Research Paper

Role of Vitamin B Complex as an Add-on Therapy to Diclofenac in Patients with Primary Osteoarthritis of the Knee

Jasmine Kaur, Seema Rani, Anil Gulia[1], Garima Bhutani, Sanjeev Kumar[1], Arvind Narwat

Departments of Pharmacology and [1]Orthopedics, BPS Government Medical College for Women, Khanpur, Kalan, Sonipat, Haryana, India

Abstract:

Objective: This study was conducted with the aim to evaluate the efficacy and safety of Vitamin B complex as an add-on therapy to diclofenac in patients with primary osteoarthritis (OA) of the knee. **Materials and Methods:** In this prospective, open-labeled, randomized, and comparative clinical study, a total of 130 patients of age >40 years with primary OA of knee attending orthopedics OPD were randomly allocated into two groups of 65 each, i.e., Group D and Group B. In Group D, patients received tablet diclofenac 75 mg and in Group B, patients received tablet Vitamin B complex along with diclofenac once daily for 4 weeks, respectively. Clinical assessment was done at baseline and at the end of 4 weeks and 8 weeks by the visual analog scale (VAS), WOMAC index, and Lequesne index. **Results:** During the intergroup comparison, it was found that Vitamin B complex as an add-on therapy to diclofenac produced statistically significant reduction in mean VAS pain score ($P < 0.05$). However, the difference in mean WOMAC index and Lequesne index was not statistically different at 4 and 8 weeks between the two groups ($P > 0.05$). Mild side effects were seen at 4 weeks, but no side effects persisted up to 8 weeks in both the groups. **Conclusion:** The present study suggested that Vitamin B complex as an add-on therapy was found to cause a significant reduction in pain score. It could be a promising drug in patients with OA to improve the analgesic effect, when combined can reduce the dose of diclofenac, thereby minimizing the side effects.

Keywords: Knee osteoarthritis, Lequesne index, visual analog scale, Vitamin B complex, WOMAC index

Introduction

Osteoarthritis (OA) is a disease primarily affects the elderly population, making it a major cause of disability in older adults worldwide with a prevalence of 22%–39%.[1] The knee is affected by OA more often than any other joint.[2] X-ray of the knee joint is diagnostic for assessing OA and other types of investigations are usually not required.[3,4] The main aim is to alleviate pain and minimize loss of physical function.[5] Diclofenac (75–150 mg), a prostaglandin (cyclo-oxygenase) inhibitor having analgesic and anti-inflammatory, is used to relieve pain, but physicians restrict its usage for long term due to its complications.[6] Today, various supplements along with analgesics are prescribed to the patients with OA. Vitamin B complex is a hydrosoluble vitamin and is the emerging drug in this field.[7,8] It has been seen in few studies that Vitamin B complex may enhance the analgesic effect of diclofenac and might decrease in the dose of nonsteroidal anti-inflammatory drugs (NSAIDs) in OA patients.[9] Vitamin B complex, i.e., thiamine, pyridoxine, and cyanocobalamin, has been studied for many years for their pain-relieving properties (at doses higher than nutritional doses) when given along with NSAIDS in patients with lumbago, polyneuropathies, rheumatic diseases, and pain after tonsillectomy.[10] The purpose of the study was to determine the efficacy of Vitamin B complex as a pain reliever in patients with OA of the knee and compare it with NSAID, diclofenac.

Materials And Methods

This was a prospective, open-labeled, randomized, comparative clinical study conducted from February 2019 to December 2019 at a tertiary care hospital in Haryana. The study was conducted after obtaining ethical clearance from the Institutional Ethics

Address for correspondence: Sanjeev Kumar, Department of Orthopedics, BPS Government Medical College for Women, Khanpur, Kalan, Sonipat, Haryana, India.
E-mail: sanjeev26122007@gmail.com

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Committee and after written informed consent. Diagnosed cases of primary OA knee of either sex >40 years of age having grade 2 and 3 osteoarthritic changes on radiological imaging according to Kellgren–Lawrence classification and patients with unilateral and bilateral knee involvement with a visual analog scale (VAS) score >5 at baseline were included in the study, while patients who did not meet the above criteria and with body mass index (BMI) >29.9, history of trauma, infection, or surgical intervention were excluded from the study.

