PMS9

Placebo Effect in Knee Osteoarthritis: A Targeted Literature Review on The Challenges, Hypotheses, And Potential Solutions

Hofer K[1], Lin M[1], Pourrahmat MM[1], Fazeli MS[1]

[1] Evidinno Outcomes Research Inc., Vancouver, BC, Canada

Introduction

- Although knee osteoarthritis (KOA) is one of the leading causes of disability globally,[1] there are currently no treatments to prevent, slow, or reverse disease progression.
- Viscosupplementation through intra-articular (IA) injections of hyaluronic acid (IA-HA) or corticosteroids (IA-CS) have shown promise for the long-term treatment of KOA symptoms such as pain.[2,3]
- Although treatment with IA-HA delivers a clinically meaningful response for pain reduction, many IA treatments have failed to demonstrate significant improvements compared to IA placebo.[4]
- Such findings may be attributed to a consistently large placebo effect that has been reported in clinical trials of KOA measuring pain relief. Within these clinical trials, results may be confounded by factors such as patient expectations for treatment.[5-7]
- The placebo effect is a well-known phenomenon that has been documented in many diseases including depression, pain, migraine, chronic fatigue syndrome, asthma, hypertension, irritable bowel syndrome, and Parkinson's disease. In a clinical trial setting, it has been documented to have substantial impact on subjectively measured outcomes.[8]
- Although it is not necessary to separate the placebo effect from the treatment effect in clinical practice, the same cannot be said for clinical trials, within which a treatment's efficacy must be demonstrated relative to placebo to be brought to market.[9]
- Therefore, it is important to understand the impact of IA placebos when assessing subjective outcomes in KOA.

Objective

- The aim of this review was to describe the existing evidence on the **challenges**, **hypotheses**, and **potential solutions** to mitigate the intra-articular (IA) placebo effect in clinical trials investigating the effect of IA therapies in reducing pain in KOA.

Methods

- A comprehensive search was performed in MEDLINE®, Embase, and CENTRAL via OvidSP (inception to December 16, 2019) to include literature on challenges, hypotheses, and proposed solutions to mitigate the IA placebo effect on pain-related outcomes in clinical trials. Study eligibility criteria were defined using the PICO (Population, Intervention, Comparator, Outcomes) framework, which guided study selection.
- The population of interest was adult KOA patients (≥18 years of age) who had received any or no intervention, compared to IA saline as placebo. Alternative placebos such as sham injection (stick needle only or no injection of fluid), acupuncture, and moxibustion were excluded, as they do not involve an injection of fluid as IA saline does.
- Study characteristics (such as publication type, study country, study design, study setting, blinding methods, length of follow-up, and sample size), patients characteristics (age, gender, disease severity, and race/ethnicity) and outcomes of interest regarding challenges, hypotheses or proposed solutions were extracted from included studies.
- Extracted hypotheses, solutions, and challenges were summarized and manually sorted into common categories.
- Results were narratively summarized.

Results and Discussion

Trial Characteristics

- A total of 40 publications were included in the literature review (**Figure 1**),[4-43] consisting of literature reviews (n=15 systematic reviews; n=6 narrative reviews; n=4 targeted reviews), randomized controlled trials (RCT; n=10), single-arm clinical trials (n=2), and one of each of the following publication types: comment on an RCT (n=1), consensus statement (n=1), and a meta-analysis protocol (n=1) (**Figure 2**).

Figure 1. PRISMA diagram

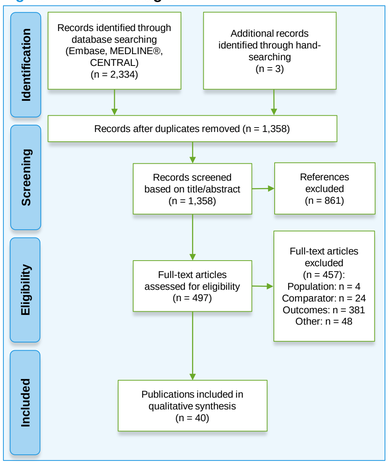
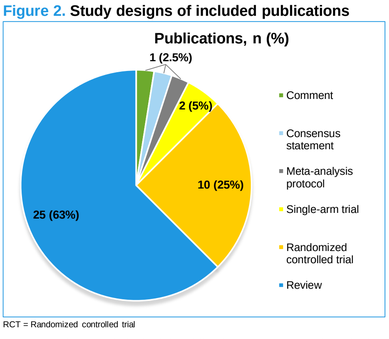


