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Original Research Article | **Orthopaedics and Traumatology**

Evaluation and Outcome of IA Hyaluronic Inj. vs. Corticosteroid Therapy for OA Knee: Tertiary Level Hospital in Bangladesh

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Abstract

Background: There are many types of arthritis, but osteoarthritis (OA) is one of the most frequent. IA injections of corticosteroids into the knee joint may improve pain and impairment by relieving joint inflammation. ***Purpose:*** To evaluate the effectiveness and safety of hylastan, a novel viscosupplements, with a single intra-articular corticosteroid injection in the treatment of knee osteoarthritis pain (OA). Because of its large molecular weight, the sodium hyaluronate in Hylastan is more likely to stay in the joint for an extended period of time than other viscosupplements. ***Methods:*** Multicentered based randomized quasi-experimental comparative study was performed in Shah Mokhdum Medical College, Rajshahi, Bangladesh, from January 2019 to December 2021. Enrolled patients aged ≥40 years. Patients were randomized 1:1:1 to one of three arms: 2 X 4 mL hylastan (n = 129; arthrocentesis then IA hylastan Day 0, same treatment Week 2); 1 X 4 mL hylastan (n = 130; arthrocentesis then IA hylastan Day 0, arthrocentesis only Week 2); steroid (n = 132; arthrocentesis then IA methylprednisolone acetate 40 mg Day 0, arthrocentesis only Week 2). The primary clinical outcome measure was changed from baseline in WOMAC A pain score overall postbaseline visits to Week 26. ***Results:*** Statistically significant pain reduction was observed in all three arms, with similar mean (95 % CI) changes in WOMAC A: 2 X 4 mL hylastan -0.9 (-1.0, -0.7); 1 X 4 mL hylastan -0.8 (-0.9, -0.7); steroid -0.9 (-1.0, -0.8); all $p < 0.0001$ versus baseline. Changes in secondary outcomes were similar in all three arms. Target knee adverse events were comparable for all treatments. ***Conclusions:*** An acceptable safety profile and effective pain relief were found with both IA hylastan injection regimens. The hypothesis of better pain relief with IA hylastan was not met compared to IA corticosteroid. The effectiveness and safety of hylastan compared to other viscosupplements require more investigation. Level of evidence Therapeutic study, Level I.

Keywords: Corticosteroid, Hyaluronic Inj. IA injection, Knee OA.

INTRODUCTION

Osteoarthritis (OA) is characterized by the slow loss of articular cartilage, the remodeling of surrounding bone, and joint inflammation [1]. The elastoviscous properties of the synovial fluid are also diminished owing to a reduction in the concentration and molecular weight of the key component hyaluronan (hyaluronic inj.). They are increasing the potential for cartilage damage due to mechanical stress [2]. The main clinical features are pain and loss of function, which may significantly affect patient quality of life [3]. Primary treatment goals are to reduce pain and stiffness, improve function and quality of life, and limit disease progression, if possible while minimizing toxicity [4]. Clinical guidelines for OA management in the knee recommend combining nonpharmacologic and pharmacologic approaches [5]. Suppose acetaminophen (paracetamol), nonselective non-steroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase-2 (COX-2), Inhibitors are ineffective or poorly tolerated. Most guidelines recommend intra-articular (IA) corticosteroids or viscosupplements [6]. Intra-articular (IA) corticosteroids reduce pain but are generally short-acting, and injection more than four times per year is not universally recommended [7].

Viscosupplementation describes the temporary supplementation of synovial fluid in the OA joint with hyaluronan. To restore normal elastoviscosity and physiological function, decreasing pain and improving mobility [8].

Several pilot clinical studies suggest that viscosupplements also have disease-modifying effects, including possible reduction of synovial inflammation. Several viscosupplements are available but vary by source (animal or bio-fermentation), molecular weight (with or without cross-linking), concentration, volume, and the number of injections required. Most are administered via multiple injections. A Cochrane meta-analysis of viscosupplements studies supported their efficacy versus placebo in relieving pain, with an acceptable safety profile, and suggested a longer duration of benefit versus IA corticosteroids. A new, high-molecular-weight hyaluronan derivative is prepared from bacterially fermented sodium hyaluronate. Hylastan is a formulation with more gel (80 %) than fluid, and its ‘‘soft’’ gel component was developed to remain in the joint. For longer (3–4 weeks after injection) compared with most other viscosupplements, which can increase the duration of treatment effect and minimize the number of injections required.