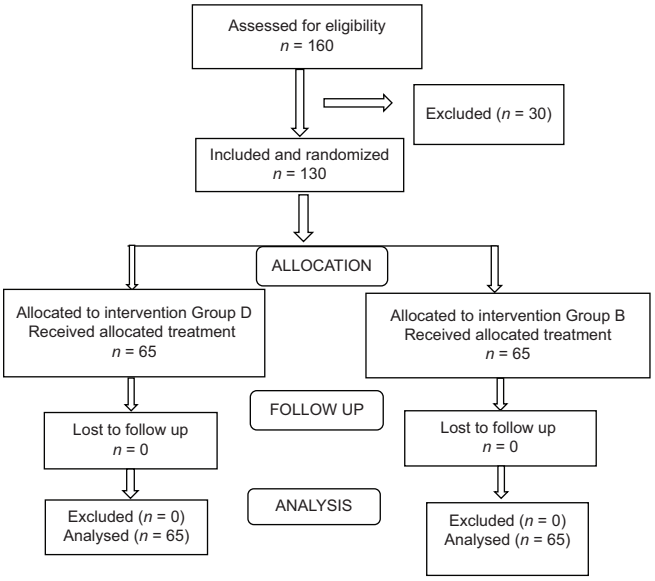
After screening, 130 eligible patients were randomly allocated to two groups: Group D and Group B, each having 65 patients calculated using nMaster 2.0 software (developed by Department of Biostatistics, Christian Medical College, Vellore), taking superiority margin 0.63, with power 80% and 5% α error. Group D patients received 75 mg diclofenac tablet orally daily and Group B patients received tablet diclofenac 75 mg orally daily along with Vitamin B complex tablet (thiamine 10 mg, riboflavin 10 mg, nicotinamide 45 mg, pyridoxine 3 mg, cyanocobalamin 15 µg, and calcium pantothenate 50 mg) orally daily for 4 weeks in the morning after breakfast, respectively. Medicines were provided to the patients from the hospital supply. All patients received standard treatment capsule omeprazole along with physiotherapy by an experienced physiotherapist and were advised quadriceps and hamstrings exercises. All patients had undergone local physical examination [Figure 1] and an X-ray of the affected knee in weight-bearing position (AP and lateral view) at the time of enrolment and at 8 weeks.

Efficacy was evaluated in terms of knee pain and function at baseline and at the end of week 4 and week 8 using VAS score, WOMAC index, and Lequesne index. VAS score is the most widely used and accepted standard for pain measurement. It was used to rate patient's pain intensity on a 100 mm horizontal line with no pain at one end and the worst imaginable pain at the other end.[11]

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is the most commonly used clinical tool for evaluating patients with knee OA. It includes five questions about pain, two about joint stiffness, and 17 on degree of disability of activities of daily living. Each item is in 5 – point Likert format: "none" scored as 0, "mild" as 1, "moderate" as 2, "severe" as 3, and "extreme" as 4. The maximum score obtained by the patients would be 96.[12] Lequesne index (0–24) was another index of severity of OA of the knee used to assess the effectiveness of therapeutic interventions. It has sections for pain or discomfort, maximum distance walked, and activities of daily living.[13]

Safety assessment was carried out at the end of week 4 and week 8 for any adverse event and was recorded in adverse drug monitoring proforma provided by Pharmacovigilance Programme of India.

Data were expressed as mean ± standard error of the mean unless specified otherwise. Both intragroup and intergroup statistical analyses were performed. Intragroup analysis was performed using repeated-measures ANOVA. Intergroup analysis was performed using unpaired *t*-test. $P < 0.05$ was considered as statistically significant.



Flow diagram showing patient enrolment and allocation.

