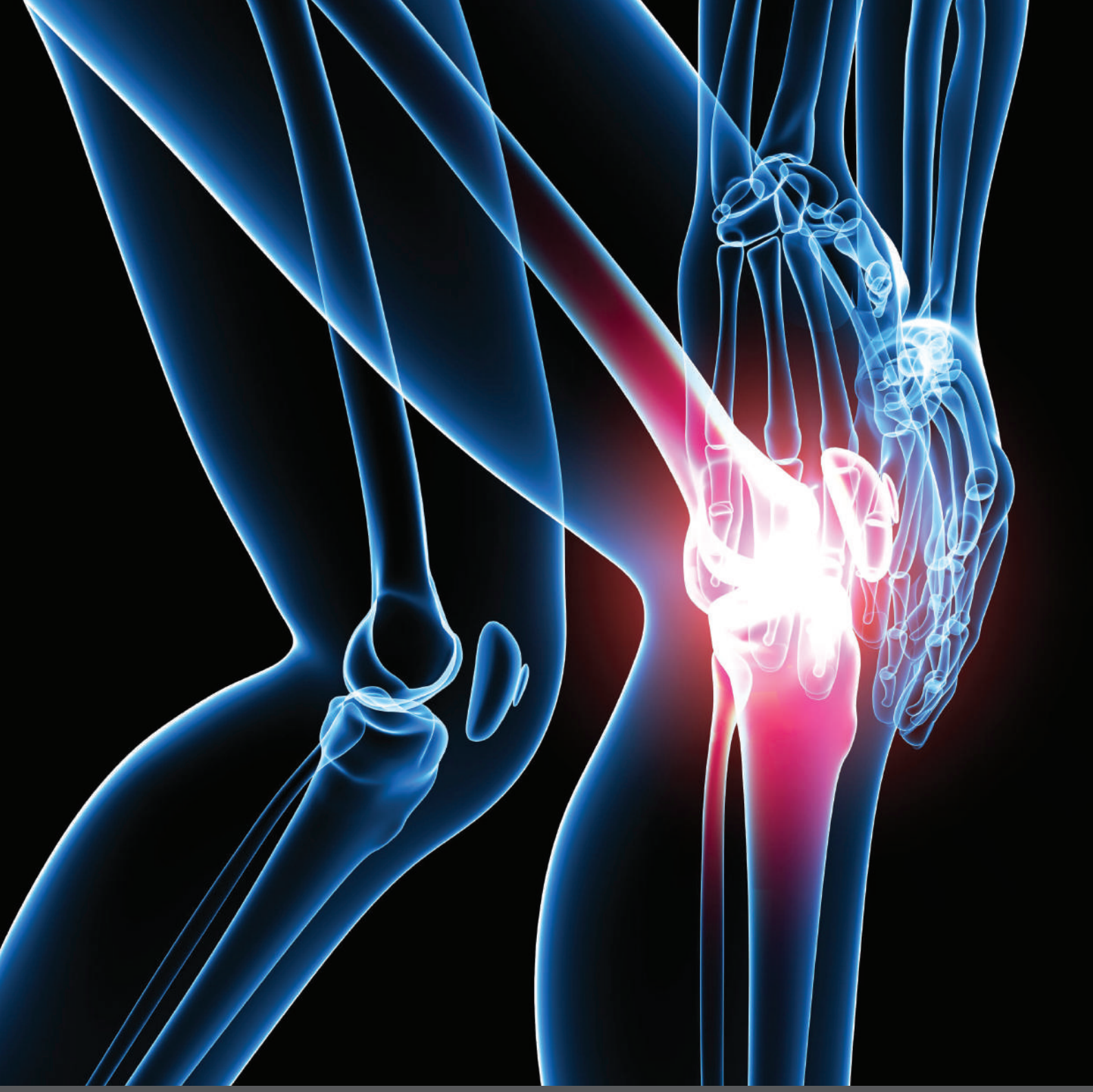


ARTHRODESMOL®

Intra - articular Filler

- Pain Relief by Lubricating and Cushioning Knee joint
- Anti-Inflammation
- Bone Formation
- Anti-Osteoclastogenesis
- Cartilage Regeneration

CE 2265

ARTHRODESMOL®

Intra - articular Filler

Arthrodesmol® is designed for:

Pain Relief by Lubricating and Cushioning Knee joint

Anti-Inflammation

Bone Formation

Anti-Osteoclastogenesis

Cartilage Regeneration

ARTHRODESMOL®
Intra - articular Filler

[Arthrodesmol® is 3~6 injection regimen given at 4 weeks intervals that provides benefits up to 6 months.]

Indication
- Intra-articular filler, Arthrodesmol® is indicated for the treatment of pain in osteoarthritic jointsand for the improvement of joint mobility through the enhancement of synovial fluid viscoelasticity.

Composition
- Sodium Hyaluronate (1.5%) Phosphate Buffered Saline, Oligopeptide-92, Nonapeptide-25, Octapeptide-11, Heptapeptide-16, Decapeptide-23.

Storage
- Store between 2℃ and 25℃, away from sunlight. Make sure there are no visible signs of damage to the packaging before use.

