ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Early experience with the use of *Cissus quadrangularis* and *Dalbergia sissoo* therapy on bone marrow edema and knee pain associated with degenerative medial compartment knee osteoarthritis

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Submission: 01-01-2024 Revision: 29-02-2024 Publication: 01-04-2024

ABSTRACT

Background: Bone marrow edema (BME) refers to the accumulation of excess fluid in the bone marrow, often indicative of injury or inflammation. Some studies suggest that incorporating plant-based therapies, rich in anti-inflammatory compounds and nutrients, may contribute to alleviating BME and promoting overall bone health. **Aims and Objective:** The study aims to evaluate the effect of *Cissus quadrangularis* and *Dalbergia sissoo* therapy on BME and knee pain associated with degenerative medial compartment knee osteoarthritis (OA). **Materials and Methods:** This retrospective study examined seven individuals with medial tibial condyle BME associated with medial compartment OA. These patients were treated with initial 10 days of non-steroidal anti-inflammatory drugs along with once-a-day tablet containing *C. quadrangularis* (500 mg) and *D. sissoo* (400 mg). Visual analogue scores (VAS) and Oxford knee score (OKS) were noted at the beginning of the therapy and at 12 weeks of completion of therapy. Before treatment, BME (percentage of the medial tibial condyle) and presence/absence of subtle subchondral fracture were diagnosed with T2-weighted magnetic resonance imaging (MRI) images, and subsequently, its resolution was confirmed with a repeat MRI scan at 12 weeks. **Results:** At the end of 12 weeks of therapy, there was a statistically significant improvement in the mean VAS score (baseline 8.14 ± 0.90 improved to 2.00 ± 0.58 at 12 weeks, [P < 0.0001]), OKS (baseline 25.71 ± 1.80 improved to 36.57 ± 1.51 at 12 weeks, [P = 0.0001]), and there was statistically significant decrease in mean BME (baseline 37.86 ± 10.35% decreased to 14.29 ± 4.50% at the end of 12 weeks, [P = 0.0001]). **Conclusion:** Our early experience shows that the combination therapy of *C. quadrangularis* + *D. sissoo* is effective in relief of pain, improvement in knee function, and resolution of BME associated with medial compartment knee OA. This combination is safe, effective, and well-tolerated by patients' population.

Key words: Bone marrow edema; *Cissus quadrangularis*; *Dalbergia sissoo*; Osteoarthritis

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v15i4.61272

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Millions of individuals worldwide suffer from osteoarthritis (OA), the most common joint condition. It is a chronic degenerative disorder of multifactorial etiology typified by loss of articular cartilage, presence of osteophytes, subchondral bone cysts and bone sclerosis, and altered bone turnover accompanied by multiple biochemical and

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morphological changes in synovial membrane and joint capsule.[1] It affects 22–39% of Indians and is more common in women and increases with age. About 45% of 65-year-old women have OA symptoms and 70% have radiological proof.[1] Knee pain reduces an individual's quality of life and is a significant contributor to lost workdays, and doctor visits.[2] The loss of articular cartilage is a hallmark pathologic event in OA, but its pathogenesis is poorly understood.[3] Specifically, information about what factors identify joints at high risk for pain and disease progression is scarce.

Magnetic resonance imaging (MRI) plays a key role in the detection of subtle or inflammatory changes in the joint environment. It permits the detection of subchondral bone marrow structural changes that are not visible in conventional radiography.[3,4] These subchondral bone marrow changes in the form of bone marrow edema (BME) become visible with low signal intensity on T1-weighted images and with high signal intensity on fat-suppressed T2-weighted (T2w).[4]

Diffuse or focal BME pattern, also termed a bone marrow lesion, is a principal MRI finding commonly associated with OA and part of all semi-quantitative grading systems.[5] These lesions have been associated with various degenerative disorders such as meniscal tears, cartilage loss and the development of subchondral cysts, mechanical misalignment, and eventually the need for arthroplasty.[6] Osteoclasts and secretion of cytokines play a key role in the pathogenesis of BME with irritation of the nearby nerve fibers triggering severe pain.[4] It can be transitory or chronic in nature and can be localized or migratory.[6]

The link between BME and symptomatic OA pain has been well documented. According to Felson et al.,[7] painful knee OA patients were 2.5 times more likely to have BME, compared with asymptomatic patients. A study by Link et al.,[8] using the radiographic Kellgren-Lawrence Score to define OA, found that the BME pattern was present in 36% of patients with mild, 77% with moderate, and 81% of patients with severe OA.

