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Research Article

Intra-Articular Injections and Emerging Strategies in the Treatment of Knee Osteoarthritis

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Abstract

Knee Osteoarthritis (KOA) is a prevalent and debilitating condition, necessitating effective interventions to alleviate symptoms and improve patient outcomes. This comprehensive review explores the etiology, epidemiology, and management strategies for KOA through a comparative analysis of Intra-articular corticosteroid, platelet-rich plasma (PRP), and hyaluronic acid (HA) injections and a discussion of emerging treatment strategies using blood flow restriction (BFR) training and nerve ablation. Each treatment modality is described in terms of its mechanism of action, clinical efficacy, and potential side effects. This review aims to provide clinicians with valuable insights into the diverse landscape of KOA management, considering patient-specific factors and pave the way for informed decision-making in clinical practice.

Keywords: Knee osteoarthritis; Intra-articular corticosteroid injections; Platelet-rich plasma; Hyaluronic acid; Blood flow restriction, Radiofrequency nerve ablation

Abbreviations

Knee osteoarthritis (KOA); Osteoarthritis (OA); Intra-articular (IA); Platelet-rich plasma (PRP); Growth factor (GF); Western Ontario and McMaster Universities Arthritis Index (WOMAC); Platelet-rich growth factor (PRGF); Knee Injury and Osteoarthritis Outcome Score (KOOS); Hyaluronic acid (HA); Blood-flow restriction training (BFRT); Repetition maximum (RM); Low-intensity resistance training (LI-RT); High-intensity resistance training (HI-RT); Radiofrequency ablation (RFA); Genicular radiofrequency ablation (GNRFA); Conventional radiofrequency ablation (CRF).

Introduction

Knee Osteoarthritis (KOA) is a multifactorial condition influenced by systemic and local factors. Advancing age is a prominent risk factor [1] with KOA becoming more prevalent as individuals grow older. Increased body mass leading to higher joint loads is also recognized as a significant contributor [2,3], with a four-fold reduction in knee load for each pound of weight loss [4], highlighting the impact of weight on joint health. Prior knee injuries, whether due to trauma or overuse, elevate the risk of KOA [1], emphasizing the role of joint integrity in the disease process. Occupation, particularly involving repetitive joint stress such as construction, firefighting, and agriculture industries [5] is another factor influencing KOA susceptibility. Sex differences are observed, with females being more prone to KOA compared to males [6], suggesting a potential hormonal influence. Additional risk factors include bone density [7], knee malalignment [8] and genetic predisposition [5]. Understanding the diverse interplay of these factors is crucial for comprehensive OA management and prevention strategies tailored to individual risk profiles.

Osteoarthritis is the most prevalent joint disorder in the United States; with symptomatic KOA affecting approximately 10% of men and 13% of women aged 60 years or older [9]. This condition significantly contributes to work disability among U.S. adults, with one in 25 working-age adults experiencing limitations attributed to arthritis [10], and at least one in four individuals with arthritis reporting work limitations [10]. This not only contributes to loss of work productivity but also substantial healthcare costs. Notably, OA ranked as the second most expensive health condition treated in U.S. hospitals in 2017, accounting for a substantial $19.9 billion of the combined costs for all hospitalizations [12].

The financial burden associated with KOA is expected to escalate with the aging population and ongoing obesity epidemic in the U.S. According to data from the Johnston County Osteoarthritis Project, the prevalence of radiographic KOA in adults aged 45 and above was reported to be 27.8%, and the National Health and Nutrition Examination Survey (NHANES III) found that around 37% of participants aged 60 years or older exhibited radiographic KOA [9]. These statistics underscore the significant public health impact of OA, necessitating effective and sometimes innovative management strategies to alleviate its burden on individuals and healthcare systems.

No curative treatment exists for KOA, a disease characterized by cartilage degradation reflected clinically as joint stiffness, reduced range of motion, and pain. Consequently, treatment focuses on slowing disease progression, improving movement and function, and decreasing pain. KOA management options as either conservative (e.g. physical therapy and weight loss), pharmacological (e.g. oral analgesics and anti-inflammatories), procedural (e.g. intra-articular injections), and surgical (e.g. joint replacement) [13]. Health care providers typically implement a multifaceted treatment approach to achieve desired outcomes with intra-articular corticosteroid injections used as an adjunct therapy for short-term pain relief associated with KOA [14].

