A narrative review of the progress in the treatment of knee osteoarthritis

Zhijun Cai[#], Yi Cui[#], Jing Wang, Xin Qi, Pengju He, Pengfei Bu, Yongqing Xu, Yang Li

Department of Orthopedics, 920 Hospital of Joint Logistics Support Force, PLA, Kunming, China

Contributions: (I) Conception and design: Z Cai, J Wang; (II) Administrative support: Y Xu, Y Li; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yongqing Xu; Yang Li. Department of Orthopedics, 920 Hospital of Joint Logistics Support Force, PLA, 212 Daguan Road, Xishan District, Kunming, China. Email: xuyongqing60@sina.com; kmliyang1987@sina.com.

Background and Objective: The pathogenesis of osteoarthritis (OA) involves a variety of complex mechanisms, including genetic, mechanical, metabolic, and inflammatory factors. There is evidence that inflammatory factors, abnormal chondrocyte apoptosis, and extracellular matrix degradation are closely associated with the occurrence and development of OA. The best treatment for OA is still controversial, but intra-articular injection is safer and more effective than non-surgical treatments, such as physical therapy and oral analgesics. This study sought to explore the mechanism, benefits, and adverse reactions of commonly used intra-articular injection therapy in the treatment of knee osteoarthritis (KOA).

Methods: We analyzed the safety and adverse reactions of intra-articular injection in patients with KOA, and summarized the results.

Key Content and Findings: Six weeks of the corticosteroid injection contributed to improve the symptoms of OA patients in short time. However, their symptoms did not improve significantly after this period. Using corticosteroids for a long time may result in oxidative stress, leading to adverse reactions, such as cartilage toxicity, and accelerate the progress of OA. Due to its high frequency, the local injection of hyaluronic acid can result in more adverse reactions when compared with the corticosteroids. Due to the lack of standardized factors for platelet-rich plasma (PRP) preparation, leukocyte-rich or leukocyte-free variants may be produced. Adverse reactions include injection-site pain, joint stiffness.

Conclusions: Thus, it is necessary to promote further clinical trials to promote the clinical application of PRP.

Keywords: Knee osteoarthritis (KOA); steroid; hyaluronic acid; platelet-rich plasma (PRP)

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Introduction

Osteoarthritis (OA) is a degenerative joint disease, mainly characterized by slowly progressive destruction of the articular cartilage. Knee osteoarthritis (KOA) is mostly caused by the aseptic inflammation of articular cartilage due to wear and tear. The incidence of KOA has increased significantly as the number of elderly and obese individuals has increased worldwide (1). Under the guidelines of the International Association of Osteoarthritis, conservative treatment is preferred for KOA. Conservative treatments include physical therapies, such as weight loss and exercise, and drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) and proprotracyclines (2). Single agents are not optimal in improving pain and function in KOA patients. Drugs, such as NSAIDs, are not effective, and may even have adverse effects on the cardiovascular system, stomach

Table 1 The search strategy summary

Items	Specification
Date of search	November 5, 2021 to November 11, 2021
Databases and other sources searched	PubMed, Web of Science, Embase, and the Cochrane Library
Timeframe	2009–2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	Inclusion criteria included studies focus on the treatment of OA
	Exclusion criteria included studies did not focus on the treatment of OA
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Articles retrieved from the searches were evaluated independently by 2 reviewers (Zhijun Cai and Yi Cui) using predefined standardized data extraction forms, and then data were evaluated by a third reviewer (Yongqing Xu) independently

OA, osteoarthritis.

Table 2 The detailed search strategy (take PubMed for example)

Items	Specification
MeSH	198 references were found and after carefully checked the abstract and full text, 51 reference were included in this study
Free text	Knee osteoarthritis; steroid; hyaluronic acid; platelet-rich plasma; treatment; management; intra-articular injection; drug
Filters	Studies did not focus on intra-articular injection

and kidneys, and thus their use has to be limited in elderly KOA patients (3).