Different studies have documented that conservative therapy regimens, such as non-steroidal analgesics or reduction of weight-bearing and operative management with core decompression did not resolve the BME-associated pain.[4] Therefore, alternative therapy options have been studied, for example, bisphosphonates or prostacyclins. Prostacyclins have a broad range of contraindications (e.g., for patients with coronary heart disease, heart failure, or high risk of bleeding), and are more complicated in terms of application while bisphosphonates are associated with various adverse effects such as nausea, esophageal irritation, heartburn, muscle and bone pain, and osteonecrosis of jaw.[5] Poor adherence to oral bisphosphonates can mitigate their therapeutic benefit.[9]

Due to their pharmacological property, *Cissus quadrangularis* and *Dalbergia sissoo* are likely to help in cases of BME. A possible mechanism for the benefits of *C. quadrangularis* and *D. sissoo* is through modulation of BMP2/Wnt/ß -catenin signal transduction pathways.[10,11]

Aims and objectives

The current study aims to evaluate the effect of tablets containing *C. quadrangularis* (500 mg) and *D. sissoo* (400 mg) therapy on BME and knee pain associated with degenerative medial compartment OA of the knee. We hereby report our early experience with this novel treatment.

MATERIALS AND METHODS

Study design and participants

The study was approved by the Ethics Committee and carried out in accordance with the Declaration of Helsinki's tenets. This study is a single-center, retrospective study (between January 2022 and January 2023). Each patient completed an informed consent form after learning about alternative treatment choices (such as analgesics and physical therapy).

Inclusion criteria

Patients above the age of 18 years of age with BME of the medial tibial condyle associated with medial compartment OA changes and willing to participate were included in the study.

Exclusion criteria

Involvement of joints other than the knee (e.g., the hip or the ankle) affected by the bone marrow or complex regional pain syndrome being the source of pain.

Clinical information

The clinical information, that is, pain intensity assessed by visual analog score (VAS score) from 0 to 10, and Oxford knee score (OKS) from 0 to 48, was assessed by an independent observer who was not part of the treating team/study. The VAS and OKS were observed at the initiation of the treatment and at 12 weeks of completion of therapy. The BME and presence/absence of the subtle subchondral fracture were diagnosed with the T2-weighted MRI images at the beginning of the treatment and subsequently at 12 weeks.

In addition, questions regarding the history of past injuries (including those to the knee that was injured), the usage of analgesics, and existing illnesses were asked of the patients. Adverse effects were documented as mild

adverse effects if they did not require treatment, moderate side effects if they required outpatient care, and severe side effects if they necessitated hospitalization, death, or incapacity because of the given medication. To protect the confidentiality of each participant's identity, all this data were anonymized.

Radiological analysis

All MRIs were evaluated by an experienced musculoskeletal radiologist and the percentage of BME (% affection of the medial tibial condyle) was calculated.

Statistical analysis

The information was documented using Excel (Microsoft, US) spreadsheets. The Student's t-test was applied to compare the pre- and post-treatment VAS scores and OKS. The comparison between the pre-treatment and post-treatment percentage of bone edema of the medial tibial condyle was done with the help of the Chi-squared test. P<0.05 was considered significant.

RESULTS

Population characteristics for the study

Nine patients who had undergone *C. quadrangularis* and *D. sissoo* tablet therapy for BME were screened. One patient was lost-to-follow-up, while another declined to participate. As a result, our study comprised a total of seven patients (Figure 1).

