THE EFFECTIVENESS OF INTRA-ARTICULAR INJECTIONS FOR KNEE OSTEOARTHRITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction: Intra-articular (IA) injections have been used to reduce knee osteoarthritis (OA) pain. However, several side effects following the injections were reported and raised the question of whether IA injections were effective and safe. Hence, this study aimed to identify the most common type of IA injections used in treating knee OA and to determine its effectiveness, duration of pain relief and most common side effects. **Methods**: Online literature searches on PubMed, Wiley Online Library, and Cochrane Library were performed by using the keywords "intra-articular injection" AND "knee osteoarthritis" OR "knee OA" AND "randomised controlled trial" OR "RCT". Only randomised controlled trial studies that analysed the effects of intra-articular injections for knee OA patients and published in English were included. A total of 2823 articles were identified, 22 full-text articles were assessed, and six articles have been included in this study. National Institutes of Health (NIH) Quality Assessment Tools were used to evaluate the risk of bias in these six articles, and only four articles were included for meta-analysis. **Results**: The present data showed that intra-articular hyaluronic acid injection was the most common type of IA injection. However, only intra-articular corticosteroid injections (IACI) are effective for knee OA treatment. The pain relief duration provided by each intra-articular injection type varies between 1 month to 6 months. Side effects such as arthralgia and joint swelling were recorded following the administration of IA hyaluronic acid injection and IA stem cell injection, but not in the IACI therapy groups. **Conclusion:** Although IACI has been shown to reduce pain in patients with knee OA, the long-term consequences of IACI therapy in this population have yet to be confirmed.

KEYWORDS: intra-articular injection, knee osteoarthritis, randomised controlled trial, side effects

INTRODUCTION

Osteoarthritis (OA) is characterised by the gradual loss of articular cartilage and commonly affects the joints in the knees. The main symptoms of OA are joint pain and stiffness that will cause difficulties in moving. Globally, OA was estimated to be the fourth leading cause of disability and is highly associated with the ageing Asian population (Fransen et al., 2011). Other than age, overweight, obesity, and previous

knee injury are regarded as modifiable risk factors for the development and progression of OA (Ministry of Health Malaysia, 2013).

One of the non-surgical treatments for knee OA is intra-articular (IA) injections. IA injections are the administration of medication directly into the joint with the main purpose of alleviating pain. Several studies have indicated that IA injections can effectively relieve pain in individuals suffering from knee OA (Saturveithan et al., 2016; Tian et al., 2018; Xu et al., 2020). To date, there are several different types of IA injections, such as corticosteroid injections (IACI), hyaluronic acid (HA) injections, platelet-rich plasma (PRP) injections, and so on.

Different types of IA injections were used to treat knee OA depending on the severity of knee OA in every patient. Ayhan et al. (2014) reported that IACI relieves pain in moderate and severe knee OA, while intra-articular HA injection was administered to reduce pain in mild knee OA. On the other hand, a study conducted by Taniguchi et al. (2018) suggested that intra-articular PRP injection was a safe treatment for the Japanese with mild to moderate knee OA and effectively alleviated pain up to 6 months (Taniguchi et al., 2018). Despite its effectiveness, previous studies have also shown that the administration of these intra-articular injections needs to be repeated as they presumably provide a short-term pain relief effect only (Raynauld et al., 2003; Ayhan et al., 2014; Chen et al., 2019).

Cole and Schumacher (2005) claimed that there is no consistent data on the duration of pain relief after injection, even though the literature shows that many patients respond positively to intra-articular injection therapy. Not only that, the manifestation of side effects after receiving intra-articular injection among knee osteoarthritis patients was also considered a significant issue to be highlighted (Grillet & Dequeker, 1990; McAlindon et al., 2017). Hence, it raises the question of whether intra-articular injections are effective and safe for knee OA. Thus, the present study aimed to determine the effectiveness of intra-articular injections in treating knee osteoarthritis by using a systematic review and meta-analysis of randomised control trials on the effects of intra-articular injections among patients with knee OA.

MATERIALS AND METHODS

Identification

This study was based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The articles were retrieved from four databases, including Wiley Online Library, PubMed, and Cochrane Library. Boolean operators' AND' and 'OR' were employed with the combinations of the following keywords: "intra-articular injection*" AND "knee OA" OR "knee OA" AND "randomised controlled trial*" OR "RCT".

Screening and Eligibility

All identified articles were screened for duplication, and their eligibility was assessed based on the inclusion and exclusion criteria. The inclusion criteria were human study, randomised controlled trial (RCT), English journal, published or peer-reviewed journals and journal articles published within ten years, while the exclusion criteria were review or case report study, proceeding and dissertation.