In relation to surgical treatments, arthroscopic debridement, autologous or allogeneic bone cartilage graft have been used in the treatment of OA. Arthrescope has the advantage of being a simple operation with minimal trauma, and has a certain curative effect; however, repaired fibrous cartilage is much less wear-and-tear resistant than normal cartilage (4). Autologous chondrocyte transplantation is suitable for a large area of bone cartilage defects left behind after initial treatment failure (5); however, this method is expensive without reliable clinical effect. Periosteal bone transplantation can be used to treat patients with large osteochondral lesions with the advantage of chondrometaplasia ability. Moreover, the periosteum can closely combine with the bone, which solves the repair problem of cartilage and subchondral bone dislocation (6). However, if the periosteum is hyperplastic, a secondary arthrescope may be required. Thus, local injection drugs may be better than other treatments and could play a key role in the treatment of OA (7). Intra articular injection refers to the direct injection of drugs into the articular cavity with a syringe. Intra articular injection is one of the main treatment measures to limit the further aggravation of joint injury. In recent years, studies have analyzed the value of intra-articular injection of drugs in patients with KOA, but there have been many new studies in the last two years, so it is necessary to analyze it again. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-818/rc).

Methods

A comprehensive literature search of all published studies was conducted using PubMed, Web of Science, Embase, and the Cochrane Library [2000–2022]. Inclusion criteria included studies focus on the treatment of OA. Articles retrieved from the searches were evaluated independently by two reviewers (Zhijun Cai and Yi Cui) using predefined standardized data extraction forms, and then data were evaluated by a third reviewer (Yongqing Xu) independently (see *Table 1*). The detailed search strategy (see *Table 2*).

Steroids

OA is a degenerative joint disease; however, the aseptic inflammation of the joint provides a reliable rationale for the application of anti-inflammatory drugs to the joint. Critical steroids inhibit the inflammatory by regulating the T cells and B cells (8). Intra-articular steroid (anti-inflammatory drug) therapy is a practical treatment, as it directly targets

the affected joint, and has little systemic effect. The current guidelines of The European League Against Rheumatism, The American College of Rheumatology, and the Osteoarthritis Research Society International all recommend intra-articular steroid injections for the treatment of hip OA. However, as the panel of The American College of Rheumatology has noted, research focusing on patients with symptomatic KOA is limited (9).

Currently, triamcinolone acetonide and methylprednisolone are most commonly used to treat KOA. Triamcinolone is a better choice for diabetics concerned about increased blood sugar after injection as it is less water soluble than methylprednisolone (10). Triamcinolone acetonide takes 3 weeks for complete absorption in the joint, and is detectable in plasma after 6 weeks, with an average stay of 2.5–4.3 days in plasma. Sustained-release triamcinolone acetonide ensures pain relief for more than 12 weeks (11). The intra-articular injection of sustained-release triamcinolone acetonide was found to effectively relieve pain symptoms while having a minimal effect on blood glucose in OA patients (12). According to a previous study, Methylprednisolone acetate significantly relieves early pain in OA patients, and the efficacy of the local injection of methylprednisolone acetate peaked 2 weeks and lasted for 24 weeks (13). And studies showed that the efficacy of methylprednisolone acetate may last for 3 months or more(14,15). Intra-articular injection of corticosteroids significantly relieves the symptoms in early OA patients (14). However, the relief is very short, and most patients no longer benefit from the treatment after half a year (14). Most patients with OA show a functional improvement within 6 weeks after the local injection of corticosteroid (16,17). Additionally, using corticosteroids for a long time results in oxidative stress, changes gene expression in chondrocytes, and causes adverse reactions, such as chondrotoxicity, which accelerate the progression of OA (18). A recent study found a causal association between high doses and the prolonged administration of corticosteroids and the chondrotoxicity (19). Thus, symptomatic joints should not be injected with articular corticosteroids >4 times a year (20). Studies have showed that the corticosteroids provides mild and temporary analgesic effects only, and surgeons are gradually beginning to doubt the sustainability of this treatment (21,22).

