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Comparing Bone Marrow Stimulation And Intraarticular Injection Of Hyaluronic Acid Triamcinolone Combination And Bone Marrow Stimulation Alone On Functional Outcome, Cartilage Repair And Serum Interleukin 15 Level On Moderate Stage Knee Osteoarthritis Patients

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ABSTRACT

Background: *Knee osteoarthritis (KOA) is the most prevalent musculoskeletal disorder and the leading cause of disability in adults over the age 45 years. Many patient and provider think of arthroplasty as the only surgical option for treatment of KOA advanced stage. However, there are several surgical options for KOA which can be therapeutic alternative. This study aims to compare the effect of bone marrow stimulation (BMS) and intraarticular injection of hyaluronic acid (HA) triamcinolone combination vs BMS alone on functional outcome, cartilage repair and serum interleukin 15 level in moderate stage KOA patients.*

Method: *This study was conducted on patients who presented to Orthopedic Department Hasri Ainun Habibie Hospital from February 2023 to June 2024. 36 consecutive patients who diagnose as moderate KOA based on Kellgren-Lawrence classification, divided into 2 groups. Observation group underwent BMS and intraarticular injection of HA triamcinolone combination and control group underwent BMS alone. WOMAC score, MRI AMADEUS score, and serum IL-15 level was examined before the procedure and 6 months after the procedure.*

Result: *study showed that WOMAC score significantly increased on both groups, but the change in observation group was better, especially in pain and stiffness subscale. MRI AMADEUS score significantly increased on observation group. IL-15 serum level significantly decreased on both groups. We found positive significant correlation between IL-15 and functional outcome on observation group.*

Conclusion*: BMS and intraarticular injection of HA triamcinolone improve functional outcome, cartilage repair and reducing serum IL15 level better than BMS alone in moderate stage KOA patients.*

Keywords: *Bone Marrow Stimulation, Osteoarthritis, WOMAC score, Interleukin 15, cartilage repair.*

1. INTRODUCTION

Osteoarthritis is the most common form of arthritis and a leading cause of disability worldwide, largely due to pain, the primary symptom of the disease (1). Some studies showing that OA of the

knee occurs in at least 30% of people after the age of 50 years, and in 80% of people older than 75 years. Of the patients with OA, over 80% will have limitation of movement and greater than 25% cannot perform their activities of daily living (2).

Treatment designed for osteoarthritis should aim at reducing pain, improve joint mobility, and limit functional impairment. It can be achieved by pharmacological and non-pharmacological means (3). In mild OA, lifestyle alterations, physical therapy, and painkillers are widely used (4). However, these therapies only treat the symptoms and have no chondroprotective effect. The cartilage is wholly worn in end-stage OA, and the subchondral bone is exposed. As such patients cannot benefit from chondroprotective therapies, knee arthroplasty remains the treatment of choice. In the best case, patients have increased mobility and decreased pain levels after surgery, leading to improved quality of life. With increasing life expectancy and the limited lifetime of the implants, chondroprotective approaches to postponing surgery have been extensively researched. Intra-articular injections of various drugs, preferably used in patients with moderate OA, offer a promising approach. They are administered locally, targeting the chondrocytes directly while limiting systemic side effects (4). A number of clinicians have confirmed that hyaluronic acid (HA) and corticosteroid (CS) supplementation is an effective means of controlling the symptoms of OA in the knee (5). Hyaluronan is critical for the homeostasis of the joint as an organ, in part, because it provides the rheological properties (viscosity and elasticity) of the synovial fluid. These properties depend upon both the concentration and the molecular weight of the hyaluronan in the synovial fluid. In osteoarthritis, the hyaluronan is both smaller in size and lower in concentration (6).