Data Extraction and Collection

Extracted data from the selected articles were the first author's name, year of publication, place of study, number and demographic information of participants, types of IA injection, administration, side effects manifestation, the usage of other medications, importance outcome measures, and funding source. These

data were recorded independently by the first author (NFS), presented in the table form using MS Excel 2019 and validated by the corresponding author (ZZ).

Meta-Analysis

Meta-analysis was performed to statistically and critically evaluate the strength of the evidence presented between the intervention or treatment, IA injection and knee OA disease by combining the results of comparable studies. Meta-analysis was conducted according to the following steps: (1) frame a question (based on a theory); (2) read the individual papers' abstracts and titles; (3) extract information from a selected set of final articles; (4) construct a forest plot by estimating the summary effect size in the form of Inverse Variance and applying appropriate effects models; and (5) determine the degree of heterogeneity in these articles (Basu, 2017). The degree of heterogeneity was managed using a random-effect model and 95% prediction interval to determine the overall interval effect. The result of the meta-analysis was presented as a forest plot, which was constructed using RevMan software. It represents the estimates of effects for each type of intra-articular injection in relieving pain among knee OA patients and was interpreted by observing the direction of effect, mean differences, heterogeneity, and p-value for the overall effect (Sedgwick, 2015; Cochrane, 2021).

Risk of Bias

The NIH Quality Assessment Tool for Controlled Intervention Studies was used to assess the risk of bias in each selected study (Ma et al., 2020). This tool provides signalling questions (i.e., randomisation and allocation concealment, the similarity of compared groups at baseline, use of intent-to-treat (ITT) analysis, adequacy of blinding, the overall percentage of subjects lost to follow-up, and so on) to address the potential for bias. The overall quality of the included studies was assessed as good, fair, or poor.

RESULTS AND DISCUSSIONS

From 2823 records identified through database searching, 109 duplicate records were removed (Figure 1). In the screening stage, 2692 records were excluded based on the title and abstract. Twenty-two full-text articles were assessed for eligibility, and six studies were included in qualitative synthesis. Among the six included studies, four studies were included in the meta-analysis. Sixteen full articles were excluded at the eligibility stage based on the inclusion and exclusion criteria, and two journal articles were excluded from meta-analysis due to inadequate data.

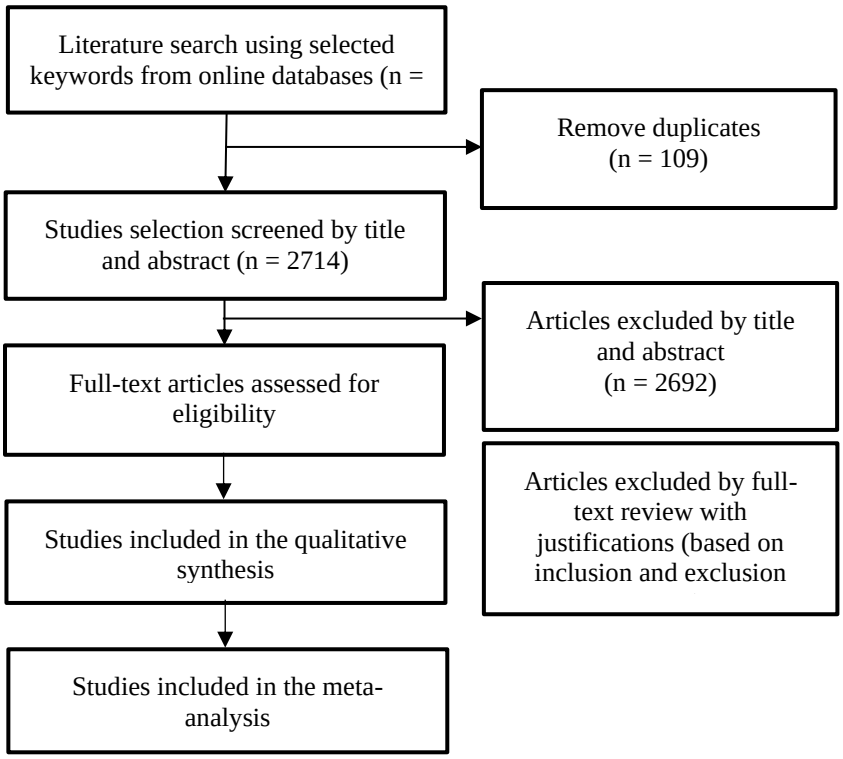

Figure 1 The flow of identification, screening, eligibility and included studies based on PRISMA guidelines.