Hyaluronic acid

Hyaluronic acid is also commonly used in OA. It is glycoaminoglycan, consisting of β-glucuronoside and β-acetaminoglucose produced by type B synovial cells (23). As a major component of the intra-articular synovial fluid, hyaluronic acid is present at 1–2 um in the upper layer of the articular cartilage. Normal knees contain 2.5–4 mg/mL hyaluronic acid, while the knees of OA patients contain only 1–2 mg/mL (24). Hyaluronic acid has been widely used since the Food and Drug Administration (FDA) approved its use in OA patients in 1997.

In relation to OA, intra-articular hyaluronic acid treatment may: (I) serve as a supplement to the mechanical viscosity of the joint by providing lubrication and vibration absorption, reducing friction, and protecting the joint (25); and (II) direct the reconstruction of joint homeostasis via its endogenous secretion. Presently, hyaluronic acid not only has a structural function, but also functions as a signaling molecule. In its interaction with different cell surface receptors, it can regulate cell proliferation, chondrocyte migration (26), which affect the extracellular matrix, which in turn not only promotes endogenous hyaluronan synthesis, but also reduces cartilage destruction. It can also inhibit the inflammatory; for example, it reduces the secretion of prostaglandin, leukotriene, interleukin-1 (IL-1), and interleukin-6 (IL-6). In addition, hyaluronic acid is an important component of articular cartilage extracellular matrix, which is of great significance to maintain the integrity of cartilage biomechanics (27).

The use of hyaluronic acid for OA has attracted the attention of many scholars. A study showed that the injections of hyaluronic acid in OA patients can significantly reduce the pain symptom within 1 year when compared with the betamethasone treatment group (28). Research has shown that hyaluronic acid of different molecular weights affect patients differently (7,8). It was believed that the molecular weight of hyaluronic acid can influence the efficacy and safety (29). Low molecular weights (LMWs) appear to be less effective (30,31). In a clinical study examining the use of mixed with high molecular weight (HMW) hyaluronic acid to treat OA patients, the hybrid hyaluronic acid was more effective than the HMW hyaluronic acid (32). The study also compared the efficacy of a mixture of LMW and HMW hyaluronic acid, and found that the mixed hyaluronic acid was better than the HMW hyaluronic acid (32). The researchers conjectured that the combination of the anti-inflammatory effect of LMW hyaluronic acid on chondrocytes combined with the biomechanical effect of HMW hyaluronic acid accounted for these results (32).

The contraindications to intra-articular hyaluronic acid injection are not clear, but most scholars are of the view that they are similar to the local contraindications of corticosteroid injection. A previous study found that scleroderma should be considered a contraindication to the injection of hyaluronic acid, as the proinflammatory effects of hyaluronic acid may lead to keratinocyte migration and the deterioration of skin ulcers (33). The American College of Plastic Surgeons did not find any evidence to support the treatment of KOA using hyaluronic acid (34). Intra-articular injection of hyaluronic acid alleviated pain symptoms in patients with early and moderate KOA more than saline without increased adverse events within 6 months (35). However, late stage KOA patients treated with hyaluronic acid had lower levels of pain relief and a significantly higher risk of treatment-related adverse events than those treated with saline. If a single treatment does not work well, the frequency of intra-articular hyaluronic acid injections could have increased from 1 cycle to 4 cycles (36). Thus, the intra-articular injection of hyaluronic acid may cause local adverse effects, such as synovitis and pain.

Platelet-rich plasma (PRP)

PRP is plasma rich in high concentrations of platelets, and can be obtained from the whole blood of animals or humans after centrifugation. PRP has been shown to delay senescence and increase cell viability, and thus has been widely used in plastic surgery (37). PRP is essentially an autologous plasma, with higher platelet concentrations than normal plasma; PRP usually contains 150,000 to 300,000 platelets per microliter (38). It is widely believed that PRP that contains 2–8 times higher platelet concentrations than normal plasma can be used for therapeutic purposes (39). PRP contains large amounts of growth factors and anti-inflammatory cytokines, which can be released at the healing site when the platelets were activated. Additionally, PRP also adds type Ⅰ collagen to the extracellular matrix. Growth factors after PRP injection, such as Platelet-derived Growth Factor-BB, increase at different times (24). It also reduces the concentrations of proinflammatory cytokines by inhibiting IL-1 and nuclear factor kappa-B, thereby alleviating the inflammatory effects during OA. Further, it has been proposed that TGF-β increases the mitotic effect of osteoblasts (40).

