Research Article / Araştırma Makalesi

Spor Hekimliği Dergisi, 55(1): 6-13; 2020
Turkish Journal of Sports Medicine
DOI: 10.5152/tjsm.2020.153

Comparison of Intraarticular Injections of Hyaluronic Acid versus Dextrose Applied with Periarticular Prolotherapy in the Treatment of Recreational Athletes with Knee Osteoarthritis

Rekreasyonel Sporcularda Diz Osteoartriti Tedavisinde Periartiküler Proloterapi ile Birlikte Uygulanan İntraartiküler Dekstroz ve Hiyalüronik Asit Enjeksiyonlarının Etkinliğinin Karşılaştırılması

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ABSTRACT

Objective: The aim of the present study was to compare the effectiveness of intraarticular injections of hyaluronic acid (HA) versus dextrose (DX) in combination with periarticular prolotherapy (PrT) in the treatment of recreational athletes with knee osteoarthritis.

Material and Methods: A total of 54 patients who had chronic knee osteoarthritis (OA) were included in the study. The patients were divided into two groups as PrT+HA (intraarticular hyaluronic acid combined with periarticular prolotherapy, n=27) and PrT+DX (intraarticular dextrose combined with periarticular prolotherapy, n=27). Clinical efficacy and pain were evaluated via the Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) at pre-treatment and one, three and six-month follow-ups.

Results: Intra-group statistical analyses revealed significant improvements in PrT+HA and PrT+DX groups for WOMAC and VAS scores compared with baseline ($p<0.001$). When the two groups were compared, VAS and WOMAC scores in the first month follow-ups were significantly better in the PrT+DX group ($p=0.022$ and $p=0.03$, respectively) while sixth month follow-up scores were significantly better in the PrT+HA group ($p<0.001$ and $p<0.005$ respectively).

Conclusions: Both of the intraarticular injections (HA and DX) are efficacious and safe in treating knee osteoarthritis. HA offers advantage of higher treatment success, while DX offers clinical efficacy with less cost.

Keywords: Dextrose, hyaluronic acid, injection, knee, osteoarthritis, prolotherapy

ÖZ

Amaç: Bu çalışmanın amacı, rekreasyonel sporculardaki diz osteoartritinin tedavisinde periartiküler proloterapi (PrT) ile birlikte uygulanan eklem içi hiyalüronik asit (HA) ve dekstroz (DX) enjeksiyonlarının etkinliğini karşılaştırmaktır.

Gereç ve Yöntemler: Kronik diz osteoartriti (OA) olan toplam 54 hasta çalışmaya dahil edildi. Hastalar PrT+HA (periartiküler PrT ile kombine intraartiküler HA, n=27) ve PrT+DX (periartiküler PrT ile kombine intraartiküler DX, n=27) olarak iki gruba ayrıldı. Klinik etkinlik ve ağrı, Visual Analog Skala (VAS) ve Western Ontario ve McMaster Üniversitesi Artrit İndeksi (WOMAC) kullanılarak tedavi öncesi, bir, üç ve altı aylık izlemlerle değerlendirildi.

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Geliş Tarihi/Date Received:
13.02.2019

Kabul Tarihi/Date Accepted:
13.05.2019
Yayın Tarihi/Published Online:
24.09.2019

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Bulgular: Grup içi değerlendirmede her iki grupta da WOMAC ve VAS skorlarında tedavi öncesine göre anlamlı iyileşme gözlendi (p<0.001). Gruplar arası karşılaştırmada, VAS ve WOMAC skorları ilk ay takipleri PrT+DX grubunda anlamlı olarak daha iyi iken (sırasıyla p=0.022 ve p=0.03), altıncı ay takiplerde PrT+HA grubunda daha iyi olarak saptandı (sırasıyla p<0.001 ve p<0.005).

Sonuç: Her iki intraartiküler enjeksiyon yöntemi de (HA ve DX), diz osteoartritinin tedavisinde etkili ve güvenlidir. HA, daha yüksek tedavi başarısı avantajı, DX ise daha az maliyetle anlamlı klinik etkinlik sunmaktadır.