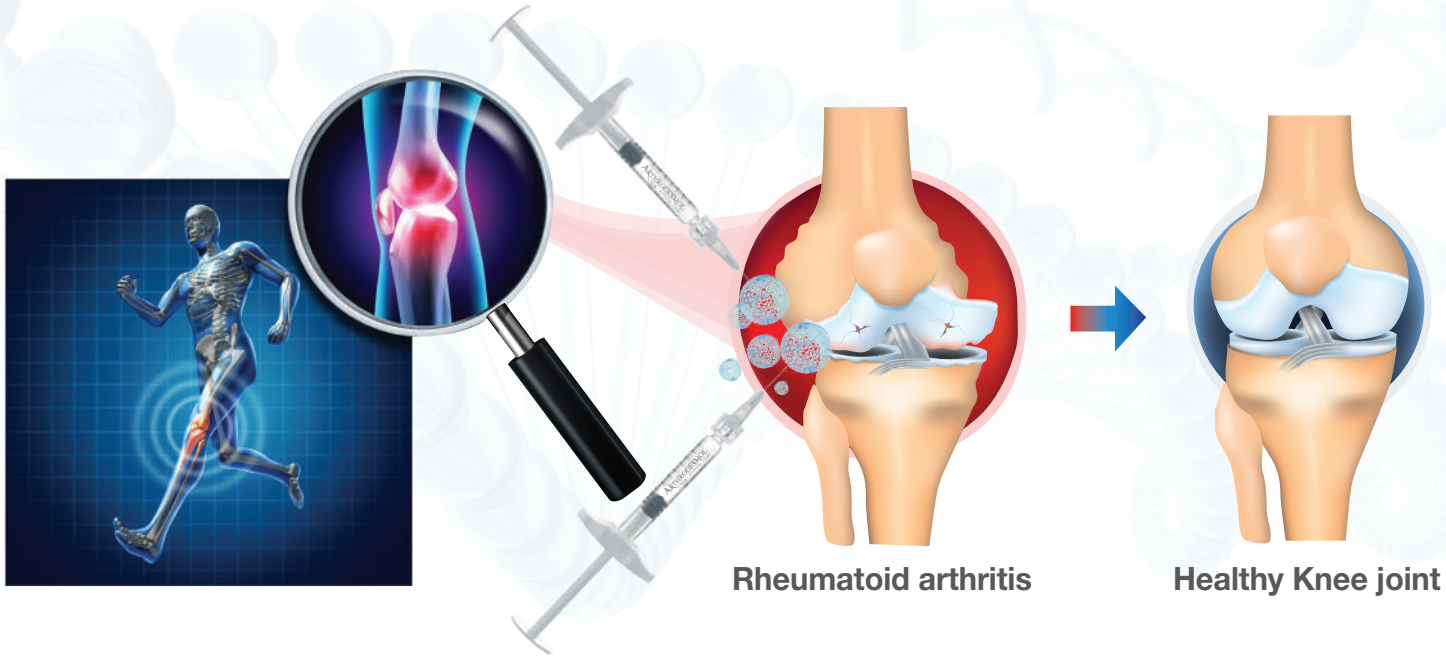
Package
- 1 x prefilled syringe, 2 x traceability labels

Precautions / Dosage and adverse events
- Refer to instruction for use.

Sustained Release & Peptide Technology

ARTHRODESMOL®
Intra - articular Filler
[Medical Device in formation of Filler]

Arthrodesmol® is 3~6 injection regimen given at 4 weeks intervals that provides benefits up to 6 months.



Rheumatoid arthritis

Healthy Knee joint

CG-SEPERIN
Octapeptide-11
Anti-Inflammation

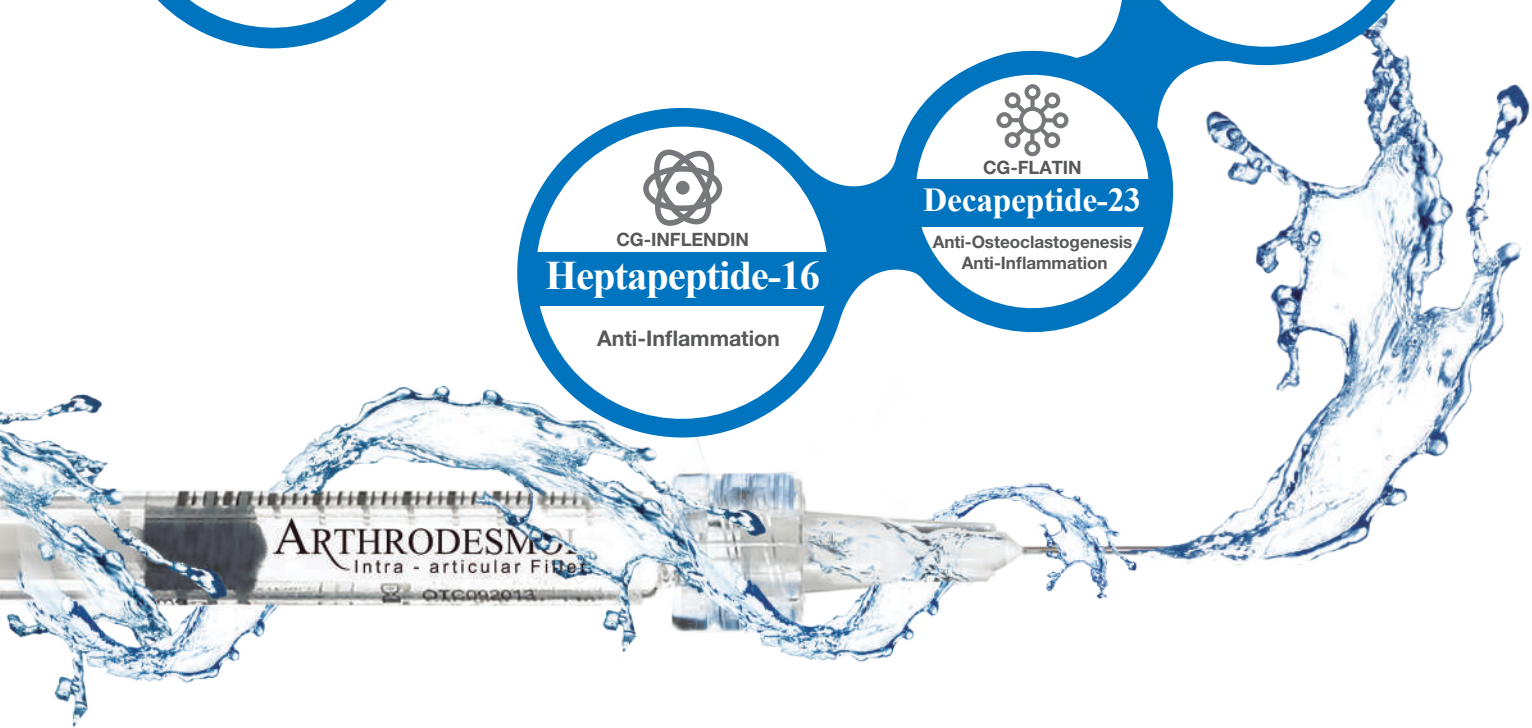
Hyaluronic Acid
Pain Relief:
- Anti-Inflammation
- Angiogenesis

