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The effects of B vitamins on pain relief and improving physical function in patients with medial compartment knee osteoarthritis

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ABSTRACT

The anti-inflammatory and analgesic effects of B vitamins have been already demonstrated. It seems that these agents are effective in treating knee osteoarthritis (KOA), which is associated with an inflammatory status of the joint. However, the available documents showing the efficacy of these vitamins are so limited. In the current study, we investigated the effects of B vitamins on pain relief and function improvement in patients with KOA. Sixty patients with mild to moderate KOA were randomly divided into two equal groups of celecoxib (control) and celecoxib with B vitamins (neurobion). Patients were treated for two months. Before and after the treatment, patients' pain intensity and function were measured using visual analogue scale (VAS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) respectively. On the last visit, the pain intensity significantly decreased and WOMAC scores significantly increased in both groups, respectively ($p < 0.001$). However, the WOMAC scores were the same in both groups, while the pain intensity was significantly lower in neurobion group on the last visit ($p < 0.001$). Our findings showed that prescribing B vitamins can effectively exacerbate the analgesic effect of celecoxib in patients with KOA without any complications.

Keywords: Osteoarthritis, Knee, Pain, B Vitamins, Celecoxib

INTRODUCTION

Knee osteoarthritis (KOA) is a common problem in the world and a leading cause of admission to medical centers and is accompanied with great pain and disability [1,2]. It is reported that symptomatic KOA is seen among 24% of people [3]. This condition imposes large financial burdens on individuals and societies, due to the several problems that it creates for the afflicted [4].

KOA's definitive treatment in advanced stages is total knee arthroplasty (TKA), a very complex orthopedic surgery which can be very dangerous. Furthermore, as the life of the prosthesis is limited and the second knee surgery is much more dangerous and complicated than the primary one, surgeons try to postpone it. Thus, given the increasing prevalence of KOA because of the worldwide prevalence of obesity, aging population and the high cost and complications of surgical treatment, it is of utmost necessity to use appropriate nonsurgical treatment. KOA nonsurgical treatments include different drug regimens, such as nonsteroidal anti-inflammatory drugs

(NSAIDs), acetaminophen, glucosamine, piacledine and celecoxib, intra-articular injection of hyaluronic acid or glucocorticoids, physical therapy, braces applying valgus force and insoles with outer edge [2,4]. The goal of nonsurgical treatment is to alleviate pain and increase patients' ability to perform daily activities, while reducing the side effects [5].

The B vitamin family is made up of the most essential vitamins for the body. In several laboratory and clinical studies the analgesic and anti-inflammatory effects of them have been well illustrated [6-12]. Some studies have revealed the effects of these vitamins on nociception [13,14]. Bertollo et al, has demonstrated that riboflavin is a safe anti-inflammatory drug which exacerbates the antinociceptive effect of morphine in different experimental models [15]. The antinociceptive effects of B vitamins for pain after spinal cord trauma have recently been shown by some researchers [16]. The role of B vitamins deficiency in narrowing joint space and osteophytosis have been established, too [17]. Based on these findings, it is likely that their use in OA, which is associated with inflammatory changes in joints, can be helpful, too. However, we could only find one clinical trial, investigating the effects of these vitamins on pain resulted from OA which had reported promising results [18]. Clearly, more randomized studies are necessary to confirm the role of B vitamins in the treatment of osteoarthritic pain to help make a decision on the use of B vitamins in the treatment of OA. In the current study we evaluated the effects of B vitamins on pain relief and functional improvement in patients with KOA.

MATERIALS AND METHODS

In this randomized clinical trial, 60 patients with KOA were studied. At first, all patients were talked to about the purpose and methods of study and were asked to sign their written consent. All patients suffered medial compartment knee osteoarthritis (OA) with grade I or II based on Kellgren-Lawrence (K&L) classification criteria and needed no surgical procedures based on clinical and radiographic examinations. Also, no secondary knee deformities due to degenerative changes were seen in them. Other inclusion criteria were: knee pain for more than 6 months and being older than 40. Patients with a history of knee injury, knee surgery within 6 months, history of septic arthritis or corticosteroids injection during the previous month, were excluded. Also, patients with hip OA or liver or kidney disease and pregnant women were excluded.