In late-stage OA, the cartilage is almost completely destroyed, and subchondral bone is exposed, so knee arthroplasty (total knee replacement/total knee arthroplasty) is the treatment of choice. Total knee replacement (TKR) is a very effective treatment option for patients with disabling and severe end-stage knee pain resulting from osteoarthritis, post-traumatic arthritis and inflammatory arthritis. It is usually life-changing surgery and most patients report improvements in outcome measures scoring pain, function and quality of life. Despite the majority (71%) of TKR patients perceiving an improvement in their knee symptoms (7). Dissatisfaction rates of up to 30% are reported following surgery (8). The literature suggests that 14%–53% of TKR patients have persisting knee pain and 7%–50% have poor knee function, with mean published dissatisfaction rates ranging anywhere from 15% to 30%,5, 6 and with only 22% of patients rating their results as “excellent” (9).

Many patients and providers think of arthroplasty as the only surgical option for the treatment of late stage osteoarthritis of the knee. However, there are several other surgical options for osteoarthritis which can be therapeutic alternatives. Contemporary options include (i) arthroscopic debridement or lavage, (ii) marrow-stimulation techniques, such as microfracture, (iii) periosteal or perichondral grafting, (iv) autologous chondrocyte implantation, (v) osteochondral autograft transplantation, and (vi) osteochondral allograft transplantation. Each technique offers its own advantages and disadvantages, but there are very few controlled comparative clinical or basic science studies. In the setting of osteoarthritis with full-thickness chondral lesions, there is still debate concerning optimal treatment options (10).

Although many management modalities have been described, a method that maintains the biomechanical characteristics of the cartilage for a long time and promotes the formation of new cartilage tissue that remain healthy is not yet available (11). Currently, microfracture technique, autologous chondrocyte transplantation, and mosaicplasty have gained wide acceptance. Microfracture technique is based on the differentiation of bone marrow stem cells to chondrocytes

for repairing the chondral defect. This method is a relatively simple, cheap, and minimally invasive technique that can be performed in one session (12). On the other hand, some studies have reported insufficient differentiation of stem cells with microfracture resulting in fibrocartilage repair tissue formed on the defect site without regeneration of hyaline cartilage, which essentially determines the quality of repair (13). However, Steadman et al. indicated that tissue developed after microfracture repair is a mixture of fibrous and hyaline cartilage tissue, and the repair process occurring in the defect site can last for nearly 2–3 years, with tissue formed during this period undergoing physiologic remodeling. In addition, some investigators have also stated that new modifications should be added to the microfracture technique with the intention of decreasing the prolonged duration of physiologic remodeling and improving the quality of the repair tissue (11).

As life expectancy increases and the age at which patients are diagnosed with knee OA decreased, exploring alternative therapies for treating OA becomes necessary especially on moderate stage OA. The primary aims of this study is to determine the effect of bone marrow stimulation (BMS) and intraarticular injection of hyaluronic acid (HA) triamcinolone combination versus BMS alone on functional outcome, cartilage repair and serum Interleukin-15 level in patient with moderate stage KOA.

2. MATERIAL AND METHODS

The study was conducted in accordance with Declaration of Helsinki (as revise in 2013). This study protocol was approved by Ethic Review Board from Hasanuddin University Faculty of Medicine, Makassar, South Sulawesi, Indonesia (UH 21020115) and written informed consent was obtained from the patient for this study. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. This study has been published previously in case report with 3 patients. (14)

2.1. Participant

Thirty six consecutive patients with moderate stage KOA enrolled in the study after giving written informed consent. They diagnosed according to anamnesis, physical examination and radiographic criteria (Kellgren-Lawrence grading scale). Patients were recruited from among those attending the outpatient clinic of Orthopedic and Traumatology, Hasri Ainun Habibie Hospital, Parepare, South Sulawesi, Indonesia. Inclusion criteria included failed conservative treatment modalities of at least 1 years, but were not limited to activity modification, weight loss, physical therapy, and oral medication.

Exclusion criteria included patients with ligament rupture, diabetes mellitus, knee infection, traumatic arthritis, secondary OA, history of knee operation, Cartilage defect > 2 cm^2 based on MRI examination.