However, concerns about their potential long-term impact on cartilage health necessitate a reevaluation of their efficacy. It is imperative for healthcare providers to understand alternative treatment options, particularly when standard approaches prove ineffective. This ensures a personalized management strategy tailored to the unique needs and responses of individuals suffering from KOA. This review will explore various approaches in the management of KOA including intra-articular injections with corticosteroids, platelet-rich plasma, and hyaluronic acid as well as non-invasive methods of blood-flow restriction training and nerve ablation. With each treatment approach, we discuss the mechanism of action, clinical efficacy, and potential side effects.

Discussion

Intra-articular (IA) Corticosteroid Injections

The most commonly used adjunct for KOA management is intra-articular (IA) corticosteroid injections. Cortisone, a type of glucocorticoid, works to suppress the inflammatory process associated with OA [15]. The mechanism of action is complex and consists of decreasing synovial blood flow, reducing the numbers of leukocytes, and releasing of inflammatory mediators [16]. The inflammation suppression may decrease swelling, heat, and pain in the affected joint. Since KOA joint inflammation is associated with progression of cartilage damage, IA corticosteroid injections may also reduce disease progression [15]. Two notable studies provide insights into the short and long-term efficacy of IA corticosteroid injections on pain reduction.

Baker et al. [14] investigated the effects of corticosteroid injections in participants with KOA over a 12-week period. Participants received a single corticosteroid injection plus lidocaine in their arthritic knee and showed significant improvements in pain intensity (P=0.004), pain behavior (P=0.004), and pain interference (P<0.001) over the course of the study compared to the control group who received a lidocaine injection alone. This suggests IA corticosteroid injections are and effective intervention for short-term pain reduction. Raynauld et al. [17] investigated the long-term efficacy of IA corticosteroid injections of knee pain associated with OA. Participants received either IA corticosteroid injections or saline injections every three months for two years. The study demonstrated KOA patients who received long-term IA corticosteroid injections had a significantly greater change in range of motion (P=0.05) compared to the saline group after one year and a slightly greater but non-significant improvement in pain compared with baseline at the first year of follow-up (P=0.24) demonstrating short-term efficacy.

However, improvements in range of motion and pain were non-evident after two years suggesting IA corticosteroid injections have limited long-term efficacy. McAlindon and colleagues [15] showed similar results in their study investigating the effects of IA corticosteroid injections compared to saline injections every three months over the course of two years in participants with KOA. While there were apparent symptom improvement in pain, stiffness, and function after the first injection, they were not different from the saline group suggesting a possible placebo effect. Additionally, two years of IA corticosteroid injections showed no significant differences in knee pain supporting the notion they are not effective for long-term treatment.

Finally, in their systematic review and meta-analysis of randomized controlled trials, Najm et al. [18] assessed the effects of IA corticosteroid injections on pain and function associated with KOA at short-term (≤ 6 weeks) and long-term (≥ 24 weeks) intervals. They found non-significant reduced pain scores after short-term follow-up compared to controls. On the other hand, the effect reversed after long-term follow-up with reduced pain scores favoring the control group, although this result was also not statistically significant. Their findings, while not statistically significant, are clinically meaningful and suggest IA corticosteroid injections are useful for short-term KOA symptom management but may not be useful long-term.

The complication rate for all IA injections is low with the most frequently reported complication of pain and bleeding at the injection site [13]. Septic arthritis is a rare but major complication of IA corticosteroid injections [13] occurring in less than one in 10,000 cases [16]. Less serious, short-term side effects are also

worth noting. They include transient increase in pain associated with "steroid flare", mild headache, insomnia, and facial flushing, which occurs in as many as 40% of patients, particularly women [19]. Diabetic patients may also experience a transient spike in blood glucose level, lasting up to five days [19].