CG-BONADE
Oligopeptide-92
Bone Formation
Anti-Osteoclastogenesis
Anti-Inflammation

CG-DENTIDE
Nonapeptide-25
Bone Formation
Anti-Osteoclastogenesis

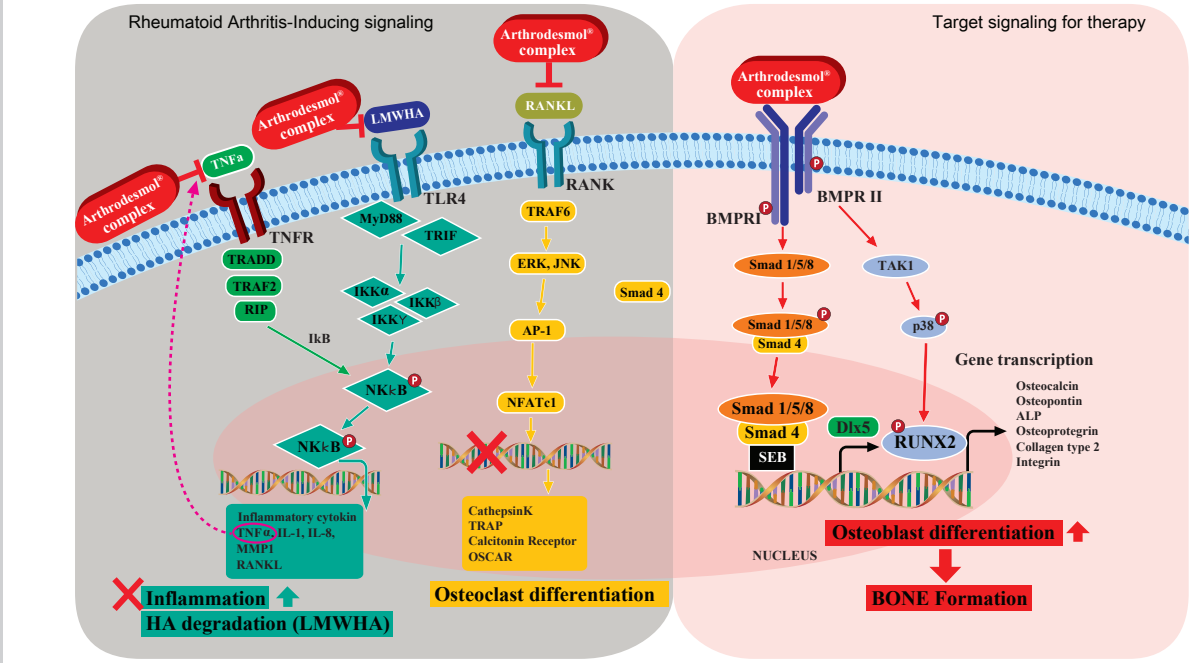
CG-FLATIN
Decapeptide-23
Anti-Osteoclastogenesis
Anti-Inflammation

CG-INFLENDIN
Heptapeptide-16
Anti-Inflammation



ARTHRODESMOL®
Intra - articular Filler

Signaling pathway of ARTHRODESMOL® intra articular filler



1. TNFR signaling pathway activated by TNFα : blocked by CG-Inflendin / CG-Flatin (Anti-inflammation)
Often, the arthritis including the rheumatoid starts with the inflammation in synovial membrane of the joint.
The expression of inflammatory cytokine such as TNFα, IL-1, IL-8, MMP, and RANKL is strong in inflammatory tissue.
One TNFα binds to the TNF receptor (TNFR), it leads to the expression of TRADD, TRAF2, RIP.
TRADD, TRAF2, RIP are the signaling molecules expressed by the binding of TNFα to its binding site, and expression of these molecules lead to the phosphorylation of NKkB.
Then Phosphorylated NKkB promotes the synthesis of inflammatory cytokine such as TNF α, IL-1, IL-8, MMP, and RANKL.
So this pathway is cycling.
More and more inflammatory cytokines in body lead to the stimulation of inflammatory cytokine synthesis, and the vicious cycle of inflammation starts.
CG-Inflendin and CG-Flatin blocks the binding of TNFα to its binding site, so it can also stop the cycle of inflammation.

ARTHRODESMOL®
Intra - articular Filler

2. TLR4 signaling pathway activated by LMWHA (Low Molecular Weight Hyaluronic Acid): blocked by CG-Seperin (Anti-inflammation)
CG-Seperin is a MMP blocker and also the inhibitor of LMWHA binding to TLR4 site.
Low Molecular weight HA is degraded hyaluronic acid which also causes inflammation by promoting synthesis of inflammatory cytokines.
Once LMWHA binds to TLR4, MyD88 and TRIF (signaling molecules) expressed, and they lead to the expression of IKK molecules,
then expression of IKK molecules lead to the phosphorylation of NKkB.
So as a result, synthesis of inflammatory cytokine such as TNFα, IL-1, IL-8, MMP, and RANKL happens.
CG-Seperin down regulates the breakdown of HA, so it keeps the HA to have higher molecular weight.

3. RANK signaling pathway activated by RANKL : blocked by CG-Bonade / CG-Dentide (Anti-osteoclastogenesis)
RANKL is a cytokine which promotes the osteoclastogenesis.
Osteoclast is the changed form of bone tissue, and it leads to the damage in bone tissue.
Binding of RANKL to its binding site leads to TRF6 expression → ERK, JNK → AP-1 → NFATc1 expression.
Then this pathway ends up with the expression of the gene which promotes the osteoclastogenesis.
CG-Bonade and CG-Dentide blocks the RANKL binds to its binding site, so it inhibits the osteoclastogenesis.
You can see its efficacy in osteoclastogenesis inhibition in the in-vitro study data C. in the leaflet too.