Table 1 displays the general characteristics of the study population. The mean age of the study population, which ranged from 51 to 72 years, was 62.57 years for 71% (n=5) of the female participants. In our study population, the right knee was affected in 57.14% (n=4) of cases.

All subjects experienced relevant limitations in daily life activities before diagnosis and movement-induced/load-dependent pain. Before therapy, the mean pain score was 8.14 with a standard deviation of 0.90, underscoring the severe degree of disability. The Oxford knee assessment of joint function yielded a mean score of 25.71±1.80, underscoring the severe degree of disability.

Radiological patterns

Figure 2 depicts the standard MRI diagnosis of a BME. In the study population (n=2), subchondral insufficiency fracture was seen in 28.57% (n=2) of the cases (Figure 3). The lateral condyle of the tibia was spared, only the medial condyle was found to be involved in all the cases.

Clinical changes after treatment

The mean VAS score at the beginning of treatment was 8.14±0.90 which improved to 2.00±0.58 at 12 weeks which is statistically significant (P<0.0001) (Table 2).

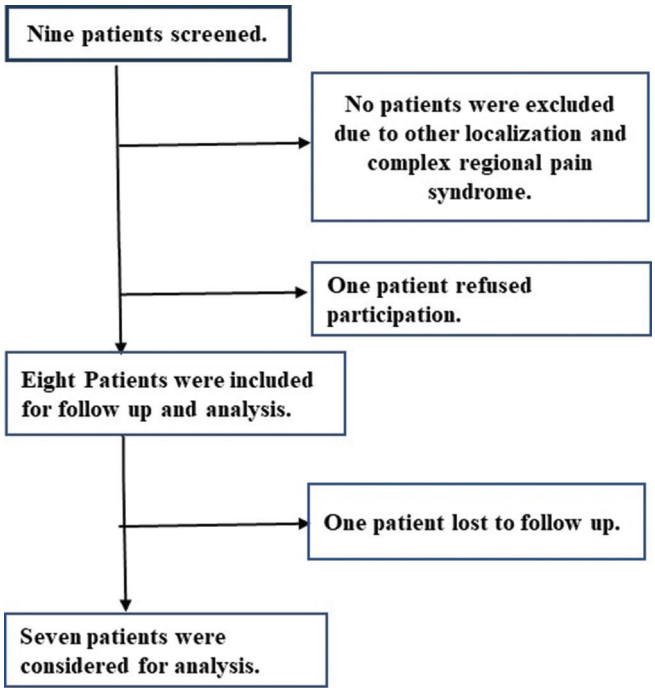

Figure 1: Patient recruitment flowchart

Table 1: Baseline characteristics of the study population (n=7)

Variables	Values
Age (years)	
Mean±SD	62.57±6.71
Range	51–72
Sex	
Females	5 (71)
Males	2 (29)
Associated comorbidities, n (%)	
Hypertension	3 (42.85)
Diabetes mellitus	2 (28.57)
Chronic kidney insufficiency	Nil
Gout	Nil
Autoimmune disorder	Nil
Steroid use	Nil
Etiology, n (%)	
Degenerative	7 (100)
Traumatic	Nil
Iatrogenic	Nil
Affected knee, n (%)	
Right	4 (57.14)
Left	3 (42.86)

SD: Standard deviation

The OKS also improved from 25.71±1.80 at the beginning of therapy to 36.57±1.51 at 12 weeks which is statistically significant (P<0.0001) (Table 3).

The mean BME at the beginning of therapy was 37.86±10.35% which decreased to 14.29±4.50% at the end of 12 weeks (statistically significant P<0.0001) (Table 4 and Figure 4).

All patients showed good tolerability to treatment and no patient experienced any significant side effects.