Intra-articular Platelet-Rich Plasma Injections

Intra-articular (IA) platelet-rich plasma (PRP) injections have emerged as an alternative to other injection therapies, leveraging the regenerative potential of platelet-derived growth factors. At its most basic level, PRP therapy attempts to take advantage of the blood's natural healing properties to repair damaged cartilage, tendons, ligaments, and muscles. Although blood is mainly a liquid (called plasma), it also contains small solid components including red cells, white cells, and platelets. Platelets contain growth factor (GF) proteins that play a vital role in the healing process [20]. Of particular significance to patients with KOA, PRP is believed to balance joint homeostasis and subsequently stimulate the repair of damaged cartilage [21]. While the exact mechanism is not clearly understood, in patients with OA, PRP therapy may inhibit inflammation and slow its' progression [22], reduce pain and friction by increasing production of natural lubricating fluid [23], alter joint pain receptors [24], and/or stimulate the formation of new cartilage [25].

The PRP preparation is relatively simple and uses the patient's own blood. Approximately 30mL of whole blood is extracted via venipuncture [26]. Platelets are separated from other blood cells via centrifuge and the patient's own PRP is extracted from the separated sample [26]. Leukocyte-deficient platelets, containing high GF concentrations 2.5-8 times greater than what is found in whole blood [27] is then injected into the patient's affected joint. The process generally takes less than 90 minutes and is completed in a single visit.

Two notable studies [21,28] investigated the effect of IA PRP injections in participants with KOA using the Western Ontario and McMaster Universities Arthritis Index (WOMAC), an OA outcomes measure for pain, stiffness, and functional limitations. Raeissadat et al. [28] compared the short and long-term efficacy of a variety of IA injections, including PRP, in 238 participants with diagnosed KOA. Participants were randomized into 4 groups and treated with either IA hyaluronic acid (3 doses weekly), IA PRP (2 doses with 3 weeks interval), IA platelet-rich growth factor (PRGF), a specialized type of PRP with a platelet activator added (2 doses with 3 weeks interval), and IA ozone (3 doses weekly). Participants in all four groups showed significant improvements in WOMAC scores two months after injection ($P<0.01$). However, only participants in the PRP and PRGF groups improved scores persisted for 12 months suggesting PRP (and PRGF) is the preferable choice for long-term management of KOA.

Huang et al. [21] conducted a prospective randomized control trial using 120 participants with symptomatic KOA. Participants received either IA PRP injections every 3 weeks for 9 weeks, IA corticosteroid injections every 3 weeks for 9 weeks, or IA hyaluronic acid each week for 3 weeks. Significant improvements in WOMAC scores, were observed in all three groups at the 3-, 6-, 9-, and 12-month follow-ups compared to pre-treatment values ($P<0.05$). However, the IA PRP group showed significantly better total WOMAC scores at 6, 9, and 12 months compared to IA corticosteroid injection and IA hyaluronic acid groups ($P<0.05$), suggesting IA PRP injections are superior to IA corticosteroid injections for long-term pain management and functional ability.

Korpershoek et al. [29] evaluated the effectiveness of three consecutive IA PRP injections over a three-week period on symptoms and function using the Knee Injury and Osteoarthritis Outcome Score (KOOS) after 3, 6, and 12 months in 140 participants with KOA. Their analysis revealed statistically significant improvements in KOOS scores at all three follow-up time points ($P<0.05$) but no differences between the follow-up time points suggesting outcomes did not get better or worse over the course of the study. Of significant value is this study was the comparison between statistically significant differences and clinically meaningful changes in KOOS scores. While statistically significant differences were observed after IA PRP injection, they did not exceed the minimal clinically important difference, suggesting a lack of clinically relevant improvements in patients suffering from KOA.

Finally, Görmeli et al. [30] compared the effectiveness of one versus multiple IA PRP injections on reducing symptoms in 162 participants with KOA. Participants received either one or three doses of IA PRP or a saline injection (control). Participants' pain and function were evaluated at baseline and at the 6-month follow-ups using the EuroQol visual analogue scale (EQ-VAS) and International Knee Documentation Committee (IKDC) subjective scores. Their analysis revealed significant improvements in the EQ-VAS and IKDC scores in both IA PRP treatments compared to the control group ($P<0.05$). Further analysis showed participants treated with three IA PRP injections had significantly better results than participants treated with a single IA PRP injection for both EQ-VAS ($P=0.001$) and IKDC ($P=0.001$) scores, suggesting a single injection of IA PRP is an effective treatment for KOA but multiple IA PRP injections may confer better clinical results.