4. BMPR signaling pathway activated by CG-Bonade / CG-Dentide (Bone formation)
Not only inhibiting the RANKL, CG-Bonade and CG-Dentide also binds to the BMP binding site and promotes the bone formation.
CG-Bonade and CG-Dentide can binds to the BMPR and activate BMP pathway.
This signaling pathway ends up to the expression of gene transcription for bone formation including the osteoblast (bone cell) genesis.
By this bone formation, the cartilage (bone tissue) can be regenerated through the time.
TRADD, MyD88, TRAF6, and etc are the signaling molecules in cytosol, and the expression of each molecule leads to the expression of another signaling molecule in the path way.

ARTHRODESMOL®
Intra - articular Filler

Unique HA with a Specific Extracellular Peptides Mimics Matrix for a reponse of OA*

HA - High Quality - Pharmaceutical Degree - CEP

Hyaluronic acid (HA), the main component of extracellular matrix, is considered one of the key players in the tissue regeneration process. It has been proven to modulate via specific HA receptors, inflammation, cellular migration, and angiogenesis, whic are the main phases of wound healing. **The role of HA in 2 major steps of wound healing is examined: inflammation and the angiogenesis process.** Finally, the antioxidative properties of HA are discussed and its possible clinical implication presented.(1)

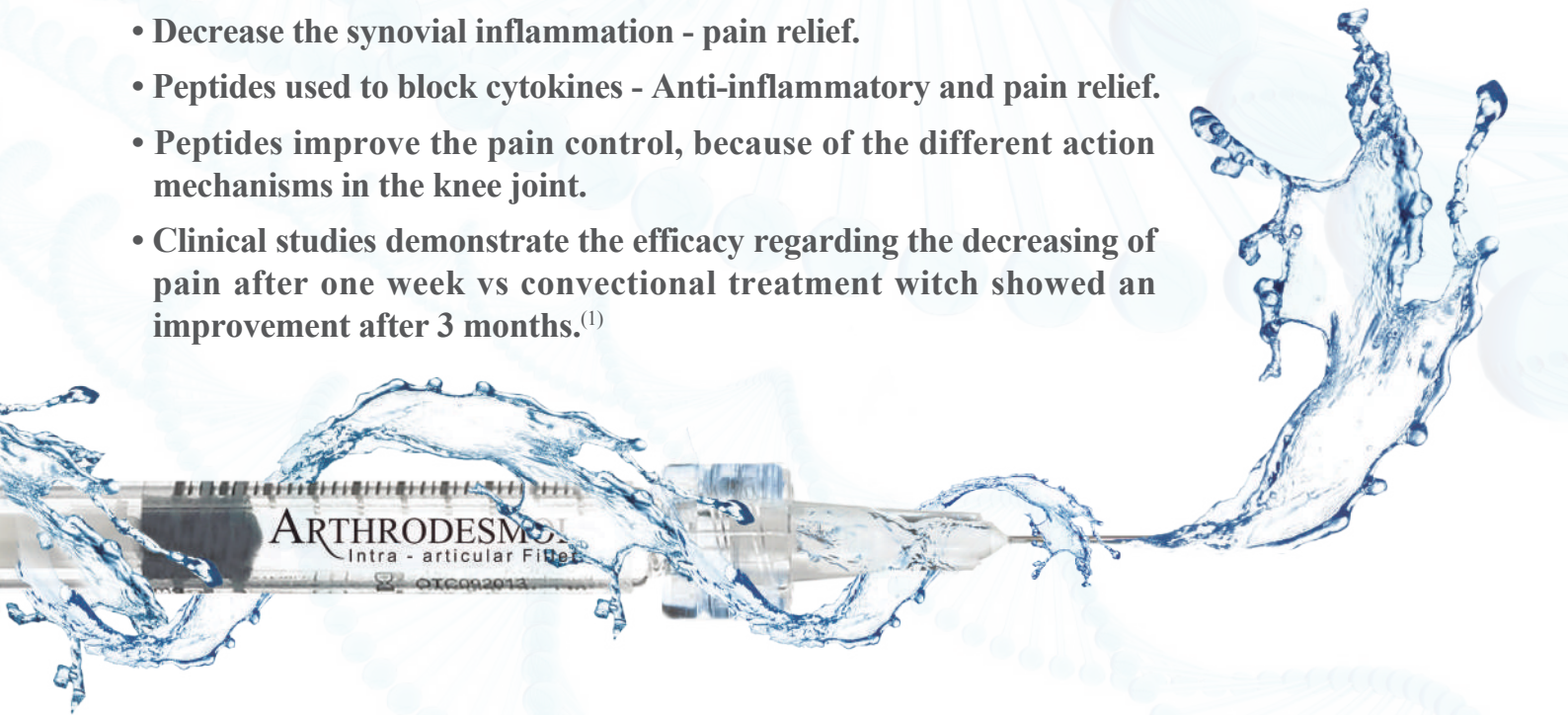
1 Hyaluronic Acid in Inflammation and Tissue Regeneration- Authors:Malgorzata Litwiniuk, Alicja Krejner, Tomasz Grzela: March 2016-Issue: Volume 28 - Issue 3 - March 2016- ISSN: 1044-7946- ndex: Wounds 2016;28(3):78-88
https://Arthrodesmol.woundsresearch.com/article/hyaluronic-acid-inflammation-and-tissue-regeneration

Arthrodesmol contains a unique HA (Low Molecular Eeight HA) obtained by fermentation. The quality of HA is granted by CEP certification.

HA's Arthrodesmol is the unique manufacturer by encimatic degradation.