Figure 2. Study designs of included publications



RCT = Randomized controlled trial

- Among the 12 clinical trial publications, seven used a single-center study design, and five were multi-center. Of the RCTs, eight studies were double-blinded, one was open-label, and one was single-blinded.
- Total sample size across the clinical trials evidence ranged from 30 to 588 KOA patients, and length of follow-up ranged from 2 weeks to 2 years.
- Most studies were conducted in the United States (n=3) and the United Kingdom (n=3), followed by Denmark (n=2), Belgium (n=1), Canada (n=1), the Netherlands (n=1), and Sweden (n=1).
- Notably, of the 12 clinical trial publications that were included due to their relevant discussions of the placebo effect, only 2 studies reported achievement of significant positive results for their active treatment arms, which may explain why the placebo effect was discussed so extensively.
- A summary of the challenges, hypotheses, and solutions to mitigate the placebo effect in KOA clinical trials identified in the literature review is provided in **Table 1**.

Table 1. Summary of identified challenges, hypotheses, and solutions to mitigate the IA placebo effect in KOA clinical trials

Evidence Type	Category	Sub-Category	n
Hypotheses (n=26)	Factors that Impact Placebo Effect (n=16)	Invasiveness	9
		Administration; Route	7
		Baseline pain	5
		Sample size	4
		Administration; Frequency	3
		Branding	2
		Colour	2
		Cost	2
		Effect of active treatment	1
		Number of tablets†	1
		Verbal suggestion mediated relief in anxiety	1
		Unclear if affected by blinding	1
		Not affected by type of pain scale (e.g., WOMAC, VAS)	1
	Biological Mechanisms (n=13)	Aspiration of synovial fluid	7
		Dilution of inflammatory mediators	4
		Neurobiological mechanisms	2
		Psychological effect	2
		Descending pain modulatory pathway	1
		Dopamine release	1
		Endogenous opioids	1
		Frontal cortex and limbic system	1
		Genetics	1
		Low levels of cholecystokinin	1
		Nociceptive pain processing pathways in dorsal horn of spinal cord	1
		Removal of debris	1
		Subcortical pain transmission centres	1
		Subcortical reward mechanism	1
	Confounders and Trial Design Factors (n=12)	Comedications*	5
		Small sample size*	5
		Natural fluctuation in disease severity*	3
		Hawthorne effect*	3
		Regression to the mean*	3
		Rescue medication*	2
		Clinical study setting and provider type	2
		Appropriate footwear*	1
		Background arthrocentesis*	1
		Assistive devices for ambulation*	1
		Occupational therapy*	1
		Physiotherapy*	1
		Weight loss*	1
		Spontaneous improvement*	1
		Lack of washout period*	1
		Lack of a natural history comparison*	1
		Prohibition of rescue medication*	1
		Response bias*	1
		Statistical methods not powered to detect between-group differences*	1
	Patient Factors (n=11)	Patient expectation/beliefs	5
		Patient education	3
		Patient perception; Physician confidence/experience/competency	2
		Personality traits	2
		Patient perception; Innovative therapy	1
		Patient perception; Knowledge of being treated	1
		Patient perception; Knowledge of high-tech equipment	1
		Desire to please	1
		Previous experience of effectiveness	1
		Observing drug effectiveness in others	1
		Not affected by age	1
		Not affected by gender	1
		Not affected by social/physical demographics	1
		Not affected by patient expectations of being randomly assigned to an active treatment	1
	Active Treatment Factors (n=4)	Strength of active treatment	2
		Treatment effect size	2
	Patient-Physician Interaction (n=3)	Patient-physician interaction	1
		Culture	1
		Religion	1
	Physician Factors (n=3)	"Personal attention factor"	1
		Confidence	3
		Optimism for treatment effects	3
		Attentiveness	1
		Certainty/assurance of diagnosis/prognosis	1
		Desire to follow-up	1
		Warmth (friendliness)	1
	Other (n=2)	IA placebo has active treatment effects	1
		No explanation for placebo effect	1
Challenges (n=19)	Impact on Active Treatments (n=11)	Diminish/mask comparative efficacy of active IA treatments	10
		Placebo effect inflates strength of treatment arm	1
		Difficult to market treatment options	1
	Impact on Clinical Trials (n=6)	Placebo effect varies across individuals, trials, outcomes, diseases, interventions, and study site	4
		Blinding attempts to mitigate placebo effect are often unsuccessful	1
		Studies with large placebo effects are less likely to be published	1
		Placebo effect is difficult to estimate	1
		Lack of standardization of placebo types	1
	Other (n=6)	Placebo effect is long-lasting	5
		Mechanism of placebo effect is unknown	1
Solutions (n=16)	Clinical Trial Design and Interpretation of Results (n=11)	Weighing relevance of trials	4
		Inclusion of a "no treatment" arm or sham injection as control	4
		IA saline not to be considered a placebo	3
		Awareness	2
		Active treatment instead of placebo for control	1
		Blinding needed	1
		Standardization of placebo across trials	1
	Harnessing the Placebo Effect (n=7)	Placebo use as treatment	3
		Make use of beneficial effects of placebo effect in chronic distressing conditions	2
	Further Research (n=2)	Research of placebo's mechanism of action	2
		Use of individual patient data (IPD) to provide insight into different predictors of placebo effect	1