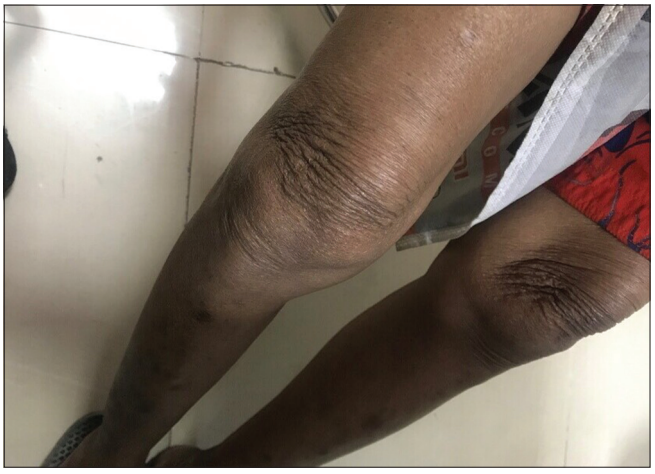


Figure 1: Photograph of both knees in patients with osteoarthritis of the knee

Results

Of 130 patients participating in the study, 65 patients are included in each group and none of them left in between the study. The mean age of the patients in both the groups was comparable - 57.48 ± 11.36 years in Group D and 56.95 ± 9.61 years in Group B. Gender distribution in both the groups is shown in Figure 2. The mean BMI of the patients was comparable - 25.3 ± 0.68 in Group D and 26.32 ± 1.01 in Group B. The Chi-square indicated no statistically significant difference in age, gender, and occupation in between the groups ($P > 0.05$).

The mean VAS in Group D and Group B at different time intervals is shown in Table 1 and Figure 3. Using ANOVA, there was statistically significant change in mean scores of VAS at 4 weeks and 8 weeks when compared with baseline in each group. On comparison between Group D and Group B, it was observed that difference in mean VAS at 4 weeks and 8 weeks was statistically significant using unpaired *t*-test ($P < 0.05$).

The mean WOMAC index in Group D and Group B at different time intervals is shown in Table 2 and Figure 4. ANOVA indicated a statistically significant change in mean scores of WOMAC score at 4 weeks and 8 weeks when compared with baseline in each group. Using unpaired *t*-test, no significant difference was observed in mean WOMAC score between the two groups at 4 weeks and 8 weeks ($P > 0.05$).

The mean Lequesne index in Group D and Group B at different time intervals is shown in Table 3 and Figure 5. Using ANOVA, there was a statistically significant change in mean scores of Lequesne index at 4 weeks and 8 weeks when compared with baseline in each group. On intergroup comparison, it was observed that the difference in mean Lequesne index was not statistically significant at 4 weeks and 8 weeks using unpaired *t*-test ($P > 0.05$).

Safety assessment was done at 4-week and 8-week follow-up period. Mild side effects such as dyspepsia, flatulence, diarrhea and nausea, and headache were seen at 4 weeks, but no side effects persisted up to 8 weeks. The side effects were almost comparable in both the groups.

Table 1: Intergroup comparison of visual analog scale score

Time interval	Group D	Group B	*P*
0 week	7.45±0.81	7.60±0.83	0.839
4 week	3.94±0.74	3.28±0.84	0.001*
8 week	5.02±0.98	4.62±1.10	0.049*

*$P<0.05$ indicates statistically significant values at 4 and 8 weeks. All values are expressed as mean±SD. SD=Standard deviation

Table 2: Intergroup comparison of Western Ontario and McMaster Universities Osteoarthritis index

Time interval	Group D	Group B	*P*
0 week	54.49±11.49	57.42±10.45	0.406
4 week	32.46±8.08	30.52±7.35	0.527
8 week	37.08±9.73	35.68±8.92	1.000

All values are expressed as mean±SD. SD=Standard deviation

Table 3: Intergroup comparison of Lequesne index

Time interval	Group D	Group B	*P*
0 week	13.98±2.93	14.45±2.67	1.000
4 week	8.42±2.42	8.20±2.20	1.000
8 week	10.38±2.58	9.80±2.38	0.543