2.2. Study design

The patients divided in 2 group (18 patients for observation group and 18 for control group). The study was explained to the participants. Each participant provided an informed consent. This study protocol was approved by the Ethics Committee of the Faculty of Medicine, Hasanuddin University, South Sulawesi, Indonesia

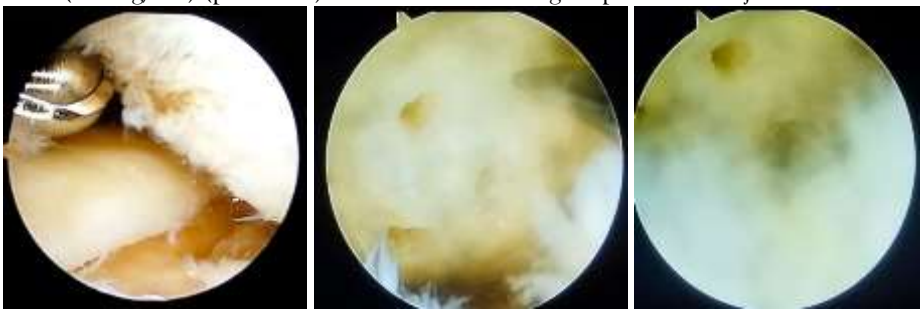
All the patients studied were subjected to demographic data collection, anthropometric measurements, which included age, gender, height, body weight, and musculoskeletal examination focusing on both knees. Assessment of functional outcome was performed using the Western

Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The WOMAC has three different subscales for the assessment of pain, stiffness, and function. The scores are summed for items in each subscale. The total WOMAC score of the three subscales was graded as follows: mild (from 0 to 24), moderate (from 25 to 48), severe (from 49 to 72), and extreme (from 73 to 96). Cartilage defect and repair assessment using MRI with Area Measurement and Depth & Underlying Structure (AMADEUS) score. Laboratory investigation in the form of measurement of IL-15 serum level was performed using the enzyme linked immunosorbent assay (ELISA) technique for the quantitative detection of IL-15.

Before operation, all patient underwent MRI examination for cartilage defect, 1 cc venous blood was taken for IL-15 serum level examination and complete the Western Ontario and McMaster Universities Osteoarthritis Index WOMAC questionnaire.

2.3. Treatment Protocol

All surgeries were performed by one physician with over 8 years of arthroscopic surgery experience and over 13 years orthopedic surgery experience. In operation room, all patients in supine position under spinal anesthesia. Knee positioned at 90^0 with routine sterilization and draping. A tourniquet was used to control surgical area bleeding, with inflation pressure set at 250 mmHg. All patients underwent arthroscopic portal establishment through anteromedial and anterolateral approaches. Arthroscopic shaver was used for joint debridement: removal of loose bodies, removal of unstable cartilage fragments, resection of proliferated and thickened synovium. After completing debridement, cartilage defect areas were treated. Specific parameters for microfracture were selected based on the following criteria; drilling depth: determined by subchondral bone plate thickness, typically 3-4mm, confirmed by observation of bone marrow exudation; hole spacing: based on cartilage defect area size, maintaining 3-4mm uniform spacing to ensure coverage of entire defect area while avoiding adjacent channel destruction of subchondral bone plate structure; hole diameter: using microfracture awls to ensure adequate bone marrow stem cell exudation without affecting bone plate stability. Care was taken to maintain perpendicular drilling direction to the joint surface, avoiding oblique channels (picture 1). After microfracture, patients in observation group were given intraarticular injection with HA 2,5 ml (10 mg/ml) combined with triamcinolone 5 ml (10 mg/ml) (picture 2). Patient in control group was not injected intraarticularly.



Picture 1. Debridement and microfracture by awl

Post-operatively, patients were allowed to weight bear as tolerated and were given prophylactic antibiotics (ceftriaxone 1 gr/12 hours) were administered for 3 days, and 1 gr paracetamol/8 hours injection for pain control, and other symptomatic treatments based on individual patient conditions. All patients were scheduled to have appointment at one week for

wound care, two weeks for opening the surgical stitches and six months for clinical function/outcome evaluation (WOMAC score), MRI and IL -15 serum examination.