The objective of this study was to compare two IA hylastan injection regimens with a single IA injection of corticosteroid (methylprednisolone acetate; MPA) in terms of pain reduction, responder rates, and improvements in target knee global assessment scores in patients with symptomatic OA of the knee. We also compared the safety profiles of all three treatments, and a repeat treatment phase was carried out to evaluate safety and efficacy in patients receiving a second hylastan treatment. IA corticosteroid therapy was selected as the comparator as it is a widely accepted treatment option and the most comparable therapy to viscosupplementation at the time of the study. The study hypothesis was that one or two IA hylastan injections would provide superior pain relief over 26 weeks compared with steroids. Two different dosing schedules of hylastan were tested to determine the most effective regimen.

MATERIALS AND METHODS

A multicentered based randomized quasi-experimental comparative study was performed in Shah Mokhdum Medical College, Rajshahi, Bangladesh, from January 2018 to December 2020. Enrolled patients aged ≥40 years. Patients were randomized 1:1:1 to one of three arms: 2 X 4 mL hylastan (n = 129; arthrocentesis then IA hylastan Day 0, same treatment Week 2); 1 X 4 mL hylastan (n = 130; arthrocentesis then IA hylastan Day 0, arthrocentesis only Week 2); steroid (n = 132; arthrocentesis then IA methylprednisolone acetate 40 mg Day 0, arthrocentesis only Week 2). The primary clinical outcome measure was changed from baseline in WOMAC A pain score overall postbaseline visits to Week 26. The study was carried out in compliance with the principles of Good Clinical Practice; all patients provided informed consent at screening. The study comprised a screening phase, a 2-week initial treatment phase with follow-up to Week 26, and a repeat treatment phase with additional follow-up to Repeat Week 26.

Patients

Patients were eligible if they were in good general health, ambulatory, and had primary OA knee pain despite conservative treatment. They were defined as a WOMAC® LK 3.1 pain subscore (WOMAC A) of 1.5–3.5 and moderate or severe walking pain (a WOMAC A1 walking pain subscore of 2–3).The main exclusion criteria were modified Grade 0 or IV; clinically apparent tense effusion; significant valgus/varus deformities, ligament laxity, or meniscal instability. Inflammatory disease, or other condition that affects the joints (e.g., rheumatoid arthritis, metabolic bone disease, gout, active infection). Prior or current symptomatic peripheral vascular disease of the study leg; any musculoskeletal condition that would impede assessment of clinical outcomes; significant mechanical problems. Viscosupplementation within the prior 12 months; systemic/IA corticosteroids within the prior 3 months; target knee arthroplasty at any time; or other surgery within 6 months.

Randomization and treatment

Randomization was carried out on Day 0 (baseline), using a computer-generated randomization scheme and Interactive. Voice Response System (IVRS) provided by Genzyme. Patients were randomized to one of three treatment arms in a 1:1:1 ratio. All patients underwent arthrocentesis on Day0. Subjects in the 1.94 mL hylastan arm received a single IA injection of hylastan SGL-80 on Day 0 and arthrocentesis only at Week 2. Those in the 2 X 4 mL hylastan group received IA hylastan SGL-80 on Day 0 and the same treatment at Week 2 (two separate injections). Subjects in the steroid group received a single 1-mL IA injection of MPA (40 mg/mL) at Day 0 and arthrocentesis only at Week 2. Patients and clinical evaluators were blinded to treatment; the injecting physician was unblinded. The injection procedure and related supplies were screened from patients to maintain blinding. Acetaminophen (paracetamol) 500-mg tablets were provided as rescue medication for target knee pain relief, with 1–2 to be taken every 4–6 h as needed (not exceeding 8 tablets in 24 h) except for within 48 h before a study visit.

Clinical assessments

Clinical evaluations were conducted at baseline and at follow-up weeks 4, 8, 12, 16, 20, and 26 of the study periods. Researchers or research associates handed out questionnaires for the WOMAC® LK 3.1 to patients, filling them out independently. The WOMAC A pain sub-score comprises five questions to measure

pain walking, using stairs, bed, sitting/lying, and standing. It was assessed for each patient using a 5-point, ordinal Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme) to capture their response to each question. Secondary clinical assessments were the proportion of responders according to the Outcomes Measures in Rheumatology Clinical Trials. The proportion of WOMAC A responders (1-category improvement from baseline at each postbaseline assessment), global patient assessment (PTGA), and clinical observer global assessment (COGA). For the PTGA and the COGA, the patient or blinded evaluator, respectively, assessed the target knee using a Likert scale (0 = very well, 1 = well, 2 = fair, 3 = poor, 4 = very poor). 102 patients enrolled, antibody testing was carried out using serum samples and urinalysis to evaluate inflammatory response.