All values are expressed as mean±SD. SD=Standard deviation

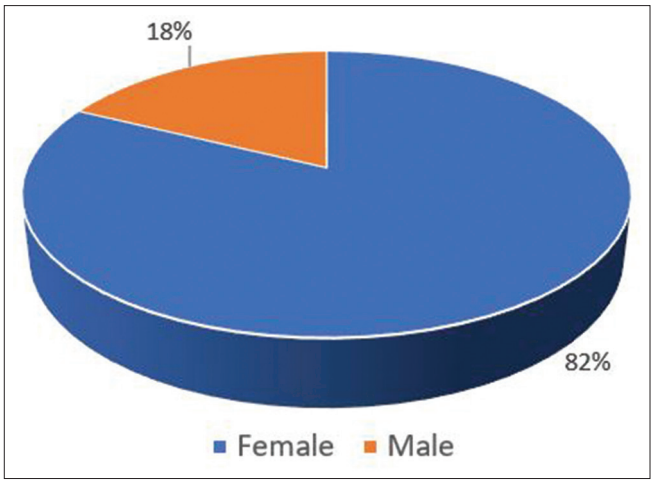


Figure 2: Pie chart showing gender distribution in both the groups

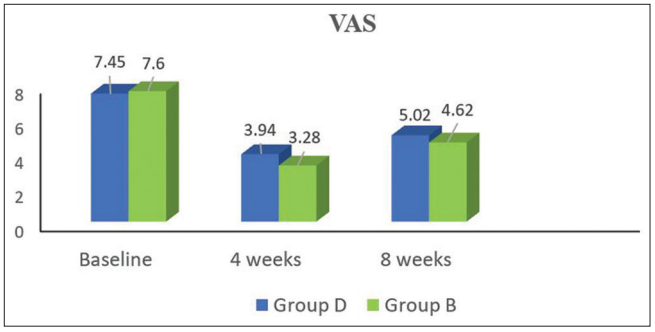


Figure 3: Bar diagram showing a comparison of visual analog scale score

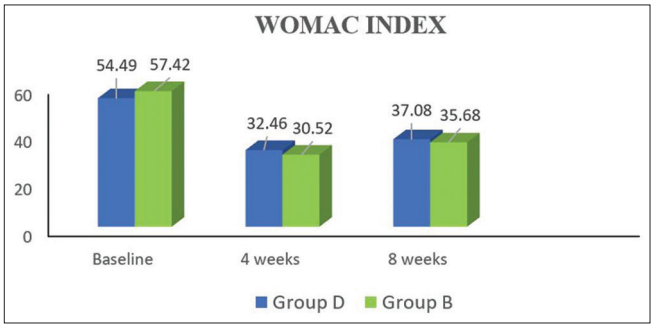


Figure 4: Bar diagram showing a comparison of WOMAC index

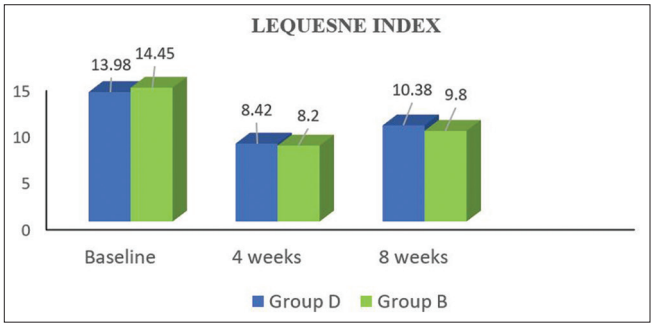


Figure 5: Bar diagram showing comparison of Lequesne index

Discussion

Pain due to OA interferes with daily activities and leads to progressive morbidity. Gradually long walks, bending, getting in and out of car, and rising out of chair can get more and more difficult in these patients.[5,14] Diclofenac has been extensively used clinically and experimentally.[15] Its major use lies in to relieve nociceptive pain arising out of bones and joints. Dose of 75–150 mg diclofenac as compared to other NSAIDs is relatively better tolerated and is the most frequently used NSAID worldwide.[16]

Types of Vitamin B complex (thiamine, pyridoxin, and cyanocobalamin) have been studied for many years for their pain-relieving properties (at doses higher than nutritional doses) when given along with NSAIDs in patients with lumbago, polyneuropathies, rheumatic diseases, and pain after tonsillectomy.[10]

This study showed oral Vitamin B complex along with diclofenac given for 4 weeks resulted in more pain relief in comparison with diclofenac alone as shown by a statistically significant reduction in VAS score at 4 weeks and 8 weeks. Although there was an improvement in stiffness and functionality in both the groups at 4 and 8 weeks, it was not statistically significant.