Biomimetic Matrix Peptides Specific in OA

- **Stopping the cartilage degradation and joint degeneration.**
- **Decrease the synovial inflammation - pain relief.**
- **Peptides used to block cytokines - Anti-inflammatory and pain relief.**
- **Peptides improve the pain control, because of the different action mechanisms in the knee joint.**
- **Clinical studies demonstrate the efficacy regarding the decreasing of pain after one week vs convectional treatment witch showed an improvement after 3 months.**(1)



ARTHRODESMOL®
Intra - articular Filler

Benefits of Peptides in OA

Osteoarthritis (OA) is the most common degenerative joint disease characterized by articular cartilage degradation, joint degeneration, synovial inflammation and changes in periarticular and subchondral bone, being a leading cause of disability. **The articular cartilage is mainly formed by chondrocytes and a collagen-proteoglycan extracellular matrix that contains high levels of glycosylated proteins.** The Metastatic cell phenotype or Sialyated glycoproteins as peptides, attenuates NF-kB activation, protecting chondrocytes from arthritic insults that lead to articular cartilage degradation.(1)

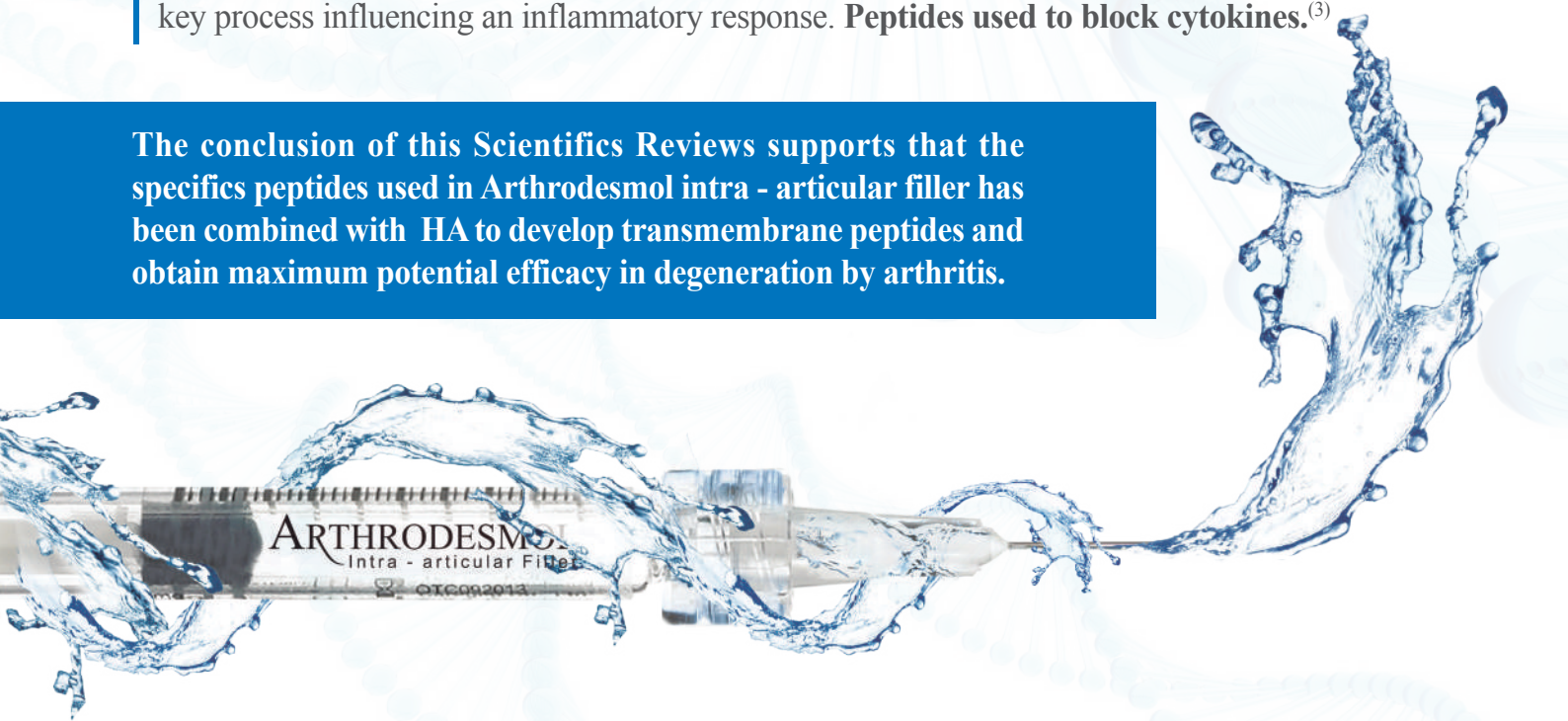
Recently studies demonstrate that the use specific peptides which combines with a high-quality Hyaluronic Acid:

> Provide **support for neo-tissue osteochondral repair/regeneration** whilst conferring proper mechanical and functional features as well as **protecting biomolecular agents from premature degradation.**

> Challenges used in biomaterials functionalization with peptides that can mimic ECM proteins or other natural soluble biomolecules, important to induce the complex interactions between cells and the ECM. Treating OA by means of **peptide-biofunctionalization of biomaterials which can be designed to be recognizable, induce differentiation, prevent infection, degrade at an intended rate or act as drug delivery systems for controlled release or even as simple triggers of cell behavior.**(2)

> Peptide and peptidomimetic-based approaches in the treatment of inflammatory arthritis is the key process influencing an inflammatory response. **Peptides used to block cytokines.**(3)

The conclusion of this Scientifics Reviews supports that the specifics peptides used in Arthrodesmol intra - articular filler has been combined with HA to develop transmembrane peptides and obtain maximum potential efficacy in degeneration by arthritis.



ARTHRODESMOL®
Intra - articular Filler

OCTAPEPTIDES - CG SEPERIN

Octapeptides reducing the production of cytokines (IL-17, IL-23, IL-6 and TNF-α) and chemokines monocyte chemoattractant protein 1 in the joints of arthritic or in synovial cell culture supernatant, and increased the levels of IFN-γ and TGF-β.