Study Characteristics

Table 1 shows the characteristics of the included studies. Generally, all the included studies discussed the pain-relief effects of intra-articular injections within knee osteoarthritis patients, with one study from Turkey, Japan, South Korea, and Brazil and two from the USA. All the studies were conducted between 2017 and 2019 and consisted of one or two treatment groups. Moreover, all studies indicated that the duration of pain relief provided by each type of IA injection varies from one month (short-term) to nearly seven months (long-term). IA steroid injection, IA stem cells injection, and IA hyaluronic acid injection were proven to relieve pain from 1-3 months, up to 6 months, and from 6 to 6.5 months, respectively.

In addition, all the included studies used either the Visual Analogue Scale (VAS) or Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores to measure the pain scores after administering IA injections. Studies by Eker et al. (2017) and Takamura et al. (2019) indicated improved VAS/WOMAC mean scores for the IA injections vs. control (T = 2.8, CR = 4.8) and (T = 43.02, CR = 47.55), respectively. Meanwhile, a study conducted by Farr et al. (2019) demonstrated a reduction in VAS mean

scores vs. control for only one treatment group, i.e., IA stem cells injection (T = 44.38, CR = 61.02), but not in the IA hyaluronic acid injection group, (T = 68.69, CR = 61.02).

Other than that, a study conducted by Mendes et al. (2019) presented alleviated VAS and WOMAC mean scores vs. control for both treatment groups, IA Botox and IA hyaluronic acid injection. For IA Botox injection, the VAS mean score was (T = 3.8, CR = 4.0), and WOMAC mean score was (T = 30.3, CR = 34.4), while for IA hyaluronic acid injection, the VAS mean score was (T = 1.8, CR = 4.0), and WOMAC mean scores were (T = 23.3, CR = 34.4), respectively. Other studies (Lee et al., 2019; Petterson & Plancher, 2019) did not state their VAS/WOMAC scores but reported improved pain after the IA injection.

For the types of IA injections used, three out of six studies used intra-articular HA injections to treat knee OA (Farr et al., 2019; Petterson & Plancher, 2019; Takamura et al., 2019). Meanwhile, two studies used intra-articular corticosteroids and intra-articular stem cell injection to treat knee OA, respectively (Eker et al., 2017; Mendes et al., 2019; Farr et al., 2019; Lee et al., 2019). Only one study used intra-articular Botox injection as the treatment group (Mendes et al., 2019). Among all studies, two studies conducted by Petterson and Plancher (2019) and Lee et al. (2019) demonstrated the manifestation of side effects. The side effects are arthralgia (i.e., joint pain) and joint swelling or effusion following intra-articular injections—hyaluronic acid and stem cells.

Table 1 Characteristics of included studies

Study	Total Subjects M/F	Group	Age Mean (SD)	KL Grade	Type of IA Injection	Type of Administration	VAS Score Mean (SD)	WOMAC Score Mean (SD)	Duration of Pain Relief (month)	NSAIDs / Analgesic Usage	Side Effects
Eker, et al., 2017	52 28/24	T	65.15 (10.23)	2-4	CS	Repeated	2.8 (1.3)	-	3	Tramadol	-
		CR	69.73 (7.26)		Saline		4.8 (2.5)	-			-
Takamura, et al., 2019	311 124/187	T	61 (9.38)	2-3	HA	Single	-	43.02 (26.1)	6.5	-	-
		CR	62.8 (8.85)		Saline		-	47.55 (26.7)			-
Lee, et al., 2019	24 6/18	T	62.2 (6.5)	2-4	Stem Cells	Single	3.4 (1.5)	26.7 (13.3)	6	AO	AG JE
		CR	63.2 (4.2)		Saline		-	-			

M, Male; F, Female; T, Treatment; CR, Control; SD, Standard deviation CS, Corticosteroids; HA, Hyaluronic Acid; VAS, Visual Analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index scale; NSAIDs, nonsteroidal anti-inflammatory drugs; AO, Acetaminophen; AG, Arthralgia; JE, Joint Effusion

Table 2 Characteristics of included studies (continue)

Study	Total Subjects M/F	Group	Age Mean (SD)	KL Grade	Type of IA Injection	Type of Administration	VAS Score Mean (SD)	WOMAC Score Mean (SD)	Duration of Pain Relief (month)	NSAIDs / Analgesic Usage	Side Effects
Mendes, et al., 2019	105 9/96	T1	62.5 (6.8)	2-3	Botox	Single	3.8 (2.4)	30.3 (15.2)	1	AO, Lidocaine	-
		T2	65.5 (6.9)		CS		1.8 (2.3)	23.3 (17.7)			-
		C R	64.6 (6.7)		Saline		4 (3.2)	34.4 (16.3)			-
Farr, et al., 2019	200 105/ 95	T1	55.9 (12.3)	2-3	Stem Cells	Single	44.38 (33)	-	6	-	-
		T2	55.4 (11)		HA		68.69 (36)	-			-
		CR	54.9 (9.9)		Saline		61.02 (32)	-			-
Petterson & Plancher, 2019	369 154 / 215	T	59.5 (8)	2-3	HA	Single	-	-	6	GS	AG, JE
		CR	58.7 (9.2)		Saline		-	-			