Our results are comparable with a study by Dehghan[8] that also demonstrated that oral Vitamin B complex combined with diclofenac reduced the total pain severity (VAS score) significantly higher as compared to diclofenac alone after 21 days.

Magaña-Villa *et al*.[17] also reported that combination of diclofenac plus Vitamin B (intramuscular injection) showed better efficacy in relieving pain in patients with OA programmed to knee arthroplasty in the 12 h period of assessment as compared to diclofenac alone. Several studies have highlighted the role of methylcobalamin in neuropathic pain.[18,19] In an *in vitro* study, effect of Vitamin B was inhibited by naloxone suggesting that it has opioid-like action.[20] Thiamine, pyridoxine, and cyanocobalamin are having individual effect on pain pathway, but their effects are enhanced when combined.[21] Ponce-Monter *et al*.[22] also showed that injectable thiamine (100 mg), pyridoxine (100 mg), and cyanocobalamin (1 mg) augment the analgesic efficacy of diclofenac in acute pain associated to lower limb fracture before and after surgery. In one study, it was also observed that Vitamin B not only potentiated analgesic effect of diclofenac in acute episode of lower back pain but also improvement in mobility and specific aspects of functionality.[16]

Mibielli *et al*.[16] observed that adverse events reported over 1 week in their study were minor and not significant such as gastrointestinal symptoms such as dyspepsia, flatulence, diarrhea, and constipation and central nervous system symptoms such as nausea and headache similar to our study. Although less but side effects do occur with diclofenac such as damage to gastric mucosa, liver, and renal impairment and increase cardiovascular risk.[23]

Since, Vitamin B complex could potentially enhance the analgesic efficacy of diclofenac, as it is used as an add-on therapy to diclofenac, it may reduce the dose of diclofenac, thereby minimizing the side effects of NSAIDS.

In animal studies, B complex vitamins (thiamine and cyanocobalamin) have been found to provide pain-relieving and antineuralgic action. This is possibly by acting on mediators in nociceptors, by making more norepinephrine available in pain inhibitory pathway, regeneration of damaged nerve fibers, and inhibiting ectopic discharges.[9]

Conclusion

Vitamin B complex as an add-on therapy to diclofenac was found to cause a significant reduction in pain score. It could be a promising drug in patients with OA to improve the analgesic effect, when combined can reduce the dose of diclofenac, thereby minimizing the side effects.

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Conflicts of interest

There are no conflicts of interest.