† The evidence cited for this hypothesis was in the context of the placebo pills. However this may be applicable to number of treatments (i.e., number of intra-articular injections), although this is unclear. IA = Intra-articular, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, VAS = Visual Analog Scale. * Indicates challenges, hypotheses, or solutions that were not consistently regarded by authors as related to the placebo effect, but rather to the inability to detect differences between treatment groups. Note that the "n" in this table refers to the number of publications reporting each of the categories and subcategories, and it is likely that several primary papers have been counted more than once..

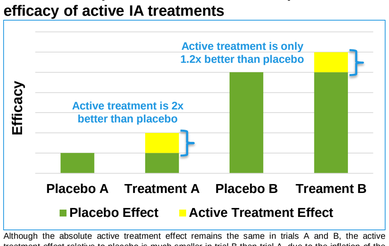
Patient Characteristics

- Among the 12 clinical trial publications, all but one study reported mean age, within which age ranged from 54 (Standard deviation [SD]: 11) to 72.1 (SD: 1.7) years at baseline across treatment groups.
- Most studies (n=9) had a higher proportion of female participants (>50%), with female proportion ranging from 39% to 87% across all studies reporting.
- Across five studies reporting, the proportion of patients with Kellgren-Lawrence grade I, II, and III at baseline ranged from 0% to 15.9%, 32.0% to 67.6%, and 29.9% to 68.0%, respectively. No studies included patients with Kellgren-Lawrence grade IV.
- Race was poorly reported across studies, with only two studies providing proportion of Caucasian patients, which was up to 81% of the total population in one study, and 100% and 97.6% of patients in either treatment arm in the other study.

Challenges

- Challenges identified in the publications were extracted and sorted into three categories:
  1. Challenges impacting active treatments
  2. Challenges impacting clinical trials
  3. Other
- Across these categories, the most commonly reported challenge was the diminishing or masking effects of the placebo effect on the comparative efficacy of active IA treatments in clinical trial publications (n=10).
  - Masking or diminishing of the relative efficacy is commonly observed across the KOA literature, due to a particularly high placebo effect in this population, and can have detrimental effects on the ability to prove the efficacy/effectiveness of these treatments.
- In support of this finding, one study also reported that large placebo effects make it difficult to bring treatment options for KOA to market, as these treatments often do not show clinically meaningful benefit over placebo in clinical trials, and therefore do not move forward into approval and distribution to this patient population in need of treatments.
- The masking effects of inflated placebo effects on relative active treatment effects is demonstrated in **Figure 4**.

Figure 4. Demonstration of the diminishing/masking effects of the placebo effect on the comparative efficacy of active IA treatments



Although the absolute active treatment effect remains the same in trials A and B, the active treatment effect relative to placebo is much smaller in trial B than trial A, due to the inflation of the placebo effect.