Patients were divided into two groups using a table of random numbers. The members of the first group (control) were treated with celecoxib, calcium and vitamin D and the other group had an additional neurobion injection (neurobion group). It is worth noting that the patients were administered with celecoxib 100 mg twice a day, calcium and vitamin D tablets once a day. The neurobion group had 8 injections, 4 in four successive days in the first week, and 4 were injected at weekly intervals. The treatment period lasted for 2 months. During this period, patients in both groups underwent 10 sessions of similar physiotherapy by an experienced physiotherapist. The patients were also asked about their living conditions and were asked to change their lifestyle as much as possible by for example using table and chair while eating.

The variables included in the study were OA pain intensity and its impact on patients which were evaluated before treatment and on the final visit. The visual analogue scale (VAS) was used to measure pain intensity. On this scale, zero indicated no pain and 10 indicated the worst pain imaginable; and patient had to choose a number between zero to ten. Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire was used to evaluate the functions of the patients. The questionnaire score ranged from zero to 100: the higher the score, the better the status of the individual.

Finally, after collecting and classifying data, statistical software SPSS ver.15 was used for data analysis. The quantitative data as mean and standard deviation and qualitative data were presented as number and percentage. To compare quantitative data between the two groups t-test and to compare qualitative data between groups chi-square test were used. The quantitative data before and after treatment in each group were compared using paired t test. P values at <0.05 were considered as significant.

RESULTS AND DISCUSSION

Demographic data of the two groups are presented in Table 1 which shows that there were no significant differences between the two groups in terms of age, gender and body mass index. In neurobion group, the pain intensity decreased significantly from 5.8 ± 1.3 at the beginning of the study to 2.1 ± 0.9 on the last visit ($p < 0.001$). A similar

finding was achieved in control group as pain decreased significantly from 5.3 ± 1.2 to 3.2 ± 1 ($p < 0.001$). Also, the WOMAC score improved significantly after the treatment in both groups. The WOMAC score increased from 63.4 ± 8.5 to 78.3 ± 10.1 in the neurobion group and from 61.5 ± 10.3 to 76.7 ± 10.6 in the control group ($p < 0.001$).

When comparing the two groups in terms of pain intensity and WOMAC score it was found that in spite of the same VAS at the baseline, the pain intensity on the last visit was significantly lower in neurobion group compared to control group ($p < 0.001$) showing the analgesic role of B vitamins which exacerbated the analgesic effect of celecoxib in these patients (Table 2). However, based on our findings, the B vitamins had no further effect on improving the functional status measured by WOMAC score. The WOMAC scores were the same at baseline and on the last visit between the two groups (Table 2).

Group		Neurobion (n=30)	Control (n=30)	p-value
Age (y)		54.6 ± 11.2	55.1 ± 13.3	0.297
Gender	Male	13	11	0.598
	Female	17	19	
BMI (kg/m ²)		29.2 ± 1.1	29.7 ± 1.4	0.791

Group		Neurobion (n=30)	Control (n=30)	p-value
Before the treatment	VAS	5.8 ± 1.3	5.3 ± 1.2	0.471
	WOMAC	63.4 ± 8.5	61.5 ± 10.3	0.213
After the treatment	VAS	2.1 ± 0.9	3.2 ± 1	< 0.001
	WOMAC	78.3 ± 10.1	76.7 ± 10.6	0.193

OA is a degenerative rheumatic disease characterized by mechanical and enzymatic degradation of extra cellular matrix and subsequent degeneration of the articular cartilage [19,20]. OA causes a sharp decline in the quality of life and increases dissatisfaction with life [21].

Because of their role in weight bearing and mobility, knees are more affected by OA than other joints. This heavily affects the patients' mobility and ability to work and to have proper social relation. Now, due to the aging process in the human population and the increasing prevalence of obesity, high financial burdens are imposed on the health care systems for the treatment of OA. So, this disease deserves special attention [4].

Medications used in the treatment of OA are in three categories: drugs with immediate effect such as acetaminophen and NSAIDs, drugs with slow effects such as chondroitin sulfate and piacledine, and the structural remedies to stop the disease or to improve the involved structures whose effects of course are not yet clearly approved [22].