- Is effective in **suppressing both inflammatory** and Th17 responses in CIA.
- Represent a **new therapeutic** modality for rheumatoid arthritis.[4]

OLIGOPEPTIDES - CG BONADE

- **BONE FORMATION:** The results suggest that acidic oligopeptide is useful for drug delivery to bone and E2-(L-Asp)6 is a good candidate as an anti-osteoporosis drug without the adverse side effects of E2.[5]

- **ANTI-OSTEOCLASTOGENESIS:** The shTACE/peptide carrier complex alleviate arthritic symptoms in collagen induced arthritis (CIA) models by demonstrating **enhanced anti-inflammatory and anti-osteoclastogenic** effects.[6]

- **ANTI-INFLAMMATORY:** This peptide inhibits the biological activities of IL-6 in vitro and in vivo. This approach is an interesting development among other strategies aimed at targeting IL-6 in inflammatory diseases.[7]

NONAPEPTIDES - CG DENTIDE

- **BONE FORMATION:** this peptide in binding to transmembrane proteins to promote intracellular events leading to cell functions. It promote bone formation without any recognizable antigenic activity. Its potential application value for regenerative medicine, especially for bone tissue engineering.[8]

- **ANTI-OSTEOCLASTOGENESIS:** Receptor activator of nuclear factor-κB (RANK) and RANK ligand play a pivotal role in bone metabolism, and selective targeting of RANK signaling has become a promising therapeutic strategy in the management of resorptive bone diseases. Nonapeptides is a small peptide inhibitors specifically targeting the receptor RANK and it is new therapeutic opportunity for the treatment of resorptive bone-disease.[9]

ARTHRODESMOL®
Intra - articular Filler

DECAPEPTIDES - CG FLATIN

- **ANTI-INFLAMMATORY:** the decapeptide is a potent anti-inflammatory peptide that has potential therapeutic applications, especially for PLA2- **in synovial fluid from patients with RA inflammatory arthritis.**[10]

- **ANTI-OSTEOCLASTOGENESIS:** Activate the proliferation of type II collagen specific T cell response and antibody formation in rheumatoid arthritis (RA) and their relations to HLA-DR4 subtype.[11]

HEPTAPEPTIDE - CG INFLENDIN

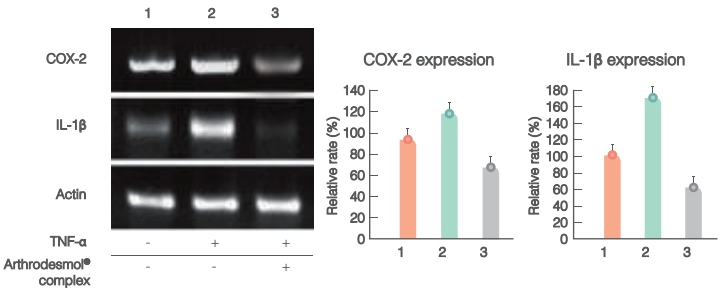
- **ANTI-INFLAMMATORY:** the RGD peptide (RGD-4C) was covalently linked to a proapoptotic heptapeptide binds selectively to the αvβ3 and αvβ5 integrins accumulated in inflamed synovium but not in normal synovium. Homing of RGD-4C phage to inflamed synovium was inhibited by co-administration of soluble RGD-4C. **Intravenous injections** of the RGD-4C–D(KLAKLAK) 2chimeric **peptide significantly decreased clinical arthritis and increased apoptosis of synovial blood vessels**, whereas treatment with vehicle or uncoupled mixture of the RGD-4C and the untargeted proapoptotic peptide had no effect. **Targeted apoptosis of synovial neovasculature caninduce apoptosis and suppress clinical arthritis**. **This form of therapy has potential utility in the treatment of inflammatory arthritis.**[12]

ARTHRODESMOL®
Intra - articular Filler

In-vitro study

A Pro-inflammatory Cytokine Gene Expression of Arthrodesmol® complex

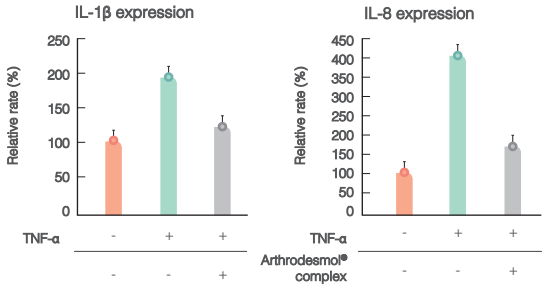
Cell line: HaCaT keratinocyte cell line
Method: RT-PCR analysis
Concentration: TNF-α 50ng/ml, Arthrodesmol complex 1ug/ml



When inflammation is stimulated by TNF-α and treated with Arthrodesmol® complex, the expression of pro-inflammatory molecules, COX-2 and IL-1β, were decreased.

B Inhibition of Pro-inflammatory Cytokines

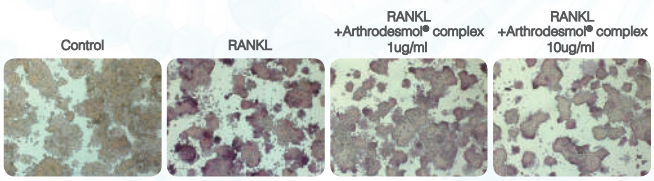
Method: ELISA test
Concentration: TNF-α 50ng/ml, Arthrodesmol complex 1ug/ml



When inflammation is stimulated by TNF-α and treated with Arthrodesmol® complex, the expression of pro-inflammatory cytokines, IL-1β and IL-8, was decreased.