Anahtar Sözcükler: Dekstroz, diz, enjeksiyon, hiyalüronik asit, osteoartrit, proloterapi

Available at: http://journalofsportsmedicine.org and http://dx.doi.org/10.5152/tjsm.2020.153

Cite this article as: Erdem Y, Gul D, Akpancar S. Comparison of intraarticular injections of hyaluronic acid versus dextrose Applied with periarticular prolotherapy in the treatment of recreational athletes with knee osteoarthritis. *Turk J Sports Med*. 2020;55(1):6-13.

INTRODUCTION

Osteoarthritis (OA) is the most common degenerative knee disorder, accompanied by joint pain and dysfunction, and reduced quality of life (1). Many treatment methods ranging from analgesic medications to complex surgical methods to reduce complaints and improve knee functions have been described for the management of OA (2).

Proliferative methods have recently gained popularity in the management of OA. In this context; stem cell therapies, prolotherapy, hyaluronic acid and platelet rich plasma injections are most commonly used methods described in the literature (3). Prolotherapy (PrT) is a popular method with high success rates in clinical studies due to regeneration of ligamentous and cartilage structures of joints. The therapeutic effect of PrT depends on initiation of inflammatory processes in the applied region. The inflammatory process triggers fibroblast proliferation and collagen synthesis in damaged tissues, thereby initiating tissue healing and regeneration (4). PrT has long been used in the treatment of chronic joint-ligament pathologies and chronic musculoskeletal pathologies including osteoarthritis, and most studies have reported successful clinical results (4-14).

In recent studies, periarticular PrT has been combined with intraarticular injections (6,7,12). These studies suggest that combining intraarticular injection with prolotherapy increased treatment success by healing and regeneration of both intra- and periarticular structures in OA cases. Different concentrations of hypertonic dextrose (ranging from 15 to 25%) were most commonly used solutions in combination with periarticular PrT. Hyaluronic acid (HA) is one of the most common used intraarticular solutions with lower complication rates and higher treatment success in the management of OA (15). Even if some studies reported contradictory results, HA has been strongly recommended by the American Academy of Orthopaedic Surgeons (AAOS) since it provides improved results compared with saline placebo injections (13,16).

We hypothesized that different intraarticular regenerative solutions might increase the efficacy of PrT injections. Therefore our aim was to evaluate efficacy of intraarticular hyaluronic acid (HA) and dextrose solutions in combination with periarticular PrT injections in the treatment of recreational athletes with knee osteoarthritis.

MATERIAL and METHODS

Research Design and Subjects

This is a retrospective cohort study conducted to evaluate the clinical efficacy of intraarticular HA injections and dextrose combined with prolotherapy for the treatment of OA. Recreational athletes in the study were officers, petty officers, recruits and cadets who were performing regular exercise, especially running. The Local Ethics Committee approved all study protocols (Date: 05.02.19, No: 19-KAEK-020), and an informed consent was signed by each patient enrolled in the study.

Ages of the patients ranged between 50 and 85 years. Two of the patients were at the age of 85 years and walked 30 min daily, while the others

were younger and had regular walks three to five days a week or did regular indoor sports. The patients had knee osteoarthritis of Kellgren-Lawrence grade II, III or IV. They had at least six months of symptoms resistant to at least three months of conservative methods (non-steroidal anti-inflammatory drugs, lifestyle modification, weight reduction, regular exercise, physiotherapy), and they were recreational athletes who were performing regular exercise. Patients with immune diseases, rheumatic diseases, or other systemic inflammatory diseases, patients with acute or chronic infection or osteomyelitis around the knee joint, patients who had undergone previous surgery on the knee joint, patients who had history of hereditary or acquired bleeding tendency were excluded from the study.

A total of 54 patients with chronic knee OA who had received three sessions of injections between June 2016 and June 2018 were divided into two age, gender and osteoarthritis severity-matching groups. Twenty-seven patients received PrT combined with intraarticular HA (PrT+HA Group), while a matched group received PrT combined with intraarticular dextrose (PrT+DX Group) during the same period.