Picture 2. Intraarticular injection of HA triamcinolone combination

2.4.Statistical Analysis

Data analysis was performed using SPSS 26.0 statistical software. Quantitative data were first tested for normality using the Shapiro-Wilk test. In normally distributed data, between-group comparisons were made using independent sample t-tests, pre and post operation comparisons were made using paired T test. In non-normally distributed data, between-group comparisons were made using Mann-Whitney U tests and pre and post operation comparisons were made using Wilcoxon test. The analytic measures included the Mann–Whitney test, Wilcoxon test, independent T test, paired T test and the Spearman correlation test. Statistical significance was assigned to any P value at less than 0.05.

3. RESULT

3.1. Subject Characteristic/Demographics

This study included 36 consecutive patients with moderate knee OA which divided in 2 group of 18. Observation group was patients who received bone marrow stimulation and intraarticular injection of HA Triamcinolone combination. Control group was patients who received bone marrow stimulation alone. All 36 arthroscopy procedures were performed without any intra-operative complication. No complications were documented within the six-month study period include; infection, bleeding, nerve damage, deep venous thrombosis, pulmonary embolus, allergic reaction, and other.

The mean age was 58.77 ± 4.04 (ranged from 53 to 67 years) in observation group and 58.13 ± 6.31 (ranged from 45 to 72 years) in control group (ranged from 45 to 65 years). 1 patient in observation group was drop out because patient had to move to another province. 3 patients in control group were drop out because 2 patients dead and 1 patient could not undergo MRI examination because he had undergone heart stent surgery. Different demographic data and anthropometric measures of the patients and control groups are summarized in Table 1.

Table 1 Different demographic data and anthropometric measures of the patient and the control groups

Demographics and anthropometric Data	Observation Group (n=17) (mean ± SD)	Control Group (n=15) (mean ± SD)	P

Age	58.77 ± 4.04	58.13 ± 6.31	0.735
Gender:			
Woman	15	12	-
Man	2	3	-
Height (cm)	153.36 ± 5.04	153.40 ± 8.64	0.142
Weight (kg)	65.112 ± 10.39	64.00 ± 12.68	0.309

3.2. Comparison of Functional Outcome

No statistically significant differences were found between the two groups in preoperative WOMAC score. At 6-month follow-up, both groups showed significant improvements in WOMAC score to preoperative levels ($P < 0.05$). Compared to the control group, the observation group showed significantly lower WOMAC score at 6 months postoperatively [(14.18 + 8.97) vs (23.73 + 9.79)], with statistical significance ($P < 0.05$)) (Tables 2). Comparing WOMAC score between observational group and control group before and after operation showed statistical improvement on both group ($P<0.05$) (table 4).

Table 2. Comparison between WOMAC score on observation group and control group before operation and after operation

	Observation Group (n=17) (mean ± SD)	Control Group (n=15) (mean ± SD)	P*
WOMAC score before operation	66.77 + 9.55	69.47 + 6.69	0.920
WOMAC score after operation	14.18 + 8.97	23.73 + 9.79	0.007

*independent T test

3.3. Comparison of Cartilage Repair

No statistically significant differences were found in preoperative and postoperative of cartilage repair (AMADEUS score) between the two groups ($P > 0.05$) (table 3). At 6-month follow-up, observational group showed significant improvements in cartilage repair (AMADEUS score) compared to preoperative ($P<0.05$). Control group show no significant improvement of cartilage repair (AMADEUS score) ($P>0.05$) (table 4).

Table 3. Comparison between IL15 serum level and MRI AMADEUS score on observation group and control group before operation and after operation

	Observation Group (n=17) Median (min-max)	Control Group (n=15) Median (min-max)	P*
IL-15 before operation	126.64 (54.92-129.09)	128.29 (45.75-129.64)	0.104
IL-15 after operation	56.74 (44.59-127.75)	51.41 (43.61-126.15)	0.308
AMADEUS score before operation	55 (30-65)	55 (30-75)	0.905
AMADEUS score after operation	55 (30-65)	55 (35-75)	0.650

*Mann Whitney U test

3.4. Comparison of IL-15 Serum Level

No statistically significant differences were found in preoperative and postoperative of IL-15 serum level between the two groups (P > 0.05) (table 3). At 6-months follow-up, observational and control group showed significant decreased of IL-15 serum level (P<0.05) (table 4).