Repeat treatment phase

Patients with a favorable response to initial treatment (1-point decrease in WOMAC A1 at any time and WOMAC A1 score C1) and no major safety concerns, who continued to meet the inclusion/exclusion criteria, were assigned to repeat treatment through the IVRS on Repeat Day 0. Patients initially randomized to hylastan remained in the same group, and those previously receiving steroids were re-randomized to one of the hylastan arms. Treatment was administered on Repeat Day 0 and Repeat Week 2. WOMAC A/A1, PTGA, and COGA were assessed at Repeat Weeks 4, 8, 12, 16, 20, and 26.

Statistical analysis

In WOMAC, a mean difference of 0.32 (a common SD of 0.74) between the hylastan and steroid groups could be detected with 80 percent power with 372 patients. A shift from the starting point over a period of 26 weeks, assuming a 15% dropout rate and a 5% significance level. This study was conducted based on earlier research evaluating the differing longitudinal responses to IA steroid 9 and viscosupplements.

The primary clinical outcome measure was the WOMAC A change from baseline for hylastan versus steroid overall postbaseline study visits in the intent-to-treat population (all patients randomized). This was analyzed using the average scores comprising the WOMAC LK 3.1 A subsection and a repeated measures ANCOVA model, including terms for treatment, center, time, baseline, KL grade, and relevant interactions. Means are present 1 decimal place more than that at which the outcome was recorded, according to the standard statistical procedures of the study sponsor. Sequential hypothesis testing was used to maintain a Type I error rate of 5 %: 2.9 4 mL hylastan was tested against steroids first. If the difference was significant at the 0.05 level, 1.9 4 mL hylastan was then tested against steroids. Generalized estimating equations were used to estimate the odds ratio of positive response over 26 weeks according to OMERACT- OARSI responder criteria. The odds ratio for a positive response was analyzed using logistic regression for the PTGA, COGA, WOMAC A1, and WOMAC A responders.

RESULTS

Patient flow through the study is shown in Fig 1. Patient characteristics and target knee history were similar in all three arms (Table 1).

Clinical outcomes

The estimated mean changes from baseline after 26 weeks for the WOMAC A pain score were similar in all three arms:2 X 4 mL hylastan -0.9 (95 % CI -1.0, -0.7); 1 X 4 mL hylastan -0.8 (-0.9, -0.7); steroid -0.9 (-1.0, -0.8), with no significant difference between hylastan and steroid. Within-group changes from baseline over 26 weeks were statistically significant in all three arms (all P \ 0.0001; Fig. 2). OMERACT-OARSI and WOMAC A responder rates at Week 26, and the improvements from baseline to Week 26 in PTGA, COGA, and WOMAC A1 walking pain, were similar in all three treatment groups (Table 2). There were no significant differences between treatment groups in the overall odds ratio estimates for a positive response for any of the secondary clinical outcomes (data not shown). A significantly higher mean daily dose of rescue medication was taken in the 2 X 4 mL hylastan group versus the steroid group (Table 2); there was no statistically significant difference between the 1 X 4 mL hylastan and steroid groups.

Repeat treatment phase

For all four efficacy measures, mean scores improved in all treatment groups from Repeat Day 0 to Repeat Week 26 during the repeat treatment period (data not shown). The acceptable safety profile was confirmed in the repeat treatment phase; there was no increase in severity or incidence of target knee AEs in patients receiving repeat hylastan: 28 % of patients in the 2 X 4 mL hylastan group, 32 % in the 1 X 4 mL hylastan group, 23 % in the steroid- 2 X 4 mL hylastan group, and 38 % in the steroid- 1 X 4 mL hylastan group. In all groups, arthralgia (24 %), joint swelling (13 %), joint stiffness (10 %), and joint effusion (6 %) were the most common target knee AEs.

DISCUSSION

Results from this study showed a statistically significant increase in the WOMAC score. In all three arms, a pain score from baseline for 26 weeks. The improvements All three treatments resulted in the relief of OA-associated knee pain, as demonstrated by a reduction in WO- MAC A pain score by approximately one point. This was evident in all groups at the first assessment (Week 4) and was maintained to Week 26. Walking pain was also reduced. The positive effect of treatment on pain and function was also confirmed by the increase in patients classed as OMERACT-OARSI responders. The patient self-assessment of the target

knee OA condition was also improved with treatment, along with the clinical observer global by another meta-analysis of seven of these studies, all comparing hyaluronan with corticosteroids [12].