Intervention

Each protocol consisted of three sessions (with three weeks of intervals) of intra and periarticular injections. All injections were performed by the same researcher who had eight years of clinical experience. The injections were performed under aseptic conditions with ultrasound guidance. The patients were supinely positioned and the knee was flexed. 27G (Gauge) needles were used for injections. The injection points were determined based on tenderness in physical examination. A maximum of 18.0 mL dextrose solution (16.2 mL of 15% dextrose and 1.8 mL lidocaine) was injected to periarticular sites of the knee (medial collateral ligament, pes anserinus, patellar tendon, tuberositas tibia, medial patellar retinaculum, lateral collateral ligament & biceps femoris tendon, coronary ligaments, and rectus femoris). The PrT+DX group received 4.0 mL of 25% dextrose whereas the PrT+HA group had 4.0 mL of hyaluronic acid solution slowly infiltrated on the lateral side of the knee next to the patella, while the patella was being mildly subluxated (Figure 1).

Patients were recommended to rest and to apply hot water bags to injection points for 20 min every two hours for the first three days. All anti-inflammatory drugs were prohibited. If pain became unbearable, 500 mg of acetaminophen with a maximum dosage of four times a day was recommended. For the PrT+HA group, 2.0 ml sterile, pre-filled syringes containing 20 mg of sodium hyaluronate were used. A standard physiotherapy protocol as described by O'Reilly et al. (17) was prescribed to patients for five days after injections. The same physiotherapist performed the protocol in three sessions per week for two weeks. The patients carried out a home exercise program including the same exercises three times a day for the remaining days.

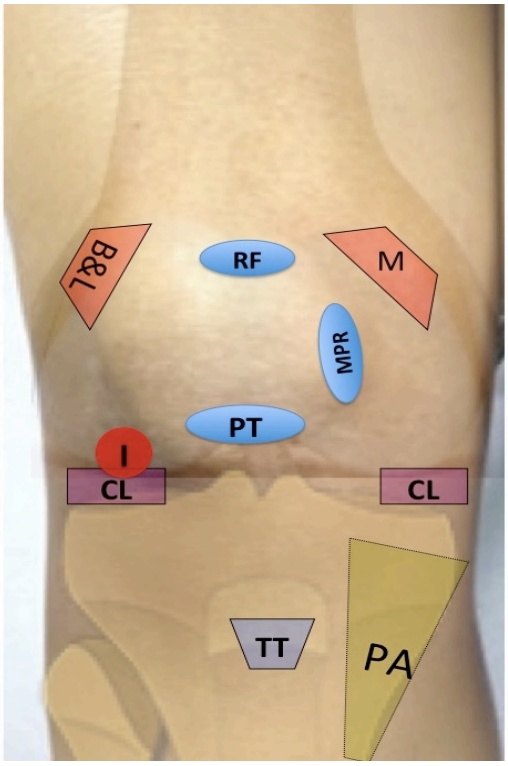

Figure 1. The injection points; I: intraarticular, P: pes anserinus, TT: tuberositas tibia, M: medial collateral ligament: B&L: lateral collateral ligament & biceps femoris tendon, CL: coroner ligaments (meniscus stabilizers), MPL: medial pa-

tellar retinaculum, RF: rectus femoris, PT: patellar tendon

Assessment of Clinical Efficacy

Pain was evaluated using a visual analog scale (VAS) (0: no pain and 10: the most severe pain). Western Ontario and McMaster Universities Arthritis Index (WOMAC) was used for the evaluation of knee functions. This is a 24-item index to assess pain, stiffness and physical function. Follow-up examinations were performed independently by one of the coauthors at baseline, one, three and six months after the treatment.

Statistical Analyses

Scores were expressed as mean ± SD. Two-way repeated measures ANOVA was used for time comparison of group effects. Analyses were conducted using a commercial software (IBM SPSS Statistics 19, SPSS Inc., IBM Co., Somers, NY). A level of $p<0.05$ was considered as statistical significance.

RESULTS

Demographic features, baseline WOMAC and VAS scores of PrT+HA and PrT+DX groups were similar (Table 1-3). Intra-group statistical analyses revealed significant improvements in PrT+HA and PrT+DX groups for WOMAC and VAS scores compared to baseline ($p<0.001$). All repeated measures displayed significant improvements ($p<0.001$) in the PrT+HA group for WOMAC and VAS scores. There was no significant differences between the first and third months in the PrT+DX group for WOMAC and VAS scores. When the two groups were compared, VAS and WOMAC scores in the first month follow-ups were significantly better in PrT+DX group ($p=0.022$ and $p=0.030$, respectively), while VAS scores were significantly better in PrT+HA group in the third and sixth month follow-ups ($p=0.033$ and $p<0.001$, respectively), and WOMAC scores were significantly better in the PrT+HA group in the sixth month follow-ups ($p<0.005$). No difference was observed between PrT+HA and PrT+DX groups for WOMAC scores in the third month follow-ups ($p=0.273$) (Table 3).