Like AI corticosteroid injections, the complication rate for AI PRP injections is low with the most frequently reported complication of pain and bleeding at the injection site [13]. Since PRP is autologous, there is no risk for allergic reaction. However, there are risks from the injection itself, including infection, nerve injuries, and tissue damage at the injection site [31]. There is also a low risk of temporary worsening of symptoms, likely due to the stimulation of the body's natural response to inflammatory mediators [31]. Healthcare providers should carefully evaluate the available evidence and adhere to established guidelines to minimize potential adverse effects.

IA HA Injections

Hyaluronic acid (HA) is a glucosamine produced by chondrocytes, synoviocytes, and fibroblasts all of which are responsible for the viscoelasticity and lubrication of joints [32]. This naturally produced glycosaminoglycan is found in synovial fluid and articular cartilage acting not only as a lubricant but

also as a shock absorber. HA injections have been prescribed as a treatment method to enhance the viscosity of the synovial fluid within the knee joint. Qiao et al. [33] supported this theory stating HA "can physically lubricate the joint surface, reduce erosion, biologically nourish the articular cartilage, and stimulate the production of endogenous HA" (p. 932). The use of HA for KOA has been considered a more conservative approach given its direct and indirect analgesic effects. Patients have reported an overall improvement in joint function, pain relief, and reduced dosage of analgesics.

There has been debate on the short and long-lasting effects of HA for KOA particularly when compared to NSAIDs, CSC, and PRP. In a meta-analysis conducted by Qiao et al. [33], at three, six, and 12-month follow-up from a PRP + HA, PRP, HA, placebo, and CSC treatments, HA ranked third behind PRP and PRP + HA. The PRP group had the best overall outcomes with a standard mean difference (SMD) of -8.79, followed by PRP + HA surface under the cumulative ranking (SUCRA) of -61.2, HA (SUCRA=-48.9), and CSC (SUCRA=-17.3 at three months. At six months, PRP remained superior with a SMD of –11.92, PRP + HA (SUCRA=-64.2), HA (SUCRA=-50.2), and CSC (SUCRA=-6.7). Finally, at 12-month, PRP reigned supreme with a SMD of 7.04, followed by PRP + HA (SUCRA=-69.0), HA (SUCRA=-42.8), and CSC (SUCRA=0.0). Furthermore, the PRP group had the best reported outcomes in safety compared to HA. In WOMAC functional scores PRP surpassed HA in functional recovery at three (P=0.007), six (P=0.011) and 12 months (P=0.000).

Additionally, Tang et al. [32] determined that PRP was more effective than HA injections in overall and functional WOMAC scores in both short and long-term recovery and relief. The three-month mark did not yield any statistically significant difference between PRP and HA. However, at six (P=0.002) and 12 months (P=0.000), PRP WOMAC overall scores decreased indicating PRP a more effective treatment for KOA. Although HA did not statistically prove beneficial in the discussed studies, HA can reduce KOA pain and increase functionality and quality of life in the short term. Tang et al. [32] note that while PRP did not provide overall clinical improvement compared to HA in functional improvement, there is overwhelming evidence that PRP is more successful than HA in treatment of mild to moderate KOA.

When compared to NSAIDs, HA had less in number and severity of adverse effects such as injection site pain, pruritus, headache, and arthralgia [34]. However, most adverse effects were short-lived and spontaneously resolved on their own. Qiao et al. [33] noted transient injection site pain was reported with HA compared to the PRP. In the same study, PRP was shown to be more effective than HA regarding pain relief and a lower incidence of adverse side effects.

Blood-flow restriction training

Although there is a lack of evidence to support the ideal intensity, duration, and frequency, exercise is strongly recommended as a non-pharmacologic treatment approach for patients with KOA [35]. Specifically, resistance training to strengthen lower extremity muscles, especially the quadriceps, is used as a first-line therapy for KOA management [36]. However, patients with KOA-associated pain are often unable to tolerate exercise doses high enough to induce strength gains. Blood-flow restriction training (BFRT) is a technique that offers a method to increase strength and hypertrophy gains when higher loads aren't tolerated by the patient [37]. BFRT uses a pneumatic cuff to apply external pressure to the most proximal region of the lower limb. When the cuff is inflated, the mechanical compression restricts arterial blood flow to tissues distal to the cuff and occludes venous return [38], creating a hypoxic environment in the occluded limb. The patient performs low load (20%–30% of 1-RM) resistance exercises while blood flow is restricted to the exercising limb. Although the exact mechanism is not clearly understood, it has been suggested that BFRT produces a metabolic "overload" normally associated with high intensity resistance exercise [39]. The hypoxic environment generated during BFRT causes metabolites to accumulate (e.g. lactate) that promote increased growth hormone production and encourage hypertrophy [40]. Since this can occur at intensities as low as 20% of 1RM, it offers an appealing alternative to traditional resistance training that may be too painful for patients with KOA.