C Inhibition of Osteoclast differentiation by Arthrodesmol® complex

Osteoclastogenesis inhibition test
Cell line: RAW264.7 macrophage cell line
Method: TRAP Staining kit
Culture time: 5 days
Concentration: RANKL 10ng/ml

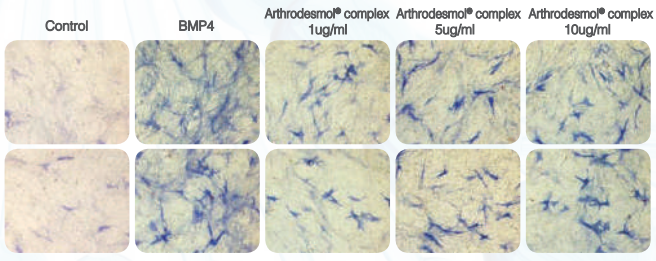


TRAP assay was performed to evaluate the inhibition effect of Arthrodesmol® complex against RANKL-induced osteoclast differentiaton. Arthrodesmol® complex protected osteoclast differentiation induced by RANKL

TRAP: Osteoclast differentiaton marker protein

D Osteoblast Differentiation analysis by Alkaline Phosphatase Staining

Cell line: C2C12 osteoblast cell line
Method: Alkaline phosphatase staining
Incubation: 4 days
Concentration: BMP4 100ng/ml



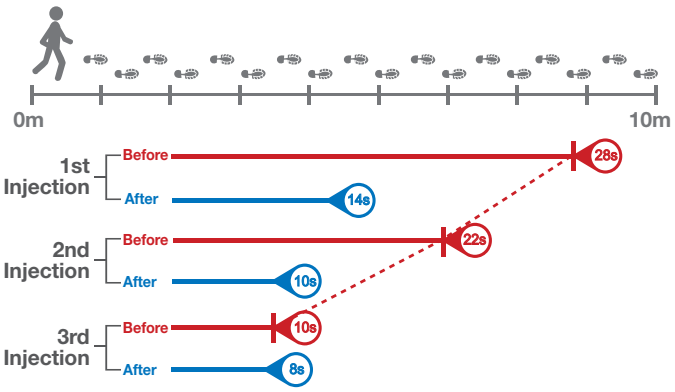
Osteoblasts were treated with Arthrodesmol® complex for 4 days and analyzed using ALP staining method. Arthrodesmol® complex increased alkaline phosphatase-positive cells compared to control group in a dose-dependent manner.