In the PrT+HA group, erythema and slight swelling occurred in three patients and excessive pain was observed in one patient, while slight swelling occurred in one patient and excessive pain was observed in two patients in the PrT+HA group. All these patients fully recovered after an average of two days hospitalization with cold application, elevation and intravenous acetaminophen administration.

Table 1. General characteristics of variables

Variables	Group		p
	PrT+HA	PrT+DX	
N	27	27	
Gender (male/female)	7 / 20	6 / 21	0,377
Side (right/left)	12 / 15	13 / 14	0,394
Age (yrs)	56.3 ± 8.9	58.9 ± 5.2	0,101
Severity of the disease	Grade II: n=9 (33%)	Grade II: n=11 (41%)	
	Grade III: n=12 (44%)	Grade III: n=11 (41%)	
	Grade IV: n=6 (22%)	Grade IV: n=5 (19%)	

Data are shown as mean ± SD or frequency/%; p: independent samples t-test or chi-square test;

PrT: periarticular prolotherapy; HA: hyaluronic acid; DX: intraarticular dextrose

Table 2. VAS scores

Measurements	Group		p_1
	PrT+HA	PrT+DX	
VAS baseline	8.11 ± 0.97 (a)	7.70 ± 1.10 (a)	0,078
VAS 1 mo	5.96 ± 0.80 (b)	5.29 ± 1.46 (b)	<0.05
VAS 3 mo	3.74 ± 1.16 (c)	4.67 ± 2.27 (b)	<0.05
VAS 6 mo	1.15 ± 0.76 (d)	2.59 ± 2.09 (c)	<0.001
p_2	<0.001	<0.001	

ANOVA was used for repeated measures. Means with the same letters (in the same column) are not statistically different, p_1: between-subject effect, p_2: within-subject effect; mo: month; PrT: periarticular prolotherapy; HA: hyaluronic acid; DX: intraarticular dextrose

Table 3. WOMAC scores

Measurements	Group		p_1
	PrT+HA	PrT+DX	
WOMAC baseline	78.0 ± 7.9 (a)	75.4 ± 5.3 (a)	0.082
WOMAC 1 mo	63.5 ± 8.0 (b)	58.4 ± 11.2 (b)	<0.05
WOMAC 3 mo	52.1 ± 11.4 (c)	54.5 ± 16.9 (b)	0.273
WOMAC 6 mo	22.4 ± 5.0 (d)	33.0 ± 19.3 (c)	<0.05
p_2	<0.001	<0.001	

ANOVA was used for repeated measures. Means with the same letters (in the same column) are not statistically different, p_1: between-subject effect, p_2: within-subject effect; mo: month; PrT: periarticular prolotherapy; HA: hyaluronic acid; DX: intraarticular dextrose

DISCUSSION

OA is a debilitating problem accompanied by joint pain and dysfunction in the middle-aged and over, and it reduces life quality. In the present study, two intraarticular approaches (DX versus HA) combined with periarticular PrT injections in the management of OA were evaluated and it was concluded that both treatment modalities were effective as measured by pain and clinical scores compared to baseline. However, HA was more efficient than DX.

PrT is one of the regenerative methods successfully used in common degenerative diseases. The therapeutic effect of PrT depends on initiating an inflammatory process in the applied regions. The inflammatory process causes fibroblast proliferation and collagen synthesis in damaged tissues, which in turn results in tissue healing and regeneration (4). PrT was investigated for the treatment of OA in previous studies, and improvements varying from 36 to 55% were observed in pain scales and WOMAC subscales (12,18,19).

PrT protocols vary in studies. Some studies preferred periarticular injections of PrT, while others used intraarticular injections combined with PrT. Robago et al. (12) compared intraarticular DX combined with PrT, saline injection and exercise in a randomized controlled study, and concluded that clinical results of intraarticular DX combined with PrT was better than saline injections and home exercises. In another triple-blinded randomized controlled study, Sit et al.