Table 1: Subject characteristics at initial treatment phase baseline (ITT population)

	2 X 4 mL hylastan (*n* = 129)	1 X 4 mL hylastan (*n* = 130)	Steroid (n = 132)
Age in years, mean (SD)	62.0 (9.7)	60.6 (9.9)	60.1 (9.3)
(range)	(39–82)	(43–85)	(42–85)
Men/women, n (%)	38 (29)/91 (71)	51 (39)/79 (61)	41 (31)/91 (69)
BMI in kg/m^2, mean (SD)	31.7 (6.6)	31.2 (6.4)	30.8 (6.5)
Kellgren–Lawrence grade, n (%)			
I	2 (2)	9 (7)	7 (5)
II	30 (24)	45 (33)	39 (30)
III	91 (73)	81 (60)	85 (65)
IV	1[a]	0	0
Target knee history			
Months since OA diagnosis, mean (SD)	30.2 (37.5)	38.9 (45.7)	38.3 (38.4)
(range)	(0.0–225.1)	(0.0–239.4)	(0.0–195.2)
Previous treatment, n (%)			
Viscosupplementation	17 (14)	35 (26)	23 (18)
IA corticosteroids	48 (39)	60 (44)	53 (41)
Arthrocentesis	10 (8)	28 (21)	26 (20)
Arthroscopy	44 (36)	56 (42)	43 (33)
Arthroplasty	0	0	0
Other surgical procedures	12 (10)	11 (8)	13 (10)

ITT intent-to-treat (all patients randomized), SD standard deviation, BMI body mass index, OA osteoarthritis, IA intra-articular
One patient in the 2 X 4 mL hylastan group had Kellgren– Lawrence Grade IV OA and therefore was erroneously enrolled in the study

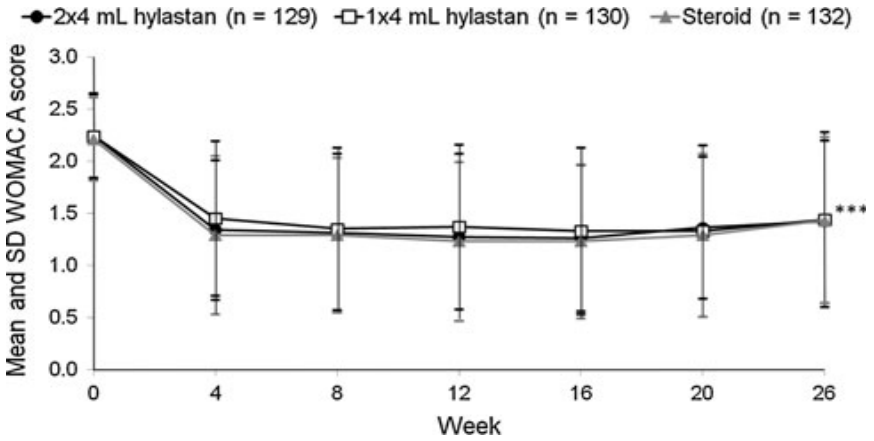

Fig 1: WOMAC A pain scores over the initial 26-week treatment period. Circles denote the 2 X 4 mL hylastan group, squares the 1 X 4 mL hylastan group, and triangles the steroid group

*P \ 0.0001 versus baseline (all groups). *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

Fig 1 WOMAC A pain scores over the initial 26-week treatment period. Circles denote the 2 X 4 mL hylastan group, squares the 1 X 4 mL hylastan group, and triangles the steroid group.

Assessment Our findings are in line with previous studies, which showed pain relief and improvements in function and global patient assessment in knee OA with viscosupplements and pain relief with corticosteroids [10]. However, the similar duration of pain relief with hylastan and steroid was unexpected and differs from most other studies comparing viscosupplements and steroids for knee OA. A Cochrane review found no statistically significant differences between IA corticosteroids and viscosupplements 1–4 weeks post-injection, but at 5–13 weeks, viscosupplements were more effective [11]. This was supported

Table 2: Secondary clinical outcomes (ITT population)