In their BFRT study, Ferraz and colleagues [36] compared the effects of 12 weeks of low-intensity (30% 1-RM) resistance training (LI-RT), high-intensity (80% 1-RM) resistance training (HI-RT), and low-intensity (30% 1-RM) BFRT in 48 KOA participants. Participants in the BFRT group demonstrated significant improvements in leg press ($P<0.05$), knee extension ($P<0.05$), and quadriceps cross-sectional area ($P<0.05$) after 12 weeks which was comparable to improvements seen in the HI-RT group suggesting BFRT was similarly effective at increasing lower limb strength, hypertrophy, and functionality. Additionally, the BFRT group demonstrated improved WOMAC pain ($P<0.05$), stiffness ($P<0.05$), and physical function ($P<0.05$) scores demonstrating participants achieved strength gains while reducing pain and stiffness. It is interesting to note that 25% of the HI-RT participants withdrew due to exercise-induced knee pain while no participants in the LI-RT or BFRT groups withdrew for that reason, reinforcing the notion that alternatives to high-intensity resistance training should be considered in KOA patients.

In a similar pilot randomized clinical trial, Harper and colleagues [41] compared the effects of 12 weeks of low-intensity (20% 1-RM) resistance training with BFRT to moderate-intensity (60% 1-RM) resistance training (MI-RT) in 35 participants with KOA to evaluate changes in muscle strength, pain, and physical function. In this study, strength gains and physical function favored the MI-RT group, but differences were not significant. However, more reports of knee pain were observed (n = 14) in the MI-RT group compared to the BFRT group (n = 3) suggesting BFRT may have lower efficacy but reduced likelihood of painful outcomes which could improve exercise compliance.

Finally, Segal and colleagues [42,43] conducted two studies of 40 women and 41 men with KOA who were assigned to complete either 4 weeks of low intensity (30% 1-RM) resistance training with or without BFRT. In both studies, isotonic quadriceps strength was evaluated using a 1-RM leg press and an isokinetic knee

extension dynamometer. Knee pain was evaluated using the Knee Osteoarthritis Outcome Score (KOOS). In women [42], quadriceps strength improved significantly more in the BFRT group (28.3 ± 4.8 kg) compared to the LI-RT group (15.6 ± 4.5 kg) (P = .0385) as did isokinetic knee extensor strength scaled to body mass (P = .0048). No changes in knee-related pain were observed after the BFRT intervention (P=0.48) or between groups (P=0.96). For men [43], quadriceps strength measured via 1-RM leg press increased significantly in both the LI-RT (P=0.001) and BFRT (P=0.03) groups, but only the LI-RT group showed improvements in isokinetic knee extensor strength (P=0.026) and KOOS scores (P=0.04). While the BFRT was not associated with worsening of knee pain, there were no significant improvements in isokinetic knee extensor strength. From these two studies, we can conclude the addition of BFRT to a 30% 1RM resistance training program was effective in increasing leg press and knee extensor strength in women with KOA, in comparison with the same program without BFRT demonstrating more favorable strength gains with BFRT while minimizing the potential for discomfort. However, for men with KOA, the addition of BFRT to 30% 1RM resistance training did not confer the same improvements in leg strength or knee pain.

The most reported side effects of BFRT include pain and discomfort of the compressed limb during the exercise training session and delayed-onset muscle soreness [37]. Less common side effects include numbness in the treated limb, bruising or ischemic injury, dizziness or fainting, muscle damage, and rhabdomyolysis [37]. There may also be a heightened risk of cardiovascular strain including increased blood pressure, thrombus formation, and damage to the vasculature [44]. However, risks and side effects can be minimized by selecting the appropriate cuff size and pressure and screening patients for contraindications.