Table 2: Changes in Visual analogue score (VAS) from baseline to week 12 of Cissus quadrangularis and Dalbergia sissoo combination therapy (represented as Mean±SD, p value <0.05 considered significant)

Serial number	Age (years)	Gender	Pretreatment VAS score	Posttreatment VAS score	P-value
1	68	Female	7	2	
2	59	Female	9	3	
3	72	Female	9	1	
4	51	Female	8	2	
5	62	Female	8	2	
6	58	Male	9	2	
7	68	Male	7	2	
Mean±SD	62.57±6.71		8.14±0.90	2.00±0.58	<0.0001

VAS: Visual Analog Scores, SD: Standard deviation

Table 3: Changes in Oxford knee score (OKS score) from baseline to week 12 of Cissus quadrangularis and Dalbergia sissoo combination therapy (represented as Mean±SD, p value <0.05 considered significant)

Serial number	Age (years)	Gender	Pre-treatment OKS	Post-treatment OKS	P-value
1	68	Female	26	38	
2	59	Female	24	36	
3	72	Female	24	36	
4	51	Female	28	36	
5	62	Female	26	38	
6	58	Male	24	34	
7	68	Male	28	38	
Mean±SD	62.57±6.71		25.71±1.80	36.57±1.51	<0.0001

SD: Standard deviation, OKS: Oxford knee score

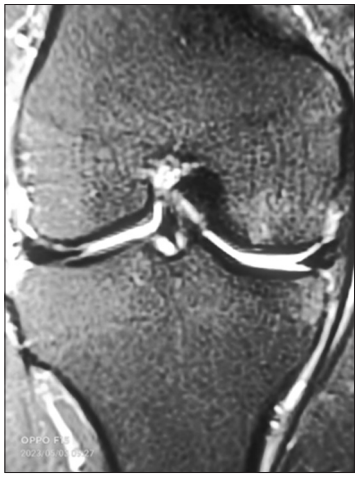

Figure 2: Typical diagnostic finding of bone marrow edema on magnetic resonance imaging

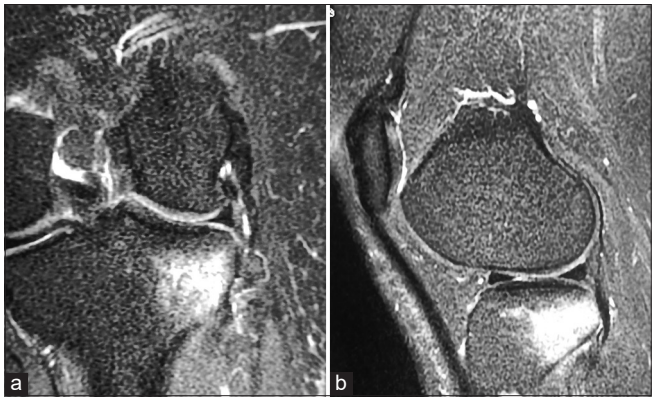

Figure 3: Subchondral insufficiency fracture on magnetic resonance imaging (Anteroposterior [a] and lateral view [b])

DISCUSSION

The results of our study show that patients of OA knee with BME benefit from the administration of formulation containing *C. quadrangularis* (500 mg) and *D. Sissoo* (400 mg) when taken for 3 months. These patients reported not only relief of pain and improved knee joint function but also a significant decrease in BME. Although BME can be a self-limiting disease, the formulation containing *C. quadrangularis* and *D. sissoo* can positively have an effect over its natural course, and potentially delay operative management.

Modulation of the Wnt/ß-catenin pathway may be one mechanism through which *C. quadrangularis* and *D. Sissoo* are beneficial. Mesenchymal stem cells (MSCs) have been demonstrated to differentiate into osteoblasts through the Wnt/ß-catenin signaling pathway.[12-16] Multipotent cells capable of developing into osteoblasts, adipocytes, or chondrocytes among other cell types are MSCs. The activation of lineage-specific transcriptional regulators by the proper regulatory factors is necessary for MSCs to commit to either of the two lineages.[17]

Table 4: Changes in Bone marrow edema (BME) % from baseline to week 12 of Cissus quadrangularis and Dalbergia sissoo combination therapy (represented as Mean±SD, p value <0.05 considered significant)