Table 4. Comparison between observational group and control group before and after operation

	Observation group (n= 17) P	Control group (n=15) P
WOMAC score	<0.001*	<0.001*
IL-15 serum	<0.001**	0.001**
AMADEUS score	0.014**	0.157**

*Paired T test, **Wilcoxon test

3.5. Correlation between IL-15 Serum Level with Functional Outcome and Cartilage Repair

On observational group showed significant positive correlation between IL-15 serum level and functional outcome but no significant correlation between IL-15 serum level and cartilage repair. On control group showed that no significant correlation between IL-15 serum level with functional outcome and cartilage repair (table 5).

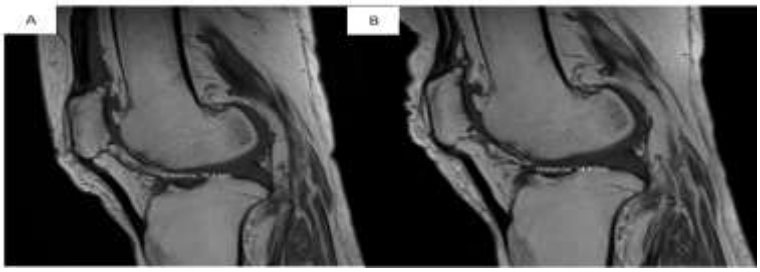
Table 5. Correlation between IL-15 serum level with functional outcome and cartilage repair (MRI AMADEUS score)

	N	Pearson Correlation	p*
Womac Score	17	0.484	0.049
AMADEUS score	17	-0.209	0.421

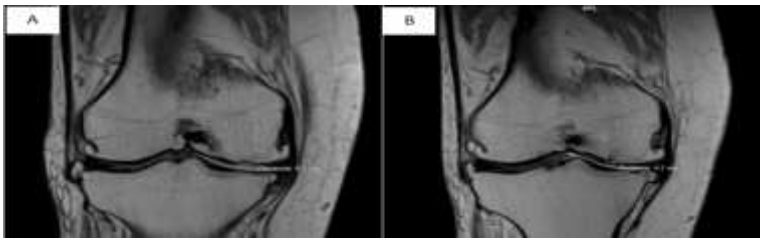
*spearman correlation test

MRI (AMADEUS score) on observation patient, before procedure and 6 months after procedure

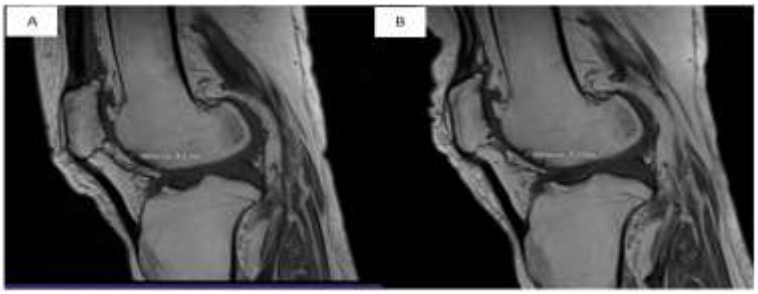
On picture 3.1,3.2,3.3 showed cartilage repair based on AMADEUS score. On picture A. MRI before procedure: cartilage defect: d1 x d2 = 6.3 x 16.1 mm = 1.01 cm^2 (30), defect depth: fullthickness (0), bony defect $\leq$ 5 mm: 4.2 mm (20), total AMADEUS score: 60. On Picture B. MRI after procedure: cartilage defect: d1 x d2 = 4.1 x 14.9 mm = 0.61 cm^2 (n35), defect depth: fullthickness (0), bony defect $\leq$ 5 mm: 3.7 mm (20), total AMADEUS score: 65