- Other notable challenges that were commonly reported were the long-lasting effects of placebo treatment (n=5), which may inhibit the ability to detect between-group differences even after prolonged periods of time. Additionally, studies reported the observation that placebo effects consistently vary across individuals, trials, outcomes, diseases, interventions, and study sites (n=4).
  - Lack of consistency in placebo effects may make it challenging to account for it, and to power one's study accordingly, when designing a clinical trial. If not accounted for, a large placebo effect may result in non-significant active treatment effects.

Hypotheses

- Hypotheses for the IA placebo effect were sorted into eight categories:
  1. Hypotheses/description of factors that change placebo effect
  2. Biological mechanisms
  3. Confounders and trial design factors
  4. Patient-related factors that impact/explain placebo effect
  5. Active treatment-related factors that impact placebo effect
  6. Patient-physician interactions
  7. Physician-related factors that impact/explain placebo effect
  8. Other
- Across these categories, the most commonly reported hypothesis explaining the IA placebo effect was the relationship between invasiveness of the intervention and increased placebo effect (n=9), which describes how more invasive treatments such as surgery show a higher placebo effect than oral placebo pills.
- Similarly, seven publications attributed a large placebo effect to be impacted by route of administration, for which studies described that the placebo effect was much greater in trials that used interventions such as intra-articular injections, compared to oral placebo pills.
- A relatively high number (n=13) of publications also reported a biological hypothesis for the placebo effect, the most common of which was IA saline's effect on aspiration of the joint, which was described to have clinical benefits in KOA patients.
- Twelve publications described confounders or factors related to clinical trial design that impacted the placebo effect, the most common of which was the use of background comedications as a potential confounder.
  - Notably, there was inconsistency across included publications on which factors were considered to be impacting the placebo effect *per se,* and which factors were affecting the difference in effect sizes between treatment groups. Generally, the expert reviews and extensive narrative reviews focused on the placebo effect were clearer to make the distinction between the two types of factors than the randomized controlled trials.

Solutions

- Solutions to mitigate the IA placebo effect were sorted into the following three categories:
  1. Considerations for clinical trial design and interpretation of results
  2. Harnessing the placebo effect and making use of it
  3. Suggestions for further research in this field
- One of the most commonly reported solutions (n=4) when interpreting results of a placebo-controlled clinical trial in KOA was to carefully consider the relevance and validity of the findings of the study, by understanding the impact of the placebo effect, determining whether blinding was sufficient, or seeing whether a control group was used (and what type of control was used).
- Another common solution for the placebo effect (n=4), which was more tailored to clinical trial designers, was the inclusion of a "no treatment" arm or sham injection as control in addition to an IA placebo arm, which would allow for the separation of the potential active treatment effects of IA saline from the "true" placebo effect.
  - Alternatively, three publications suggested that IA saline not be considered as a placebo at all.

Conclusions

- Although the underlying mechanism of the placebo effect is largely unknown, many explanations and mitigation strategies for this phenomenon have been proposed.
- Potential solutions to mitigate the overwhelming placebo effect in KOA trials include change in trial design such as addition of "no treatment" true controls, or removal of IA saline as a viable placebo altogether.
- Further elucidation and development of solutions to mitigate the IA placebo effect may help guide the strategic development of future clinical trials in KOA.
- Additionally, the effects of a patient's culture and setting on the placebo effect has been poorly investigated, and most studies report placebo effects in the context of the North America and Europe. Further exploration into the cultural factors that may impact the placebo effect is suggested to understand what role geography and culture may play in the success of clinical trials on pain in KOA.

References

- Please see online version for full reference list

Acknowledgments

- We would like to thank Alexander Wong and Jennifer Shen for their editorial support.

Disclosure

- The authors report employment by Evidinno Outcomes Research Inc. Authors report no other conflicts of interest

Presented at Virtual ISPOR 2020, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International Meeting; May 18–20, 2020

Email: mfazeli@Evidinno.com

PMS9

Placebo Effect in Knee Osteoarthritis: A Targeted Literature Review on The Challenges, Hypotheses, And Potential Solutions

Hofer K[1], Lin M[1], Pourrahmat MM[1], Fazeli MS[1]