(20) used intraarticular prolotherapy injections in the treatment of OA and concluded that PrT injections were an effective non-surgical option for OA.

Another study revealed that clinical efficacy of prolotherapy continued for up to 2.5 years (6). Mechanic instability was one of the culprits for OA due to degeneration or chronic injury in knee ligaments. Combined intra- and periarticular treatments may both provide mechanic stability of the knee and regenerate intraarticular structures and cartilage defects. In the present study, we used intraarticular DX versus HA combined with PrT injections and obtained successful results in both groups. Our protocol in the PrT+DX group was similar to previous studies in terms of using 15% dextrose concentration for PrT and 25% dextrose concentration into the intraarticular space. In the present study, results for the DX group were similar to those from the previous studies (12,18,20). However, clinical results for the HA group were better than those for the DX group. We hypothesized that a combination of PrT with intraarticular injections increases the clinical efficacy, and combination of different regenerative solutions might further improve it.

Intraarticular DX is the most commonly used solution in combination with periarticular PrT. Previously hypertonic dextrose was thought to provide liquid support to the intraarticular region through withdrawing joint fluid in the periarticular region and Baker's cyst, whose osmolalities are lower than hypertonic DX (21). Subsequent studies showed that DX solutions provide regeneration not only in the periarticular joint structures but also in the intraarticular structures and joint cartilage. Topol et al. (22) reported that cases who received prolotherapy injections had metabolically active joint cartilage featuring variable cellular organization, parallel fibers and fibro- and hyaline-like cartilage typing patterns. It was shown in animal studies that inflammatory reactions increased, and ligament and cartilage structures enlarged considerably after prolotherapy (23).

In the present study VAS and WOMAC scores significantly improved in the DX group. All procedures were performed in a state hospital, and the average cost of the procedure was 215 Turkish Liras ($41.3) while the cost of the HA procedure was 1,654 TL ($318.0). We concluded that intraarticular HA is clinically more efficient than DX. However, DX is a cost-effective and efficient method in the treatment of OA. Further studies are needed to compare the cost-effectiveness of these methods.

HA is one of the most commonly used methods to regenerate cartilage and intra-articular structures of the knee joint. It protects chondrocytes and lubricates the joint to stabilize cartilage and synovium, and also has analgesic and anti-inflammatory effects (24). Even if some studies reported contradictory results, most clinical studies had promising results about intraarticular HA use (13,16). Elmorsyl et al. used HA for the treatment of knee OA in rabbits and showed that HA has chondroprotective potency, improves joint lubrication and delays the progression of OA considerably. In a meta-analysis conducted by Miller and Block, HA was mentioned to be a safe and efficient method in the treatment of knee OA (25). On the contrary, HA was concluded to have only minimal clinical benefits and some serious side effects in another meta-analysis by Rutjes (26). In our study, the clinical success of intraarticular HA was significantly better than that of DX. Therefore, the efficacy of periarticular PrT was improved by intraarticular HA application. Contrary to Rutjes et al. (26), no serious complications were encountered. We conclude that intraarticular HA could be combined with periarticular PrT in order to improve clinical success.

Studies dealing with HA examined various concentrations and administered doses of HA (27). Hafez et al. (28) studied the efficacy of single-dose low and high cost injections with different concentrations. Crespine (14 mg HA) and Intragel (14 mg HA) were used as low-cost injections while Crespine plus (14 mg HA) and Monovisc (22 mg HA) constituted high-cost injections. They concluded that all products resulted in improved therapeutic effects compared with

baseline state, and that the differences among different HA formulations were not significant.

There is no consensus regarding the dose of HA administered. Some authors preferred multiple intraarticular injections of HA, while others preferred single injection. Navarro-Sarabia et al. (29) evaluated multiple injections of HA and reported considerable improvements in pain and functional scales in most patients in a multicenter randomized placebo controlled study. Another study reported similar results from multiple injections of HA with 28-54% reductions in pain scores (30). Some studies suggested single HA injection because of comparable functional outcomes and less side effects (31). In the present study, we observed an 85% reduction in pain scores and a 72% improvement in clinical scores in the HA group with multiple HA injections combined with PrT. Erythema and slight swelling occurred in two patients and excessive pain was observed in one patient. All these patients fully recovered after an average of two days of hospitalization with cold application, elevation and intravenous acetaminophen administration. Because a procedure combining peri- and intraarticular procedures was used in the present study, clinical improvements were higher and side effects were negligible despite the fact that knee was traumatized at multiple points.