References

1. Jayadev C, Price A. Basic science of osteoarthritis. In: Ramachandran M, Eastwood DM, Singh DB, Skinner JA, editors. Basic Orthopedic Sciences. 2nd ed. London: Hodder Arnold; 2017. p. 439-51.
2. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage 2013;21:1145-53.
3. Rogers MW, Wilder FV. The association of BMI and knee pain among persons with radiographic knee osteoarthritis: A cross-sectional study. BMC Musculoskelet Disord 2008;9:163.
4. Solomon L. Osteoarthritis. In: Solomon L, Warwick D, Nayagam S, editors. Apley's System of Orthopedics and Fractures. 9th ed. London: Hodder Arnold; 2010. p. 85-102.
5. Felson DT. Osteoarthritis. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 19th ed. New York: McGraw-Hill Publishers; 2015. p. 2226-33.
6. Verkleij SP, Luijsterburg PA, Koes BW, Bohnen AM, Bierma-Zeinstra SM. Effectiveness of diclofenac versus acetaminophen in primary care patients with knee osteoarthritis: [NTR1485], DIPA-trial: Design of a randomized clinical trial. BMC Musculoskelet Disord 2010;11:7.
7. Steinmeyer J, Konttinen YT. Oral treatment options for degenerative joint disease – presence and future. Adv Drug Deliv Rev 2006;58:168-211.
8. Dehghan M. Comparative effectiveness of B and E vitamins with diclofenac in reducing pain due to osteoarthritis of the knee. Med Arch 2015;69:103-6.
9. Gazoni MF, Malezan WR, Santos FC. B complex vitamins for analgesic therapy. Rev Dor Paulo 2016;17:52-6.
10. Calderon-Ospina CA, Nava-Mesa MO, Arbeláez Ariza CE. Effect of combined diclofenac and B Vitamins (thiamine, pyridoxine, and cyanocobalamin) for low back pain management: Systematic review and meta-analysis. Pain Med 2020;21:766-81.
11. Dixit V, Dixit M, Hegde V, Jadhav S, Sathe S. Clinical evaluation of conventional and laser tooth preparation using visual analogue scale. J Dent L 2013;7:27.
12. Ebrahimzadeh MH, Makhmalbaf H, Birjandinejad A, Keshtan FG, Hoseini HA, Mazloumi SM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in Persian speaking patients with knee osteoarthritis. Arch Bone Jt Surg 2014;2:57-62.

13. Lequesne MG, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee. Validation--value in comparison with other assessment tests. Scand J Rheumatol Suppl 1987;65:85-9.
14. Ralston SH, McInnes IB. Rheumatology and bone disease. In: Walker BR, Colledge NR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd ed. Edinburg: Elsevier; 2014. p. 1057-135.
15. Sweetman SC. Analgesics, anti-inflammatory drugs and antipyretics: Diclofenac. In: Martindale: The Complete Drug Reference. 35th ed. London: Pharmaceutical Press; 2009.p. 44-7.
16. Mibielli MA, Geller M, Cohen JC, Goldberg SG, Cohen MT, Nunes CP, *et al.* Diclofenac plus B vitamins versus diclofenac monotherapy in lumbago: The DOLOR study. Curr Med Res Opin 2009;25:2589-99.
17. Magaña-Villa MC, Rocha-González HI, Fernández del Valle-Laisequilla C, Granados-Soto V, Rodríguez-Silverio J, Flores-Murrieta FJ, *et al.* B-vitamin mixture improves the analgesic effect of diclofenac in patients with osteoarthritis: A double blind study. Drug Res (Stuttg) 2013;63:289-92.
18. Alvarado AM, Navarro SA. Complex B vitamins: Physiology and therapeutic effect on pain. Am J Pharmacol Sci 2016;4:20-7.
19. Maladkar M, Tekchandani C, Dave U. Post-marketing surveillance of fixed dose combination of methylcobalamin, alpha lipoic acid, folic acid, biotin, benfotiamine and Vitamin B6-nutripathy for the management of peripheral neuropathy. J Diabetes Mellitus 2014;4:124-32.
20. Reyes-García G, Castillo-Henkel C, Medina-Santillán R, Terán-Rosales F, Granados-Soto V. Mechanisms of analgesic action of B vitamins in formalin-induced inflammatory pain. Proc West Pharmacol Soc 2002;45:144-6.
21. Talaei A, Siavash M, Majidi H, Chehrei A. Vitamin B12 may be more effective than nortriptyline in improving painful diabetic neuropathy. Int J Food Sci Nutr 2009;60 Suppl 5:71-6.
22. Ponce-Monter HA, Ortiz MI, Garza-Hernández AF, Monroy-Maya R, Soto-Ríos M, Carrillo-Alarcón L, *et al.* Effect of diclofenac with B vitamins on the treatment of acute pain originated by lower-limb fracture and surgery. Pain Res Treat 2012;2012:104782.
23. Langman MJ, Weil J, Wainwright P, Lawson DH, Rawlins MD, Logan RF, *et al.* Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994;343:1075-8.