccharide, the compound could inhibit nitric oxide and interleukins 1β and 6, but had no effect on cyclooxygenase [32].

Boron plays an important role in the regulation or synthesis of vitamin D [31]. Reyes-Izquierdo et al. reported that calcium fructoborate intake significantly increased 1, 25-dihydroxy vitamin D levels at the seventh and 14th days [30]. Since vitamin D and Boron seem to have similar mechanisms of action in dysmenorrhea, studies on the effects of vitamin D consumption on dysmenorrhea can be compared with the present research. Similar to our findings, Lasco et al. concluded that the administration of cholecalciferol in women reduced the severity of menstrual pain by increasing serum 25-hydroxy vitamin D levels [33].

Finally, it is noteworthy that our participants did not report any major side effects for Boron supplements.

6. Conclusion

This was the first study to examine the effects of Boron on dysmenorrhea. According to our findings, two months of Boron supplementation could significantly reduce the severity and duration of pain in primary dysmenorrhea. These benefits along with the absence of side effects indicate that Boron supplements can be used in the treatment of primary dysmenorrhea. Nevertheless, further studies are required to measure levels of hormones, prostaglandins, and inflammatory biomarkers following Boron supplementation.

Ethical considerations

The study protocol was approved by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethical Code: 7554/400). The study was also registered at the Iranian Registry of Clinical Trials (ID: IRCT201207153226N5).

Conflict of interest statement
None declared.

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