M, Male; F, Female; T, Treatment; CR, Control; SD, Standard deviation CS, Corticosteroids; HA, Hyaluronic Acid; VAS, Visual Analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index scale; NSAIDs, nonsteroidal anti-inflammatory drugs; AO, Acetaminophen; AG, Arthralgia; JE, Joint Effusion

Risk of Bias

Table 2 shows the qualities of the included studies as assessed using the NIH Quality Assessment Tools of Controlled Intervention Studies. Based on this table, studies by Eker et al. (2017), Lee et al. (2019), Mendes et al. (2019) and Petterson & Plancher (2019) were rated as good because they are transparent enough to provide adequate or sufficient information, thus reducing the potential of bias that could create arguments towards their findings and helps to improve the articles' quality. Besides that, a study by Takamura et al. (2019) was rated as fair, and a survey by Farr et al. (2019) was rated as poor because they presented a moderate to low number of important information, which can lead to uncertainty in their findings.

Table 2 Risk of bias assessment on the included studies

Author/ Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Overall result
Eker, et al. (2017)	✓	✓	✓	✓	✓	✓	✓	✓	–	×	✓	✓	✓	–	Good
Takamura, et al. (2019)	✓	–	–	×	✓	✓	–	–	–	–	✓	–	✓	–	Fair
Lee, et al. (2019)	✓	–	✓	✓	✓	✓	✓	✓	✓	×	✓	×	–	Y	Good
Mendes, et al. (2019)	✓	✓	✓	✓	✓	✓	×	✓	–	×	✓	✓	✓	✓	Good
Farr, et al. (2019)	✓	–	✓	–	–	–	×	×	×	✓	✓	✓	✓	–	Poor
Petterson and Plancher (2019)	✓	✓	–	✓	✓	✓	✓	✓	–	×	✓	✓	✓	✓	Good

Effectiveness of IA Steroid Injection

Figure 2 summarises pooled estimates for treatment effect—IA steroid injection in two subgroups of trials (Eker et al., 2017; Mendes et al., 2019) that were defined according to the characteristics of participants. Eker et al. (2017) and Mendes et al. (2019) had significantly more reductions in VAS/WOMAC scores with a 95% confidence interval of mean differences, -2.00 and -2.20, respectively. Overall, these studies were homogenous (p = 0.82) and showed a statistically significant reduction of knee pain with a mean difference of -2.08 (p < 0.00001).

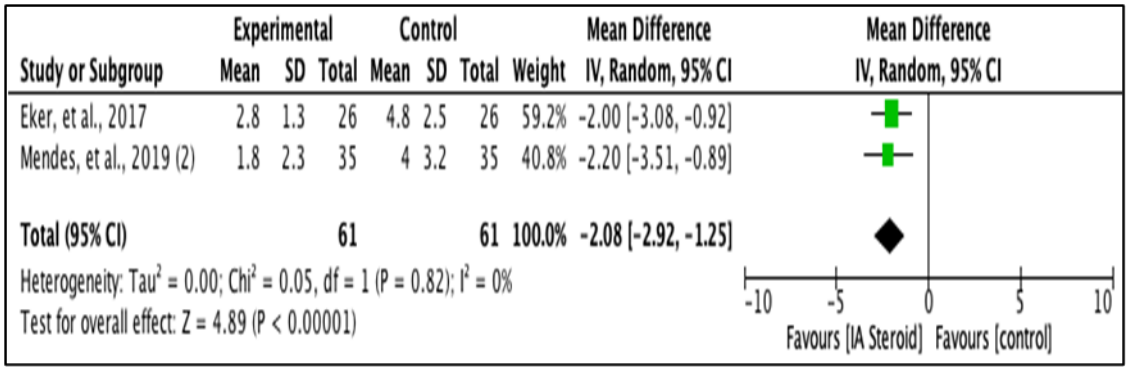

Figure 2 Results of Meta-analysis with 95% Confidence Interval comparing Intraarticular Steroid Injection and Control

Effectiveness of IA Hyaluronic Acid Injection

Figure 3 summarises pooled estimates for treatment effect—IA hyaluronic acid injection in two subgroups of trials (Farr et al., 2019; Takamura et al., 2019) that were defined according to the characteristics of participants. It was indicated that the study by Takamura et al. (2019) demonstrated an insignificantly reduced VAS/WOMAC score with a 95% confidence interval of mean differences, -4.53. In contrast, Farr et al. (2019) showed no reduced VAS/WOMAC score following IA hyaluronic acid injection, favouring the control group. Overall, both studies were heterogeneous ($I^2 > 50\%$), and the pooled estimates of the effect of IA hyaluronic acid injection in alleviating knee pain were not observed (p=0.93).