[1] Evidinno Outcomes Research Inc., Vancouver, BC, Canada

References

1. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Annals of the rheumatic diseases.* 2014;73(7):1323-1330.
2. Wehling P, Evans C, Wehling J, Maixner W. Effectiveness of intra-articular therapies in osteoarthritis: a literature review. *Therapeutic advances in musculoskeletal disease.* 2017;9(8):183-196.
3. Altman R, Hackel J, Niazi F, Shaw P, Nicholls M. Efficacy and safety of repeated courses of hyaluronic acid injections for knee osteoarthritis: A systematic review. *Semin Arthritis Rheum.* 2018;48(2):168-175.
4. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med.* 2015;162(1):46-54.
5. Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P. A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). *Semin Arthritis Rheum.* 2009;39(1):1-9.
6. Jorgensen A, Stengaard-Pedersen K, Simonsen O, et al. Intra-articular hyaluronan is without clinical effect in knee osteoarthritis: A multicentre, randomised, placebo-controlled, double-blind study of 337 patients followed for 1 year. *Annals of the Rheumatic Diseases.* 2010;69(6):1097-1102.
7. Auw Yang KG, Raijmakers NJ, van Arkel ER, et al. Autologous interleukin-1 receptor antagonist improves function and symptoms in osteoarthritis when compared to placebo in a prospective randomized controlled trial. *Osteoarthritis and cartilage.* 2008;16(4):498-505.
8. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Ann Rheum Dis.* 2008;67(12):1716-1723.
9. Zhang W. The powerful placebo effect in osteoarthritis. *Clin Exp Rheumatol.* 2019;37 Suppl 120(5):118-123.
10. Abhishek A, Doherty M. Mechanisms of the placebo response in pain in osteoarthritis. *Osteoarthritis and Cartilage.* 2013;21(9):1229-1235.
11. Ajrawat P, Dwyer T, Chahal J. Autologous Interleukin 1 Receptor Antagonist Blood-Derived Products for Knee Osteoarthritis: A Systematic Review. *Arthroscopy.* 2019;35(7):2211-2221.
12. Altman RD, Devji T, Bhandari M, Fierlinger A, Niazi F, Christensen R. Clinical benefit of intra-articular saline as a comparator in clinical trials of knee osteoarthritis treatments: A systematic review and meta-analysis of randomized trials. *Semin Arthritis Rheum.* 2016;46(2):151-159.
13. Bannuru RR, McAlindon TE, Sullivan MC, Wong JB, Kent DM, Schmid CH. Effectiveness and Implications of Alternative Placebo Treatments: A Systematic Review and Network Meta-analysis of Osteoarthritis Trials. *Ann Intern Med.* 2015;163(5):365-372.
14. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. *Osteoarthritis Cartilage.* 2011;19(6):611-619.
15. Bannuru RR, Vaysbrot EE, Sullivan MC, McAlindon TE. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: a systematic review and meta-analysis. *Semin Arthritis Rheum.* 2014;43(5):593-599.
16. Bar-Or D, Salottolo K. Comment on "clinical benefit of intra-articular saline as a comparator in clinical trials of knee osteoarthritis treatments: A systematic review and meta-analysis of randomized trials". *Semin Arthritis Rheum.* 2017;46(4):e20.
17. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database of Systematic Reviews.* 2005(2):CD005321.
18. Bennell KL, Hunter DJ, Paterson KL. Platelet-Rich Plasma for the Management of Hip and Knee Osteoarthritis. *Curr Rheumatol Rep.* 2017;19(5):24.
19. Boutron I, Tubach F, Giraudeau B, Ravaud P. Methodological differences in clinical trials evaluating nonpharmacological and pharmacological treatments of hip and knee osteoarthritis. *JAMA.* 2003;290(8):1062-1070.
20. Chahla J, Piuzzi NS, Mitchell JJ, et al. Intra-Articular Cellular Therapy for Osteoarthritis and Focal Cartilage Defects of the Knee: A Systematic Review of the Literature and Study Quality Analysis. *J Bone Joint Surg Am.* 2016;98(18):1511-1521.
21. Clarke S, Lock V, Duddy J, Sharif M, Newman JH, Kirwan JR. Intra-articular hylan G-F 20 (Synvisc) in the management of patellofemoral osteoarthritis of the knee (POAK). *Knee.* 2005;12(1):57-62.