In the treatment of knee OA, various intraarticular regenerative methods were used to date. HA, platelet rich plasma (PRP) and stem cell therapy were the most commonly used approaches and various clinical outcomes were reported. Raeissadat et al. (32) compared effectiveness of intraarticular platelet rich plasma (PRP) and HA in the treatment of knee OA in a randomized prospective study, and concluded that PRP injections were more effective than HA injections regarding the improvement of clinical results and life quality. In their systematic review and meta-analysis, Chang et al. stated that intraarticular PRP provides significant improvements in knee function and better healing effect on cartilage defects than HA (33). Lamo-Espinosa et al. evaluated single intraarticular injection of in vitro expanded autologous bone marrow-derived MSCs in a multicenter randomized controlled clinical trial and obtained clinical and functional improvement of knee OA in the long-term (34). In the present study a regenerative intraarticular solution (HA) with periarticular PrT was combined, and higher treatment success was obtained. Other regenerative solutions (PRP, stem cell therapy, etc.) could also be combined with PrT to increase the success rate.

Small sample size, short follow-up periods and retrospective design are limitations of the present study. Both DX and PrT were concluded to be efficient and safe intraarticular methods in combination with PrT in the treatment of knee OA. HA offers advantages of higher treatment success, while DX has clinical efficacy with less cost.

REFERENCES

1. Lories RJ, Luyten FP. The bone-cartilage unit in osteoarthritis. *Nat Rev Rheumatol.* 2011;7(1):43-9.
2. Jevsevar DS. Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. *J Am Acad Orthop Surg*. 2013;21(9):571-6.
3. Jones IA, Wilson M, Togashi R, et al. A randomized, controlled study to evaluate the efficacy of intra-articular, autologous adipose tissue injections for the treatment of mild-to-moderate knee osteoarthritis compared to hyaluronic acid: a study protocol. *BMC Musculoskelet Disord*. 2018;19(1):383.
4. Reeves KD, Topol GA, Fullerton BD. Evidence-based regenerative injection therapy (prolotherapy) in sports medicine. In: *The Sports Medicine Resource Manual*. Seidelberg PH, Beutler AI, Eds. Philadelphia: Saunders; p. 611-9; 2008.
5. Akpancar S, Örsçelik A, Seven MM, et al. The effectiveness of prolotherapy on failed rotator cuff repair surgery. *Turk J Phys Med Rehab*. 2019;65:1-8. DOI: 10.5606/tftrd.2020.3222.
6. Rabago D, Mundt M, Zgierska A, et al. Hypertonic dextrose injection (prolotherapy) for knee osteoarthritis: Long term outcomes. *Complement Ther Med.* 2015;23(3):388-95.
7. Akpancar S, Seven MM, Tuzun HY, et al. Current concepts of prolotherapy in orthopedic surgery. *Arc Trauma Res*. 2017;6(2):e40447.
8. Örsçelik A, Seven MM, Yıldız Y. Prolotherapy interventions in treatment of chronic lateral epicondylitis. *Turk J Sports Med*. 2016;51(4):111-6.
9. Ersen O, Koca K, Akpancar S, et al. A randomized-controlled trial of prolotherapy injections in the treatment of plantar fasciitis. *Turk J Phys Med Rehab*. 2018;64(1):59-65.
10. Joshi Jubert N, Rodríguez L, Reverté-Vinaixa MM, et al. Platelet-rich plasma injections for advanced knee os-