	2 X 4 mL hylastan (n = 129)	1 X 4 mL hylastan (n = 130)	Steroid (n = 132)
OMERACT-OARSI Responders at Week 26, n (%)	73 (57)	64 (49)	66 (50)
PTGA for target knee, mean (SD)			
Baseline	2.4 (0.7)	2.4 (0.6)	2.4 (0.6)
Week 26	1.5 (0.9)	1.7 (1.0)	1.6 (0.9)
COGA for target knee, mean (SD)			
Baseline	2.3 (0.7)	2.3 (0.7)	2.3 (0.8)
Week 26	1.3 (1.0)	1.4 (1.0)	1.5 (1.1)
WOMAC A1 walking pain, mean (SD)			
Baseline	2.3 (0.5)	2.3 (0.5)	2.3 (0.5)
Week 26	1.5 (0.9)	1.4 (0.9)	1.5 (0.8)
WOMAC A responders [a] at Week 26, n (%)	45 (35)	45 (35)	40 (30)
Rescue medication use mg/day, mean (SD)	963.8 (952.5) b	903.7 (1054.5)	706.5 (763.8)

ITT intent-to-treat (all patients randomized), OMERACT-OARSI Outcomes PTGA patient global assessment, SD standard deviation,
[a] Defined as a 1-category improvement from baseline in WOMAC A at a postbaseline assessment
[b] *P* = 0.036 versus steroid (two-sample t-test).

For the first two weeks, corticosteroids were more successful at alleviating pain than hyaluronan, but by Week 4, they were both equally effective, and by Week 8, hyaluronan was more effective until the final evaluation (Week 26). As IA corticosteroids (including MPA 40 mg) have been shown to be effective in relieving pain versus placebo in clinical trials, it is unlikely that our findings reflect a lack of clinical effect in all three arms. However, the lack of a placebo group precludes assessment of the true magnitude and duration of effect for both treatments. Limited evidence suggests that sustained effects can occur with IA corticosteroids; an earlier meta-analysis noted that benefit with corticosteroids (cortivazol3.75 mg or MPA 120 mg). Remained at 16–24 weeks compared with placebo [13], and a single-blind, randomized study comparing joint tidal irrigation and triamcinolone acetonide 40 mg found maintenance of pain relief, to Week 26 in 29 % of patients receiving corticosteroid [14]. There are likely differences according to dose and injection regimens, and the extended benefit in these studies may be related to the doses used. Studies assessing the same MPA dose as the present study (40 mg) reported a loss of pain relief by 8 weeks versus placebo [15] and improvements from baseline that were maintained up to the last assessment at 8 weeks. There is also potential for different responses according to the level of inflammation and radiological grade. Steroid efficacy may be greater in earlier diseases (KL Grade I/II) and when there is greater inflammation, but study data supporting this hypothesis are limited. Arden and colleagues noted greater benefit with IA triamcinolone acetonide in patients with KL Grade 0/I/II disease. The presence of knee effusion predicted a better response to IA corticosteroid in two studies [16].

But others did not support this association. In the present study, exploratory analyses (data not shown) indicated a greater WOMAC A change from baseline for KL Grade I/II disease in the steroid group versus the hylastan groups (p = 0.0287 versus 1 X 4 mL hylastan), whereas in patients with KL Grade III, the changes favored the hylastan groups (not significant versus steroid). Similar outcomes were seen in hip OA studies [17], although data from another hip OA study were contradictory. This possible effect of radiological grade on the duration of corticosteroid effect requires further exploration. It is also possible that strict application of the correct IA injection technique may have a prolonged impact on IA corticosteroids. In the present study, there was significant emphasis on the proper technique, but this may not always be practiced, leading to extraarticular injection and reduced duration of effect [18]. It is unlikely that the similar outcomes are due to a lack of assessment sensitivity at later time points, as the standard deviation was consistent for all three arms throughout the study (Fig 1).

The findings of this study are relevant to current clinical practice as they confirm that the new viscosupplements, hylastan, are well tolerated and provide symptomatic relief of knee pain due to OA for up to 6 months with a single injection. This information is pertinent to physicians involved in the management of patients with OA of the knee, especially those patients with continued pain despite conservative treatment. Furthermore, repeat treatment with hylastan

effectively reduced pain in patients who had previously received hylastan treatment, with no change in severity or incidence of adverse events in the target knee. These findings indicate that multiple hylastan treatments may be given in an individual patient as part of their chronic treatment for knee OA.