Radiofrequency ablation

Radiofrequency ablation (RFA) has proven to be another viable, noninvasive option among the various non-surgical treatments for KOA by denervating sensory nerves through mechanical heat production. The mechanism of action of RFA is a pulse generator creating an electromagnetic field around the tip of a probe that activates molecules by generating frictional heat [45]. Heat generated will then denervate surrounding nerves or disturb pain signals resulting in pain relief. There are several RFA procedures however, genicular radiofrequency ablation (GNRFA) has been the most successful in producing pain relief of KOA in patients with minimal side effects [46].

There are three RFA techniques commonly prescribed in treating KOA: conventional, pulsed, and cooled. Conventional radiofrequency ablation (CRF) heats the targeted tissue to approximately 60-90° C, cauterizing neural tissue [46,47]. Whereas pulsed radiofrequency ablation (PRF) does little to cause damage to the integrity of the nerve but does change pain signals. Lastly, cooled radiofrequency ablation (CRF) circulates water around the probe tip to maintain a temperature of 60° C to heat the tissue to 80° [46]. Determining which RFA technique to use was not clearly explained, however, it is most likely up to the preference of the treating physician and considerations of the patient's health.

In the review of the literature, researchers utilized several methods to evaluate the effectiveness of RFA treatment, including the WOMAC scale, a numerical rating scale (NRS), the visual analog scale (VAS), and the 36-item short form (SF-36) with follow-up assessments conducted at three, six, 12, 18, and 4 months respectively. In a study by Carafes et al. [48], patients reported a significant decrease in pain as reported in their mean NRS scores from baseline (P<0.5) at 6-12 months (1.6 ± 3.0), 12-14 months (2.9 ± 3.7) and ≥ 24 months (3.1± 3.6). Similarly, in a systematic review by Orhurhu et al. [47], short-term pain relief, defined as pain reduction lasting as long as 12 weeks, was reported in VAS scores in six of the 20 studies after RFA. They also identified three studies showing 84% of patients showed improvement in VAS scores that lasted for as long as 6 months. Additionally, Orhurhu [47] discovered three other studies that showed a reduction in VAS scores, a significant improvement in pain, and reduced analgesic consumption at 12 months. Extending the timeline up to 24 months, Chen et al. [49] found clinically notable relief with RFA treatment compared to IA HA treatment in WOMAC and SF-36 scores, as well as no risks of cartilage loss and infection commonly associated with IA corticosteroids.

There were overwhelming reports of no to mild adverse side effects with any of the RFA procedures which further supports its use as a viable treatment option. Patients with KOA who have not responded to conservative treatment, are poor surgical candidates, and/or, are the best for DNRFA treatment [46]. Given the decreased risk for adverse side effects and complications, GNRFA is proven to be an ideal treatment. As with any medical procedure, there are causes for concern just as Zhang et al. [45] found "including local hemorrhage, hematoma formation, dysesthesias, thermal injury, and infection" (p.13). Other reported symptoms were intermittent pain to touch around the treatment site, knee swelling, subcutaneous bleeding, and prolonged hypoesthesia [46]. However, Zhang et al. [45] noted adverse side effects were mild and needed no further treatment.

Summary of Evidence

In summary, the evidence supports the efficacy of various non-surgical interventions for KOA, each with its own advantages and limitations. For acute pain relief from KOA, IA corticosteroid injections remain preferred, but for longer-term relief, evidence supports the consideration of IA PRP. Moderate to strong evidence suggests that, in patients with KOA, intra-articular PRP injections may be equal to or better than intra-articular corticosteroid injections at reducing pain and dysfunction after one year. However, cost considerations and insurance coverage should be considered since insurance may not cover IA PRP injections. IA HA injections provide short-term relief, with PRP often considered more effective. While BFRT may have no advantages of clinical outcomes compared to conventional resistance training in managing patients with KOA, it may provide an alternative approach for patients unable to tolerate the pain associated with higher-load resistance training. GNRFA emerges as a promising option for pain relief with minimal adverse effects. Choosing the most suitable intervention should consider individual patient characteristics and treatment goals. Educating healthcare practitioners about emerging biologic

treatments is essential, and future research should explore longer-term benefits, repeated cycles of IA PRP, and efficacy in advanced KOA stages.

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Conflict of Interest

There are no conflicts of interest regarding the submission of this article.

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