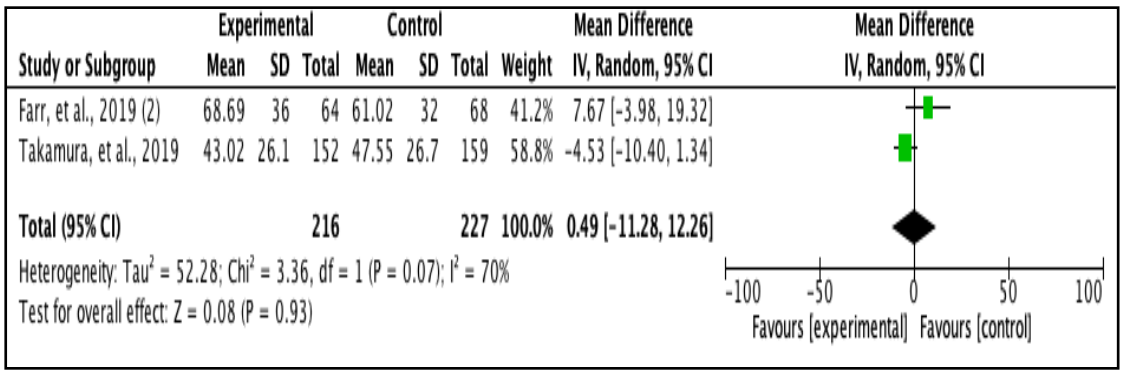

Figure 3 Results of Meta-analysis with 95% Confidence Interval comparing Intra-articular Hyaluronic Acid Injection and Control

Based on the meta-analysis, it was observed that intra-articular corticosteroid injection (IACI) at the suggested concentration had improved pain in patients with knee OA for over 1 to 3 months. The present findings are consistent with the previous studies, which offered short-term pain relief was observed up to one month after IACI (Ayhan et al., 2014; Juni et al., 2015; Wagner et al., 2015; Da Costa et al., 2016; He et al., 2017). Nevertheless, Raynauld et al. (2003) have reported that the long-term effectiveness of IACI could be achieved by frequent steroid injection. As reviewed in the present study, Eker et al. (2019) have shown that repeated administration of IACI significantly reduced the VAS pain scores up to 3 months post-injection. On the other hand, a single injection of IACI significantly reduced the VAS pain scores only up to 1 month after injection (Mendes et al., 2019). Perhaps the repetition administration of IACI could achieve cumulative benefit or restore benefit that has decreased, thus extending the duration of pain relief (Murthy et al., 2014).

Unlike IACI, IA hyaluronic acid injection had a heterogeneous finding and pooled estimates showed insignificant effects on alleviating pain among the patients with knee OA. Provided IA hyaluronic acid injection was found to be the most common IA injection used to treat pain in osteoarthritic knees; such insignificant pooled estimates resulted from the studies conducted by Farr et al. (2019) and Petterson and Plancher (2019). The former presented no reduced VAS pain scores in the IA hyaluronic acid group. At the same time, the latter was excluded from the analysis, though a significant reduction in VAS pain scores was observed due to some limitations. Two included studies (Farr et al., 2019; Takamura et al., 2019) are heterogenous because both studies indicated the contradictory direction of the IA hyaluronic acid treatment effect; Farr et al. (2019) showed negative treatment effect while Takamura et al. (2019) showed positive treatment effect. Other than that, the study by Farr et al. (2019) possessed a higher risk of bias (i.e., high withdrawal rate, poor study design and incomplete outcome data) compared to the study by Takamura et al. (2019). All these heterogeneity factors were deduced based on the guidance provided (Fletcher, 2007; Deeks et al., 2019), which were believed to be the contributing factors of insignificant findings.

In terms of duration, a single intra-articular hyaluronic acid injection resulted in adequate pain relief among individuals with osteoarthritic knees for over 3 to 6 months of follow-up (He et al., 2017; Suppan et al., 2017). Consequently, the findings of these studies are congruent with the current reviewed study of Takamura et al. (2019) and Petterson and Plancher (2019). Nevertheless, the wide range of pain alleviation duration (i.e., 3 – 6 months) of IA hyaluronic acid injection depends on the various types of HA employed, which include multiple formulations such as molecular weight and cross-linking (Aggarwal & Sempowski, 2004; Farr et al., 2019). Therefore, considering that IA hyaluronic acid

provided a longer duration of pain relief for knee OA, it is recommended to use intra-articular HA injection rather than IACI, which was found to relieve pain not more than three months (Askari et al., 2016).