22. Colen S, van den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products. *BioDrugs.* 2012;26(4):257-268.
23. Conaghan PG, Cohen SB, Berenbaum F, Lufkin J, Johnson JR, Bodick N. Brief Report: A Phase IIb Trial of a Novel Extended-Release Microsphere Formulation of Triamcinolone Acetonide for Intraarticular Injection in Knee Osteoarthritis. *Arthritis & Rheumatology.* 2018;70(2):204-211.
24. Curran MP. Hyaluronic acid (Supartz): a review of its use in osteoarthritis of the knee. *Drugs & Aging.* 2010;27(11):925-941.
25. Dougados M, LeClaire P, Van der Heijde D, Bloch DA, Bellamy N, Altman RD. Response criteria for clinical trials on osteoarthritis of the knee and hip: A report of the Osteoarthritis Research Society International Standing Committee for Clinical Trials response criteria initiative. *Osteoarthritis and Cartilage.* 2000;8(6):395-403.
26. Hameed F, Ihm J. Injectable Medications for Osteoarthritis. *PM and R.* 2012;4(5 SUPPL.):S75-S81.
27. Henderson EB, Smith EC, Pegley F, Blake DR. Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. *Annals of the Rheumatic Diseases.* 1994;53(8):529-534.
28. Henriksen M, Graven-Nielsen T, Aaboe J, Andriacchi TP, Bliddal H. Gait changes in patients with knee osteoarthritis are replicated by experimental knee pain. *Arthritis care & research.* 2010;62(4):501-509.
29. Henrotin Y, Hauzeur JP, Bruel P, Appelboom T. Intra-articular use of a medical device composed of hyaluronic acid and chondroitin sulfate (Structovial CS): effects on clinical, ultrasonographic and biological parameters. *BMC Res Notes.* 2012;5:407.
30. Jevsevar D, Donnelly P, Brown GA, Cummins DS. Viscosupplementation for Osteoarthritis of the Knee: A systematic review of the evidence. *Journal of Bone and Joint Surgery - American Volume.* 2015;97(24):2047-2060.
31. Jones IA, Togashi R, Wilson ML, Heckmann N, Vangsness CT, Jr. Intra-articular treatment options for knee osteoarthritis. *Nat Rev Rheumatol.* 2019;15(2):77-90.
32. Karlsson J, Sjogren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. *Rheumatology.* 2002;41(11):1240-1248.
33. Kirwan J. Is there a place for intra-articular hyaluronate in osteoarthritis of the knee? *Knee.* 2001;8(2):93-101.
34. Medical Advisory S. Arthroscopic lavage and debridement for osteoarthritis of the knee: an evidence-based analysis. *Ont Health Technol Assess Ser.* 2005;5(12):1-37.
35. Miller JH, White J, Norton TH. The value of intra-articular injections in osteoarthritis of the knee. *J Bone Joint Surg Br.* 1958;40-b(4):636-643.
36. Neustadt D, Caldwell J, Bell M, Wade J, Gimbel J. Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. *Journal of Rheumatology.* 2005;32(10):1928-1936.
37. Pai SK, Allgar V, Giannoudis PV. Are intra-articular injections of Hylan G-F 20 efficacious in painful osteoarthritis of the knee? A systematic review & meta-analysis. *International Journal of Clinical Practice.* 2014;68(8):1041-1047.
38. Raynauld JP, Buckland-Wright C, Ward R, et al. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2003;48(2):370-377.
39. Richardson C, Plaas A, Block JA. Intra-articular Hyaluronan Therapy for Symptomatic Knee Osteoarthritis. *Rheum Dis Clin North Am.* 2019;45(3):439-451.
40. Saltzman BM, Leroux T, Meyer MA, et al. The Therapeutic Effect of Intra-articular Normal Saline Injections for Knee Osteoarthritis: A Meta-analysis of Evidence Level 1 Studies. *American Journal of Sports Medicine.* 2017;45(11):2647-2653.
41. Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. *Journal of Orthopaedic Surgery.* 2017;12(1):16.
42. Vannabouathong C, Bhandari M, Bedi A, et al. Nonoperative Treatments for Knee Osteoarthritis: An Evaluation of Treatment Characteristics and the Intra-Articular Placebo Effect: A Systematic Review. *JBJS rev.* 2018;6(7):e5.
43. Yu SP, Ferreira ML, van Middelkoop M, et al. Predictors of placebo response to local (intra-articular) therapy in osteoarthritis: an individual patient data meta-analysis protocol. *BMJ Open.* 2019;9(5):e027372.