Like hyaluronan, there is still a lack of high-quality study demonstrating the efficacy of PRP. PRP has not been approved by the FDA. Lin *et al.* (36) conducted a randomized clinical trial comparing a hyaluronic acid treatment and a saline treatment in mild to moderate KOA patients, and found that PRP significantly improved patients' clinical function over 1 year. In 2019, a study found that that a single injection of high-purity PRP produced good clinical results, and relieved symptoms in 84.2% of the patients (41). The Lysholm score and the Lequesne index improved significantly in the 1st, 3rd, and 6th months, and no adverse effects occurred. Al-Ajlouni *et al.* (42) proposed that platelet lysates can be used to treat early and medium KOA by releasing growth factors *in vitro* through platelets, and injecting them directly into the damaged joints. The researchers treated 48 degenerative joint change patients with platelet lysates. After 1 year, they found significant improvement in patients' symptoms. This may be an important promotion for the future application of PRP. As a very promising new type of pharmaceutical product, PRP has great potential application value. However, the lack of standardized factors, such as a standard centrifugal speed and standard PRP preparation time, may produce variants enriched in or without leukocytes (43). This may lead to adverse reactions, such as pain and joint stiffness (44). Thus, it is necessary to advance further trials to promote the use of PRP.

Other treatments

An imbalance of catabolic and anabolic factors may occur in OA patient (45). Tumor necrosis factor-α (TNF-α) play a role in affecting the OA, and it is a proinflammatory cytokine. The current most commonly used TNF-α inhibitors are infliximab and etanercept. A study has demonstrated the safeness of infliximab, but research on the use of infliximab to treat OA is still in the exploratory phase. In a study of hyaluronic acid and etanercept, VAS scores of the etanercept were found to be better than those of the hyaluronic acid in the first 12 weeks, but the difference in efficacy between the 2 drugs gradually narrowed after week 4 (46).

Gene therapy includes viral-based and non-viral-based gene therapy. However, inefficient gene transduction is a major barrier to its widespread use (47). It has been demonstrated that the binding of A-10 integrin antibodies to the capsid of the helper-dependent adenovirus vector not only leads to effective chondrocyte infection, but also targets other cell types simultaneously (48). There are also some problems with adenoviral vectors in treating OA, such as immunogenicity, insertion mutations, and the sustainability of transgene expression (49). Non-viral-based gene

therapy does not lead to the complications associated with adenovirus-mediated gene therapy. However, it is difficult for chondrocytes to enter the unvascular cartilage, and the dense collagen matrix also hinders drug absorption (50). Thus, the therapeutic role of drugs in the treatment of the joint requires further research (51).

Narrative

Most OA patients showed functional improvement within 6 weeks of the corticosteroid injection, but their symptoms did not improve significantly after this period. Using corticosteroids for a long time can result in oxidative stress, change gene expression in chondrocytes, lead to adverse reactions, such as cartilage toxicity, and accelerate the progress of OA. Due to its high frequency, the hyaluronic acid may cause more adverse reactions than corticosteroids, including synovitis and pain. Due to the lack of standardized factors, such as a standard centrifugation speed and a standard time for PRP preparation, leukocyte-rich or leukocyte-free variants may be produced. Adverse reactions include injection-site pain, joint stiffness, dizziness, headache, nausea, tachycardia, infection, bleeding and peripheral tissue injury.

Summary

OA creates an imbalance in the dynamic balance between joint tissue destruction and repair, which leads to a loss of joint structure and function. Challenges in OA treatment research include various pathological mechanisms and differences in rates of disease progression. Intra-articular injection therapy can maximize local therapeutic efficacy. Treating patient pain using minimally invasive methods is an effective and promising treatment option, which requires further research and exploration.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-818/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-818/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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