For the side effects of IA injections, previous studies by Richards et al. (2016) and McAlindon et al. (2017) have found several side effects following intra-articular corticosteroids injection (IACI), namely systemic hyperglycemia, septic arthritis, and bone loss. Although the present systematic review did not find any side effects post-IACI injection in the selected studies, many reports in the literature suggest otherwise (Hauser, 2009; Wernecke et al., 2015; McAlindon et al., 2017; Zeng et al., 2019). In these reports, the side effects might manifest following its treatment for a long time. Repeated administration of IACI to sustain the pain relief for a longer timeframe (> 1 month) might induce severe side effects such as articular and bone loss. McAlindon et al. (2017) found that IACI resulted in more significant cartilage volume loss. Similarly, a larger and longer population study by Zeng et al. (2019) showed the worsening of radiographic OA in the IACI group compared to the control group. This side effect could happen due to the impact of corticosteroid itself decreasing osteoblast function, thus reducing the formation of new bone (Canalis, 2003; Briot & Roux, 2015).

On the other hand, according to a prior study by Honvo et al. (2019), IA hyaluronic acid does not appear to be linked to any safety concerns when used to treat OA. The findings of Honvo et al. (2019) are consistent with the current reviewed study of Petterson and Plancher (2019), which found that the intra-articular HA therapy group had a lower than 5% incidence of joint swelling and arthralgia. Similarly, Lee et al. (2019) also found no significant side effects in the IA stem cell injection group, further supporting the findings of previous studies (Peeters et al., 2013; Jo et al., 2014; Fodor & Paulseth, 2016; Khalifeh Soltani et al., 2019; Kim et al., 2019). Although there is no report of side effects, high-quality evidence is needed to confirm the therapeutic impact of IA stem cell injection, as few studies have identified cell malignancy as a potential risk of stem cell therapy (Suzuki et al., 2011; Zhang et al., 2020).

LIMITATIONS AND FUTURE STUDIES

To date, only the present study investigated the effectiveness of different IA injections for alleviating pain in patients with knee OA using meta-analysis approaches. Nevertheless, a few limitations have been discovered. First, the process of identification and screening articles has been done by one person only, which may increase the risk of bias during the reviewing process. Second, there were only two studies included in each meta-analysis. Although meta-analysis can be performed with at least two studies (Valentine et al., 2010; Ryan, 2016), it will still lead to some weaknesses, especially when the included studies are poor and have low quality. Third, using other oral or topical pain medications might also influence the findings of each selected study. Experimental studies on the effects of prolonged use of IACI, especially its association with bone resorption, are warranted in the future. In addition, other than alleviating pain, the potential use of IA stem cell injection in regenerating the osteoarthritic articular cartilage is interesting to explore as an alternative approach for knee OA treatment.

CONCLUSION

In conclusion, intra-articular HA injections are the most common type of IA injection used among patients with knee OA, followed by IACI. Moreover, the duration of pain relief for IA injections varies from 1 month to 6 months, depending on the types of IA injection and frequency of dosing. Side effects such as arthralgia and joint swelling manifested following administering IA hyaluronic acid and IA stem cell injection but were not reported in the IACI therapy groups. Although IACI has proven to be effective in alleviating pain among patients with knee OA, the side effects of prolonged IACI use in this population have yet to be determined.

REFERENCES

Aggarwal, A., & Sempowski, I. P. (2004). Hyaluronic acid injections for knee OA. Systematic review of the literature. Canadian Family Physician Medecin De Famille Canadien, 50, 249–256.

Askari, A., Gholami, T., NaghiZadeh, M. M., Farjam, M., Kouhpayeh, S. A., & Shahabfard, Z. (2016). Hyaluronic acid compared with corticosteroid injections for the treatment of OA of the knee: a randomised control trail. SpringerPlus, 5, 442.

Ayhan, E., Kesmezacar, H., & Akgun, I. (2014). Intraarticular injections (corticosteroid, hyaluronic acid, platelet-rich plasma) for knee OA. World Journal of Orthopedics, 5(3), 351–361.

Briot, K., & Roux, C. (2015). Glucocorticoid-induced osteoporosis. RMD Open, 1(1), e000014.
Canalis E. (2003). Mechanisms of glucocorticoid-induced osteoporosis. Current Opinion In Rheumatology, 15(4), 454–457.

da Costa, B. R., Hari, R., & Jüni, P. (2016). IA Corticosteroids for OA of the Knee. JAMA, 316(24), 2671–2672.

Deeks, J. J., Higgins, J. P. T., & Altman, D. G. (2019). Analysing data and undertaking meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions, 241–284.

Eker, H. E., Cok, O. Y., Aribogan, A., & Arslan, G. (2017). The efficacy of IA administration in chronic knee pain due to OA: A randomised, double-blind, controlled study. Critical Care & Pain Medicine, 36(2), 109–114.