Picture 3.1. A. MRI before procedure: cartilage defect area measurement (d1): 16.4 mm. B. MRI after procedure: cartilage defect area measurement (d1): 14.9 mm



Picture 3.2 A. MRI before procedure: cartilage defect area measurement (d2): 6.3 mm B. MRI after procedure: cartilage defect area measurement (d2): 4.1 mm



Picture 3.3. A. MRI before procedure: defect depth and underlying structures (bony defect: 4.2 mm), B. MRI after procedure: defect depth and underlying structures (bony defect: 3.7 mm)

4. DISCUSSION

In this study, we found that BMS and intraarticular injection of HA triamcinolone combination improve functional outcome (WOMAC score). Although in patient with BMS alone there were improvement of functional outcome but the change in BMS and intraarticular injection was better than BMS alone, especially in pain and stiffness subscale of WOMAC. 66,7% patients who received BMS and intraarticular injection of HA triamcinolone combination, confirmed that their pain reduced more than 80% after the procedure and 50% patients confirmed that stiffness reduced more than 80%. 88,2% of patients experienced a change of WOMAC score to mild compared to 46,7% patients without intraarticular injection. This is likely due to the addition of triamcinolone to injection intraarticular where triamcinolone had a rapid anti-inflammatory effect.

For patients with OA and acute synovitis, HA injection alone is typically insufficient to control the inflammation and alleviate pain. As such, co-administration of a CS injection may be necessary to achieve the desired outcome. The results of the present study revealed that combined treatment with HA and CS resulted in a greater improvement knee function compared with HA

alone for the first 3 months post-injection. However, at month 6 there was no significant difference in WOMAC scores between groups. These results suggest that, in the long-term, combined treatment with HA and CS is not superior to HA alone. For patients with acute pain, however, the use of HA and CS together may provide more effective immediate pain relief. Usually, the use of cross-linked HA results in a significant reduction in pain and improved knee function from 6->12 months, as cross-linking is a proven means for prolonging the intra-articular residence time of HA. In the present study, a linear HA was used, which has a shorter degradation half-life compared with cross-linked HA. The shorter effect duration may be due to the intrinsic characteristic of the viscosupplementation injected (16).

Our findings are supported to those reported by Bauer et al who investigates the effects of a glucocorticoid (glucocorticoid, triamcinolone hexacetonide), hyaluronic acid (HA), and a combination of both products on osteoarthritic, they found that cytokine treatment of osteoarthritic chondrocytes with 10% glucocorticoid or a combination of glucocorticoid (GC) and HA showed an anti-inflammatory effect, as TNF-α release was significantly reduced and gene expression patterns of catabolic enzymes tended to be decreased. In contrast, supplementation of HA alone did not show an anti-inflammatory effect, but when combined with GC, it reduced the adverse effects of GC (4). The combination with hyaluronic acid showed an opposite effect with increased stress fiber content. This also occurred in the HA group as a possible consequence of chondrocytes binding to their extracellular environment via focal adhesion complexes (4,17).

This study found that BMS and intraarticular injection of HA triamcinolone improve cartilage repair. Result showed that at 6 months follow up, AMADEUS score increased on 6 patients from 17 observation patients (35,5%), and AMADEUS score increased on 2 patients from 15 control patients. This finding likely because the anti-inflammatory, anabolic, analgesic, and chondroprotective effects of HA have long been recognized. In one study, HA was shown to increase the proteoglycan content of cartilage and promote DNA replication resulting in an enhancement of chondrocyte proliferation. Hagewald et al. suggested that HA might increase formation of the extracellular matrix by ensuring differentiation of matrix cells into mesenchymal stem cells (13,18).

This study similar to the study by Kang et al. who reported that one-time HA injection after microfracture improves quality of the repair tissue. However, this study relied on observational results rather than quantitative reports. Strauss et al. stated that although the quality of repair tissue does not significantly improve at the end of 6 months after 3 HA injections, other cartilaginous tissues outside of the repair site showed less degeneration. A study consisting of subchondral drilling and concomitant HA injection revealed an improvement in repair tissue; however, the short period of HA action time was reported as a major disadvantage (13,18, 19).