Some have suggested that acetaminophen should be the first line treatment of KOA [23]. But it should be noted that acetaminophen has lower efficiency than NSAIDs [24,25]. On the other hand, despite their favorable pain relieving effects, NSAIDs in the long term, often will cause adverse effects. This group of drugs can cause severe gastrointestinal symptoms and in some cases even death in patients, a fact that has led to a big controversy over the use of these drugs [26,27]. In 1999, it was reported that each year 103,000 hospitalizations and 16,500 deaths were recorded in the United States due to the complications of treatment with nonselective NSAID [28].

Regarding this fact, looking for drugs with minimal side effects and maximum efficacy is of utmost priority for the treatment of patients with OA. Celecoxib is a selective COX-2 inhibitor that inhibits the production of prostaglandins responsible for inflammation and pain, and in addition to being effective in the treatment of OA it is acceptable with regard to its low side effects, particularly with respect to gastrointestinal complications in which it is much safer than nonselective NSAID drugs [29,30].

More importantly, it has been shown that this drug can affect the disease process. Celecoxib has effects on all structures involved in the pathogenesis of OA, including bone, cartilage and synovium. In addition to preventing the activity of COX-2, it regulates the independent signal transduction pathways of COX-2. Accordingly, it appears that this drug has more effects than just anti-inflammatory ones in the treatment of OA [31]. The family of B vitamins is

abundantly used in the treatment of neurogenic pain and problems [6,7,8,9,13]. In some studies, the concomitant use of Diclofenac and B vitamins in the treatment of back pain, neuropathic and inflammatory neck pain, and the pain after tonsillectomy surgery have been reported to have good results [32,11]. Recently, Luca *et al.* have shown that methylene blue and riboflavin (2 ATP modulators) have analgesic effect on visceral pain and nociception [16].

More recently, Ponce-Monter and colleagues showed that the use of Diclofenacin combination with B vitamins could effectively help to reduce the pain left after lower limb fracture surgery [12]. The analgesic mechanism of B vitamins is not clearly known, however, it is said that increased accessibility to norepinephrine and 5HT or increased impact of the two acts as an inhibitory transmitter in nociceptive systems resulting in painlessness [33]. Furthermore, it has been shown that the effects of B vitamins can be caused by activation of an opioid mechanism and the simultaneous release of nitric oxide and free radicals. This is possible because the injection of naloxone and L-NAME can prevent the antinociceptive effects of these vitamins [12,32]. The clinical and laboratory findings can greatly indicate the importance of vitamin B in the improvement of inflammatory conditions; however, more studies are needed in this area.

OA is a degenerative rheumatic disease, together with mechanical and enzymatic degradation of extra cellular matrix and subsequent degeneration of the articular cartilage creating highly inflammatory joint conditions. So, it seems that B vitamins can be used to reduce joint inflammation in OA, which may lead to less pain in patients. Interestingly, Muraki *et al.* have found that low dietary intake of B1, B2, niacin and B6 are associated with narrowing of joint space in Japanese women [17].

Up to now, there is only one clinical trial examining the effects of these vitamins on KOA. And it was a study recently conducted by Magana-Villa and colleagues in which, based on the synergy found between Diclofenac and B vitamins in laboratory studies, they tried to investigate the effect of simultaneous injection of Diclofenac and B vitamins on KOA patients with severe pain who were TKA volunteers, and found that this compound could act better than Diclofenac alone in reducing pain 12 hours after injection [18].

For the first time we studied the impact of a combination of B vitamins family and celecoxib on KOA patients with grades I and II, based on Kellgren-Lawrence scale, and saw that although celecoxib reduced pain and improved function in patients and had no side effects, using B vitamins together with it was more effective and useful and the therapeutic effects of vitamin B were more desirable and remarkable.

This finding can be a landmark in the use of B vitamins in KOA and can encourage researchers and practitioners to test the effects of B vitamins on a greater number of patients in subsequent studies.

Like other studies, this study also had some limitations. One of the main limitations of our study was the small sample size and it seems that if more patients were studied, probably more reliable results would be obtained. In addition, it was possible that some patients at home, without telling their doctors used some other pain killers that could cause some degree of bias in the data. As the last point, although at the baseline, we tried to ask patients to change their lifestyles, it was impossible to check it for every individual patient. As a matter of fact, lifestyle differences could affect our results.

CONCLUSION

The intake of B vitamins together with celecoxib may result in greater pain relief in patients with KOA. However, further extensive and prospective studies are needed to confirm this finding.

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