Farr, J., Gomoll, A. H., Yanke, A. B., Strauss, E. J., Mowry, K. C., & ASA Study Group (2019). A Randomized Controlled Single-Blind Study Demonstrating Superiority of Amniotic Suspension Allograft Injection Over Hyaluronic Acid and Saline Control for Modification of Knee OA Symptoms. The Journal of Knee Surgery, 32(11), 1143–1154.

Fletcher, J. (2007). What is heterogeneity and is it important? BMJ, 334(7584), 94–96.

Fodor, P. B., & Paulseth, S. G. (2016). Adipose Derived Stromal Cell (ADSC) Injections for Pain Management of OA in the Human Knee Joint. Aesthetic Surgery Journal, 36(2), 229–236.

Fransen, M., Bridgett, L., March, L., Hoy, D., Penserga, E., & Brooks, P. (2011). The epidemiology of OA in Asia. International Journal of Rheumatic Diseases, 14(2), 113–121.

Hauser, R. A. (2009). The Deterioration of Articular Cartilage in OA by Corticosteroid Injections. Journal of Prolotherapy, 1(2), 107–123.

He, Wei-wei; Kuang, Ming-jie; Zhao, Jie; Sun, Lei; Lu, Bin; Wang, Ying; Ma, Jian-xiong; Ma, Xin-long (2017). Efficacy and safety of intraarticular hyaluronic acid and corticosteroid for knee OA: A meta-analysis. International Journal of Surgery, 39, 95–103.

Honvo, G., Reginster, J.-Y., Rannou, F., Rygaert, X., Geerinck, A., Rabenda, V., McAlindon, T., Charles, A., Fuggle, N., Cooper, C., Curtis, E., Arden, N., Avouac, B., & Bruyère, O. (2019). Safety of IA hyaluronic Acid injections In OA: Outcomes of a systematic review and meta-analysis. Drugs & Aging, 36(S1), 101–127.

Jo, C. H., Lee, Y. G., Shin, W. H., Kim, H., Chai, J. W., Jeong, E. C., Kim, J. E., Shim, H., Shin, J. S., Shin, I. S., Ra, J. C., Oh, S., & Yoon, K. S. (2014). IA injection of mesenchymal stem cells for the treatment of OA of the knee: a proof-of-concept clinical trial. Stem cells (Dayton, Ohio), 32(5), 1254–1266.

Jüni, P., Hari, R., Rutjes, A. W., Fischer, R., Silletta, M. G., Reichenbach, S., & da Costa, B. R. (2015). IA corticosteroid for knee OA. The Cochrane Database of Systematic Reviews, 10, CD005328.

Khalifeh Soltani, S., Forogh, B., Ahmadbeigi, N., Hadizadeh Kharazi, H., Fallahzadeh, K., Kashani, L., Karami, M., Kheyrollah, Y., & Vasei, M. (2019). Safety and efficacy of allogenic placental mesenchymal stem cells for treating knee OA: a pilot study. Cytotherapy, 21(1), 54–63.

Kim, S. H., Ha, C. W., Park, Y. B., Nam, E., Lee, J. E., & Lee, H. J. (2019). IA injection of mesenchymal stem cells for clinical outcomes and cartilage repair in OA of the knee: a meta-analysis of randomised controlled trials. Archives of Orthopaedic and Trauma Surgery, 139(7), 971–980.

Lee, W. S., Kim, H. J., Kim, K. I., Kim, G. B., & Jin, W. (2019). IA Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Knee OA: A Phase IIb, Randomized, Placebo-Controlled Clinical Trial. Stem Cells Translational Medicine, 8(6), 504–511.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J. P., Clarke, M., Devereaux, P. J., Kleijnen, J., & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that Evaluate Healthcare INTERVENTIONS: Explanation and elaboration. BMJ, 339(jul21 1).

Ma, L.-L., Wang, Y.-Y., Yang, Z.-H., Huang, D., Weng, H., & Zeng, X.-T. (2020). Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: What are they and which is better? Military Medical Research, 7(1).

McAlindon, T. E., LaValley, M. P., Harvey, W. F., Price, L. L., Driban, J. B., Zhang, M., Ward, R. J. (2017) Effect of IA Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee OA: A Randomised Clinical Trial. JAMA, 317(19), 1967-1975.

Mendes, J. G., Natour, J., Nunes-Tamashiro, J. C., Toffolo, S. R., Rosenfeld, A., & Furtado, R. (2019). Comparison between IA Botulinum toxin type A, corticosteroid, and saline in knee OA: a randomised controlled trial. Clinical Rehabilitation, 33(6), 1015–1026.