In this study, at 6 months follow up showed significant decreased of IL-15 serum level on both groups, this might be because on both group we performed debridement before microfracture which remove loose bodies, debris and other fragment in the knee, so its reduced inflammation and causing decreased of IL-15 serum level. The addition of intraarticular injection of HA triamcinolone combination will help reduce inflammation more quickly and is expected to last longer.

This finding similar to study by Ibrahim et al. that found statistically significant positive correlations between serum IL-15 level with different aspects of primary knee OA indicated that the higher the serum level of IL-15, the more the patient perceived pain, the worse the stiffness and

functional disabilities, and the prediction of disease progression. This was in agreement with the concept that systemic inflammatory markers are associated with a severe course of OA (21,22).

Our study found that there is a positive correlation between decreased of IL-15 serum and functional outcome (WOMAC score), but no correlation between decreased of IL-15 serum level with cartilage repair (AMADEUS score) on microfracture and intraarticular injection of HA triamcinolone group. IL-15 is proinflammatory cytokine that have a contribution on decreased of OA inflammation, so with the decreased of IL-15 serum level, by reducing inflammation pain will decreased. This finding similar to study by Jian Min Sun et al, they found that serum IL-15 levels were independently associated with the intensity of pain but not radiographic severity in OA patients. These results indicated that IL-15 may represent a new potential serum biochemical marker for reflecting the severity of pain in OA patients (22).

This study also support study Warner et al who found that there was association of IL15RA variants with symptoms in knee OA, supporting a role for IL-15 signaling in symptomatic manifestations in patients with established OA. In contrast, we found no evidence to support a role for IL15 in promoting structural damage, as there was no association with radiographic severity in the cohort studies, and IL-15 did not stimulate cartilage degradation despite promoting MMP production in the explants. (23).

The most important thing in the results of this study is the significant improvement in clinical function, decreased serum IL-15 and cartilage levels in moderate KOA patients who underwent bone marrow stimulation and HA triamcinolone combination injection, this shows that bone marrow stimulation and intraarticular injection of HA triamcinolone combination can be used as one of the therapeutic protocols for the treatment of moderate KOA to delay conversion to TKR. In younger patients, this procedure can be a more effective and feasible option for moderate KOA therapy to postpone TKR.

Research by Kim et al. on 32 patients who underwent microfracture with a 10-year follow-up stated that most patients showed 50% defect filling on MRI examination within 2 years after surgery, clinical function improved 1 year after surgery, but gradually worsened after 10 years postoperatively. The average duration of conversion to TKA after microfracture was 7 years (24).

Research by Phua et al. in 38 male and 71 female knee OA patients who underwent microfracture or arthroscopic procedures, stated that arthroscopic procedures could potentially delay TKA for approximately 65 months (5.5 years) in elderly patients with advanced OA (25).

LIMITATION

This study has the following limitations: the follow-up period of only 6 months prevents evaluation of long-term efficacy for both surgical approaches and the lack of postoperative histopathology assessments results in insufficient objective evaluation of cartilage repair quality.

CONCLUSIONS

This study found BMS and intraarticular injection of HA triamcinolone combination shows significant advantages over BMS alone. Results showed that BMS and intraarticular injection of HA triamcinolone combination had better functional outcome, cartilage repair, and decreased of IL-15 serum level at 6 months postoperatively compared to BMS alone group. This indicates that combined treatment can effectively improve patient pain symptoms while enhancing quality of life. This study provides important reference evidence that BMS and intraarticular injection of HA triamcinolone combination can be a valuable treatment for moderate knee osteoarthritis patients.

AUTHOR CONTRIBUTION

Conception and design (AA), analysis and interpretation of data (all author), drafting of the article (BD, MS, MAS), critical revision of article for important intellectual content (all authors), statistical expertise (AAL, BM, EA), collection and assembly of data (AML, AB, FH), final approval (all authors)

DECLARATION OF GENERATE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

All author did not use generative AI and AI assisted technologies in the writing process.

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DECLARATION OF COMPETING INTEREST

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