CONCLUSION

Knee osteoarthritis (OA) sufferers could benefit from the addition of Hylastan as an alternative therapy option. Both first and repeat 26-week treatment phases of Hylastan had acceptable tolerability profiles; there were no safety concerns and target knee AEs were comparable to those reported in the steroid group. Other viscosupplements or other therapy for knee OA should be studied further to see how hylastan compares clinical efficacy and safety.

REFERENCES

1. Altman, R. D. (2009). Practical considerations for the pharmacologic management of osteoarthritis. *The American journal of managed care*, *15*(8 Suppl), S236-243. https://pubmed.ncbi.nlm.nih.gov/19817510/
2. Pelletier, J. P., & Martel-Pelletier, J. (1993). The pathophysiology of osteoarthritis and the implication of the use of hyaluronan and hylan as therapeutic agents in viscosupplementation. *The Journal of rheumatology. Supplement*, *39*, 19-24.
3. Kauppila, A. M., Kyllönen, E., Mikkonen, P., Ohtonen, P., Laine, V., Siira, P., ... & Arokoski, J. P. (2009). Disability in end-stage knee osteoarthritis. *Disability and rehabilitation*, *31*(5), 370-380.
4. Jordan, K. M., Arden, N. K., Doherty, M., Bannwarth, B., Bijlsma, J. W. J., Dieppe, P., ... & Dougados, M. (2003). EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Annals of the rheumatic diseases*, *62*(12), 1145-1155.
5. Moskowitz, R. W. (2009). The burden of osteoarthritis: clinical and quality-of-life issues. *The American journal of managed care*, *15*(8 Suppl), S223-229.
6. Gamble, R., Wyeth-Ayerst, J., Johnson, E. L., Searle, W. A., & Beecham, S. (2000). Recommendations for the medical management of osteoarthritis of the hip and knee. *Arthritis Rheum*, *43*(9), 1905-1915.
7. Zhang, W., Moskowitz, R. W., Nuki, G., Abramson, S., Altman, R. D., Arden, N., ... & Tugwell, P. (2008). OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis and cartilage*, *16*(2), 137-162.
8. Bellamy, N., Campbell, J., Welch, V., Gee, T. L., Bourne, R., & Wells, G. A. (2006). Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane database of systematic reviews*, (2), CD005321.
9. Caborn, D., Rush, J., Lanzer, W., Parenti, D., Murray, C., & Synvisc 901 Study Group. (2004). A randomized, single-blind comparison of the efficacy and tolerability of hylan GF 20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee. *The Journal of rheumatology*, *31*(2), 333-343.
10. Bjordal, J. M., Klovning, A., Ljunggren, A. E., & Slørdal, L. (2007). Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials. *European Journal of Pain*, *11*(2), 125-138.
11. Bellamy, N., Campbell, J., Welch, V., Gee, T. L., Bourne, R., & Wells, G. A. (2006). Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database of Systematic Reviews*, (2).
12. Bannuru, R. R., Natov, N. S., Obadan, I. E., Price, L. L., Schmid, C. H., & McAlindon, T. E. (2009). Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: A systematic review and meta-analysis. *Arthritis Care & Research*, *61*(12), 1704-1711.
13. Arroll, B., & Goodyear-Smith, F. (2004). Corticosteroid injections for osteoarthritis of the knee: meta-analysis. *Bmj*, *328*(7444), 869.
14. Arden, N. K., Reading, I. C., Jordan, K. M., Thomas, L., Platten, H., Hassan, A., & Ledingham, J. (2008). A randomised controlled trial of tidal irrigation vs corticosteroid injection in knee osteoarthritis: the KIVIS Study. *Osteoarthritis and cartilage*, *16*(6), 733-739.
15. Jones, A., & Doherty, M. (1996). Intra-articular corticosteroids are effective in osteoarthritis but there are no clinical predictors of response. *Annals of the rheumatic diseases*, *55*(11), 829-832.
16. Gaffney, K., Ledingham, J., & Perry, J. D. (1995). Intra-articular triamcinolone hexacetonide in knee osteoarthritis: factors influencing the clinical response. *Annals of the rheumatic diseases*, *54*(5), 379-381.
17. Migliore, A., & Anichini, S. (2017). Intra-articular therapy in hip osteoarthritis. *Clinical Cases in Mineral and Bone Metabolism*, *14*(2), 179-181.
18. Jones, A., Regan, M., Ledingham, J., Pattrick, M., Manhire, A., & Doherty, M. (1993). Importance of placement of intra-articular steroid injections. *BMJ: British Medical Journal*, *307*(6915), 1329.