Murthy, N. S., Geske, J. R., Shelerud, R. A., Wald, J. T., Diehn, F. E., Thielen, K. R., Kaufmann, T. J., Morris, J. M., Lehman, V. T., Amrami, K. K., Carter, R. E., & Maus, T. P. (2014). The effectiveness of repeat Lumbar Transforaminal epidural steroid injections. Pain Medicine, 15(10), 1686–1694.

Peeters, C. M. M., Leijs, M. J. C., Reijman, M., van Osch, G. J. V. M., & Bos, P. K. (2013). Safety of IA cell-therapy with culture-expanded stem cells in humans: A systematic literature review. OA and Cartilage, 21(10), 1465–1473.

Petterson, S. C., & Plancher, K. D. (2019). Single IA injection of lightly cross-linked hyaluronic acid reduces knee pain in symptomatic knee OA: a multicenter, double-blind, randomised, placebo-controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy : Official Journal of The ESSKA, 27(6), 1992–2002.

Raynauld, J.-P., Buckland-Wright, C., Ward, R., Choquette, D., Haraoui, B., Martel-Pelletier, J., Uthman, I., Khy, V., Tremblay, J.-L., Bertrand, C., & Pelletier, J.-P. (2003). Safety and efficacy of long-term intraarticular steroid injections in OA of the knee: A randomised, double-blind, placebo-controlled trial. Arthritis & Rheumatism, 48(2), 370–377.

Richards, M. M., Maxwell, J. S., Weng, L., Angelos, M. G., & Golzarian, J. (2016). IA treatment of knee OA: from anti-inflammatories to products of regenerative medicine. The Physician and Sports Medicine, 44(2), 101–108.

Saturveithan, C., Premganesh, G., Fakhrizzaki, S., Mahathir, M., Karuna, K., Rauf, K., William, H., Akmal, H., Sivapathasundaram, N., & Jaspreet, K. (2016). IA Hyaluronic Acid (HA) and Platelet Rich Plasma (PRP) injection versus Hyaluronic acid (HA) injection alone in Patients with Grade III and IV Knee OA (OA): A Retrospective Study on Functional Outcome. Malaysian Orthopedic Journal, 10(2), 35–40.

Suppan, V., Wei, C. Y., Siong, T. C., Mei, T. M., Chern, W. B., Nanta Kumar, V. K., Sheng, K. R., & Sadashiva Rao, A. (2017). Randomised controlled trial comparing the efficacy of conventional and new single larger dose of IA viscosupplementation in the management of knee OA. Journal of orthopaedic surgery (Hong Kong), 25(3), 2309499017731627.

Suzuki, K., Sun, R., Origuchi, M., Kanehira, M., Takahata, T., Itoh, J., Umezawa, A., Kijima, H., Fukuda, S., & Saijo, Y. (2011). Mesenchymal stromal cells promote tumor growth through the enhancement of neovascularisation. Molecular medicine (Cambridge, Mass.), 17(7-8), 579–587.

Takamura, J., Seo, T., & Strand, V. (2019). A Single IA Injection of Gel-200 for Treatment of Symptomatic OA of the Knee Is More Effective than Phosphate Buffered Saline at 6 Months: A Subgroup Analysis of a Multicenter, Randomized Controlled Trial. Cartilage, 10(4), 417–422.

Tian, K., Cheng, H., Zhang, J., & Chen, K. (2018). IA injection of methylprednisolone for reducing pain in knee OA: A systematic review and meta-analysis. Medicine, 97(15), e0240.

Wagner, B. S., Howe, A. S., Dexter, W. W., Hatzenbuehler, J. R., Holt, C., Haskins, A. E., & Lucas, F. L. (2015). Tolerability and Efficacy of 3 Approaches to IA Corticosteroid Injections of the Knee for OA. Orthopaedic Journal of Sports Medicine, 3(8), 232596711560068.

Wernecke, C., Braun, H. J., & Dragoo, J. L. (2015). The Effect of IA Corticosteroids on Articular Cartilage: A Systematic Review. Orthopaedic Journal of Sports Medicine, 3(5), 2325967115581163.
Xu Z, He Z, Shu L, Li X, Ma M, Ye C. (2020). IA platelet-rich plasma combined with the hyaluronic acid injection for knee OA is superior to PRP or HA alone in inhibiting inflammation and improving pain and function. Arthroscopy.

Zeng, C., Lane, N. E., Hunter, D. J., Wei, J., Choi, H. K., McAlindon, T. E., Li, H., Lu, N., Lei, G., & Zhang, Y. (2019). IA corticosteroids and the risk of knee OA progression: Results from the OA initiative. OA and Cartilage, 27(6), 855–862.

Zhang, Y., Chen, X., Tong, Y., Luo, J., & Bi, Q. (2020). Development and prospect of IA injection in the treatment of OA: A review. Journal of Pain Research, Volume 13, 1941–1955.