Serial number	Age (years)	Gender	Pre-treatment percentage of marrow edema (medial tibial condyle)	Post-treatment percentage of marrow edema (medial tibial condyle)	P-value
1	68	Female	40	10	
2	59	Female	60	10	
3	72	Female	35	15	
4	51	Female	30	20	
5	62	Female	35	15	
6	58	Male	35	20	
7	68	Male	30	10	
Mean±SD	62.57±6.71		37.86±10.35	14.29±4.50	<0.0001

SD: Standard deviation

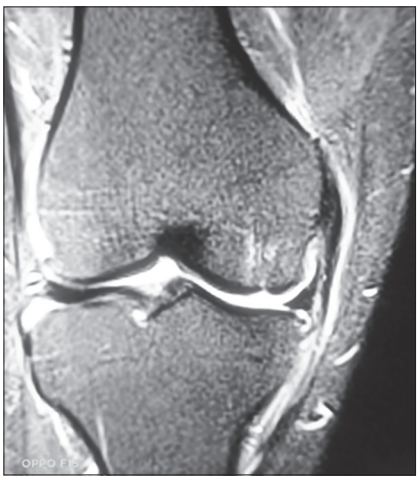

Figure 4: Resolution of the bone marrow edema after 12 weeks of Cissus quadrangularis and Dalbergia sissoo combination therapy on magnetic resonance imaging

C. quadrangularis stimulates the proliferation and differentiation of MSCs and promotes new bone formation through the Wnt-ß-catenin signaling pathway for pre-osteoblast formation and reduces adipocyte differentiation by regulating adipogenesis-related genes and proteins.[12-14] *D. sissoo* can stimulate osteoblastogenesis and inhibit osteoclastogenesis and adipocyte differentiation through Wnt/b-catenin signaling pathway.[15-17] MSCs instead of adipocytes lineage are diverted toward osteoblast lineage, Inhibiting osteoclast formation and cytokine activity (interleukin-1β). Less adipocyte volume may lead to a decrease in intraosseous pressure which ultimately can decrease BME.

A study by Bhujade et al., demonstrated that *C. quadrangularis* treatment for 14 days leads to normal bone marrow with the absence of edema formation in an adjuvant-induced arthritis model.[18] Animal study by Kothari et al., done in OA model of rats, *D. sissoo* protected joint cartilage and prevented subchondral bone deterioration *in vivo* while *in vitro*, its active ingredient caviunin glycoside prohibited interleukin-1β induced effects and inhibited OA. *D. sissoo* could be a potential treatment option to treat OA.[19]

The mean reduction in VAS score after 3-month treatment observed in our study was 6.14. A study by Küchler et al., showed a significant mean reduction of VAS score by 3.6 (from 7.4 to 3.8) with ibandronate during a median follow-up of 41.5 months.[4]

To the best of our knowledge, this is the first study to assess the positive benefits of *D. sissoo* and *C. quadrangularis* tablets on BME and knee pain related to degenerative medial compartment OA of the knee. The advantage of this study is that each MRI was evaluated by a skilled radiologist with expertise in musculoskeletal radiology. In addition, because it was a single-center trial with the same study team throughout the follow-up period, patient management was well standardized.

Limitations of the study

Our study has certain limitations. The first is a small number of patients and the second is the absence of a comparator group. Encouraged by the findings of this study, further prospective studies with a placebo/active comparator are needed and planned to assess the magnitude of the beneficial effects of *C. quadrangularis* and *D. sissoo*.

CONCLUSION

Our early experience shows that the combination therapy of *C. quadrangularis* (500 mg) + *D. sissoo* (400 mg) helps in the relief of pain, improvement in knee function, and resolution of BME in the medial compartment degenerative knee OA. The study also shows that this combination therapy is safe, effective, and well-tolerated by the patient population.

ACKNOWLEDGMENT

None.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Authors Contribution:
SBL- Definition of intellectual content, implementation of the study protocol, data collection, data analysis, manuscript preparation, and submission of article; **RVS-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **CD and VL-** Design of study, statistical analysis, and Interpretation; **DS-** Manuscript preparation and review, Literature survey, Coordination, and Manuscript finalization.

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Source of Support: Nil, **Conflicts of Interest:** None declared.