teoarthritis: a prospective, randomized, double-blinded clinical trial. *Orthop J Sports Med.* 2017; 5(2): 2325967116689386.
11. Apaydın AH, Örsçelik A, Yıldız Y. The effects of prolotherapy in recreational athletes with plantar fasciitis. *Turk J Sports Med*. 2018;53(1):37-46.
12. Rabago D, Patterson JJ, Mundt M, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. *Ann Fam Med.* 2013;11(3):229-37.
13. Ada AM. Prolotherapy applications in sports medicine. *Turk J Sports Med.* 2015:50(2):57-64.
14. Eroğlu A, Sarı A, Durmuş B. Platelet-rich plasma vs prolotherapy in the management of knee osteoarthritis: randomized placebo-controlled trial. *Turk J Sports Med*. 2016;51(2):34-43.
15. Jevsevar D, Donnelly P, Brown GA, et al. Viscosupplementation for osteoarthritis of the knee: a systematic review of the evidence. *J Bone Joint Surg Am.* 2015;97(24):2047–60.
16. Bannuru RR, Vaysbrot EE, McIntyre LF. Did the American Academy of Orthopaedic Surgeons osteoarthritis guidelines miss the mark? *Arthroscopy*. 2014;30(1):86-9.
17. O'Reilly SC, Muir KR, Doherty M. Effectiveness of home exercise on pain and disability from osteoarthritis of the knee: a randomised controlled trial. *Ann Rheum Dis*. 1999;58(1):15-9.
18. Rabago D, Zgierska A, Fortney L, et al. Hypertonic dextrose injections (prolotherapy) for knee osteoarthritis: results of a single-arm uncontrolled study with 1-year follow-up. *J Altern Complement Med*. 2012;18(4):408-14.
19. Kim JM. The effect of prolotherapy for osteoarthritis of the knee. *J Korean Acad Rehabil Med*. 2002;26(4):445-8.
20. Sit RWS, Wu RWK, Reeves KD, et al. Efficacy of intra-articular hypertonic dextrose prolotherapy versus normal saline for knee osteoarthritis: a protocol for a triple-blinded randomized controlled trial. *BMC Complement Altern Med*. 2018;18(1):157.
21. Yavuz F, Kibar S, Balaban B. Hypertonic dextrose injection for the treatment of a Baker's cyst. *J Clin Diagn Res.* 2016;10(2):YD01-2.
22. Topol GA, Podesta LA, Reeves KD, et al. Chondrogenic effect of intra-articular hypertonic-dextrose (prolotherapy) in severe knee osteoarthritis. *PM R.* 2016;8(11):1072-82.
23. Jensen KT, Rabago DP, Best TM, et al. Early inflammatory response of knee ligaments to prolotherapy in a rat model. *J Orthop Res*. 2008;26(6) 816-23.
24. Elmorsy S, Funakoshi T, Sasazawa F, et al. Chondroprotective effects of high-molecular-weight cross-linked hyaluronic acid in a rabbit knee osteoarthritis model. *Osteoarthritis Cartilage*. 2014;22(1):121-7.
25. Miller LE, Block JE. US-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. *Clin Med Insights Arthritis Musculoskelet Disord.* 2013;6:57-63.
26. Rutjes AW, Jüri P, da Costa BR, et al. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med.* 2012;157(3):180-91.
27. Levett PA, Hutmacher DW, Malda J, et al. Hyaluronic acid enhances the mechanical properties of tissue-engineered cartilage constructs. *PLoS One*. 2014;9(12):e113216.
28. Hafez MA, Askar M, Nabeel A, et al. Comparison between four types of single-dose hyaluronic acid injection in patients with knee osteoarthritis: a randomized control trial. *Remedy Open Access*. 2017;2:1063.
29. Navarro-Sarabia F, Coronel P, Collantes E, et al. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. *Ann Rheum Dis*. 2011;70(11):1957-62.
30. Abate M, Salini V. Hyaluronic acid in the treatment of osteoarthritis: what is new. *Intech Open.* 2012;101-22.
31. Aaltonen K, Niemelä T, Sankari S, et al. Determination of the unsaturated disaccharides of hyaluronic acid in equine synovial fluid by high-performance liquid chromatography and fluorescence detection. *Acta Vet Scand.* 2015;57(1):12.
32. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Knee osteoarthritis injection choices: platelet-rich plasma (PRP) versus hyaluronic acid (a one-year randomized clinical trial). *Clin Med Insights Arthritis Musculoskelet Disord*. 2015;8:1-8.
33. Chang KV, Hung CY, Aliwarga F, et al. Comparative effectiveness of platelet-rich plasma injections for treating knee joint cartilage degenerative pathology: a systematic review and meta-analysis. *Arch Phys Med Rehabil.* 2014;95(3):562-75.
34. Lamo-Espinosa JM, Mora G, Blanco JF, et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: multicenter randomized controlled clinical trial (phase I/II). *J Transl Med*. 2016;14(1):246.