ARTHRODESMOL®
Intra - articular Filler

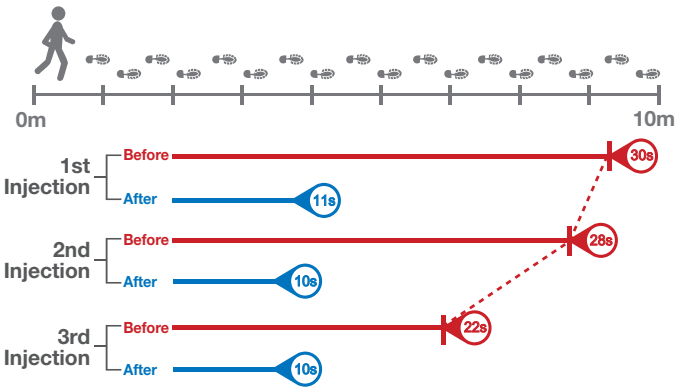
Clinical study

Clinical study Walking Speed Before & After Arthrodesmol® Injection

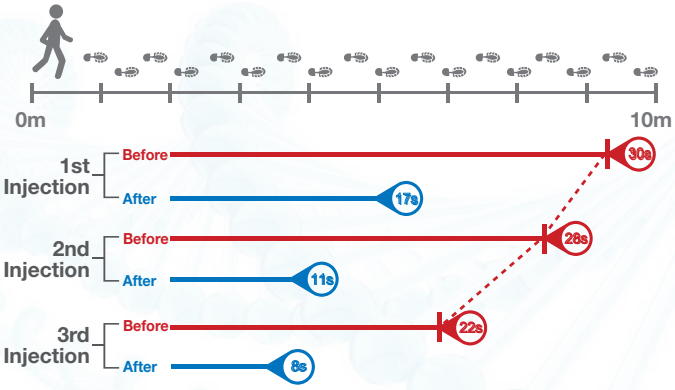
Subject 1 Pt: AD



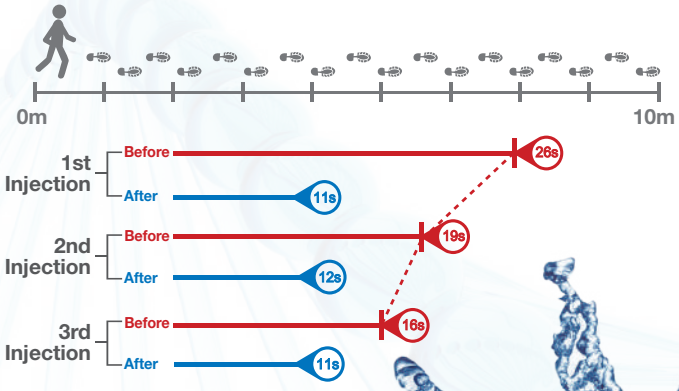
Subject 2 Pt: KK

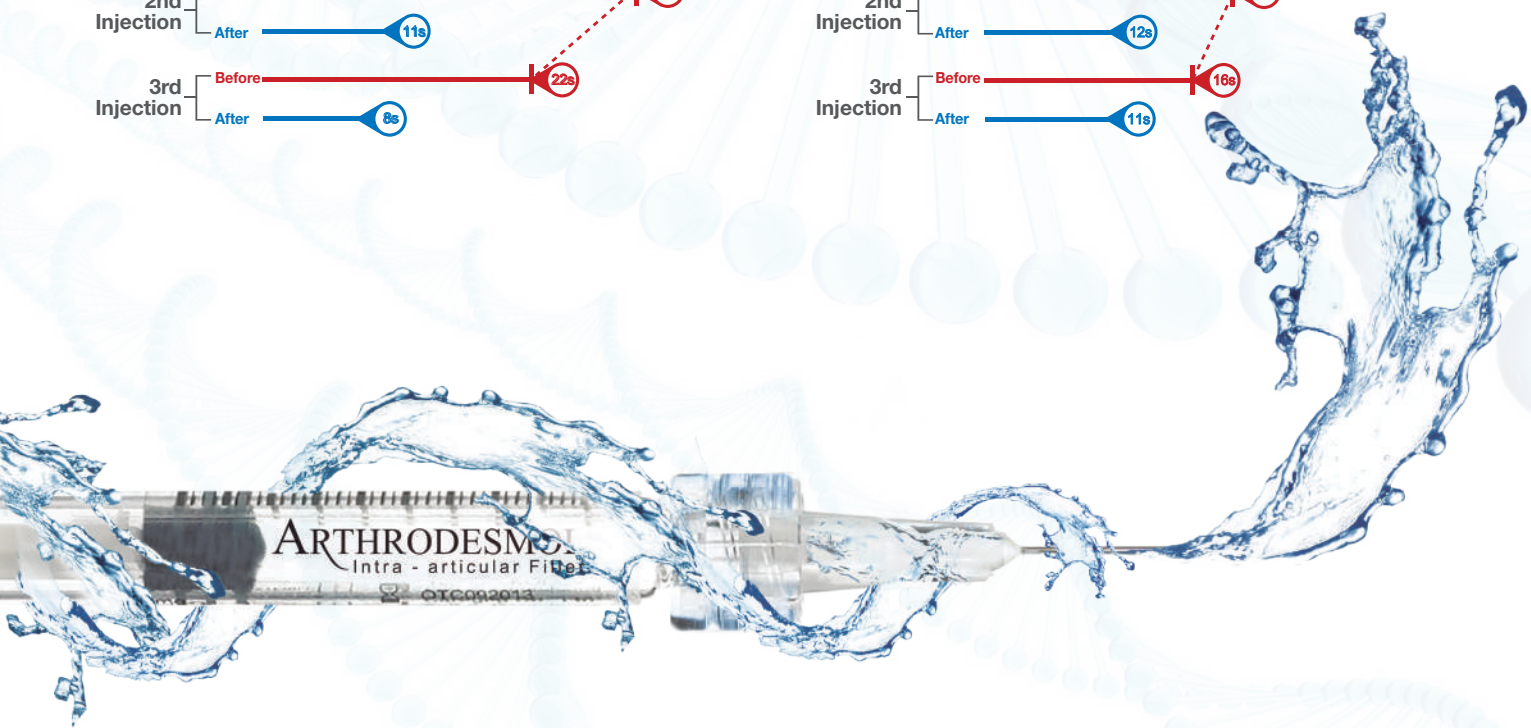


Subject 3 Pt: NM



Subject 4 Pt: MK





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ORIGINAL ARTICLE

Comparison of the short-term results of single-dose intra-articular peptide with hyaluronic acid and platelet-rich plasma injections in knee osteoarthritis: a randomized study

Fatma Nur Kesiktas[1] · Bahar Dernek[1] · Ekin Ilke Sen[2] · Havva Nur Albayrak[1] · Tugba Aydin[1] · Merve Yildiz[1]

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Abstract

Introduction/objectives Intra-articular injections may be useful in terms of pain and functional status, in knee osteoarthritis (OA). Besides hyaluronic acid (HA) and platelet-rich plasma (PRP), peptide molecules recently begin to be used. The aim of this study was to compare the efficacy of intra-articular peptide Prostrolane® (CAREGEN Co. Ltd.) injection with that of the HA and PRP in the persons with OA.

Method Fifty-four patients with OA were included in this prospective, randomized study. Patients were randomized into three groups as intra-articular HA, peptide, and PRP groups. Paracetamol was permitted three times a day to all groups. All the patients were evaluated by the Western Ontario and McMaster Universities Arthritis Index (WOMAC), Health Assessment Questionnaire (HAQ), and visual analogue scale (VAS) at rest and during movements. Measurements performed at the baseline, after the first week of injection, and at the first and third months of follow-up.

Results Mean age was 55.8 ± 8.9 years. Forty-four (81.6%) were women. A week after the injections, rest and movement pain severity was measured by VAS decreased significantly in all the study groups ($p < 0.05$). There were no statistically significant differences between the groups in terms of first week pain relief ($p > 0.05$). WOMAC pain, stiffness, function, and total scores were improved significantly in all the groups a week after the injections ($p < 0.05$). Improvement continued at the third month control; however, the improvement in the WOMAC pain score was significantly better in the peptide group at the third month control ($p < 0.05$). The decrease in the rest and movement pain was continued for 3 months except the HA group's rest pain. There were no differences among the groups for all measurements, except for the WOMAC pain score at 3 months after treatment, which was significantly lower in the peptide group.

Conclusion As a result, pain relief and functional improvement were obtained after the intra-articular HA, peptide, and PRP injections in OA, and decrease in pain was better in the peptide group.

Key Points
- *The short-term effects of intra-articular HA, peptide, and PRP injections were compared in knee osteoarthritis.*
- *HA, peptide, and PRP injections may be useful in pain relief and functional improvement in knee osteoarthritis.*

Keywords Hyaluronic acid · Intra-articular injections · Knee osteoarthritis · Peptide molecules · Platelet-rich plasma

Introduction

Knee osteoarthritis (OA) is the most common cause of chronic arthritis and is associated with severe pain, disability, loss of function, and adverse effects on quality of life [1–3]. Intra-articular injections are widely used for treatment, because of the relatively faster pain relief effect and no systemic side effects. As we know prolonged, use of non-steroidal anti-inflammatory (NSAII) agents may cause nephrotoxic and gastrointestinal side effects [3, 4]. Recent studies have reported that hyaluronic acid, intra-articular thrombocyte-rich plasma

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(PRP), and applications are particularly effective in treating knee OA [1, 4–8]. Viscosupplementation may help pain reduction and functional improvement [5, 6, 9]. There are conflicting results about intra-articular hyaluronic acid (HA) injections [10, 11]. Intra-articular PRP injections are widely used all over the world [4, 7–13]. PRP content contains more than 1500 active proteins, including alpha and dense granules. These platelet-derived mediators have anti-inflammatory, pro-inflammatory, anabolic, and catabolic effects [4, 7–13]. Alpha granules consist of various growth factors (GFs) that can effectively promote articular cartilage repair, such as platelet-derived GF (PGDF), transforming GF (TGF-β), platelet-derived epidermal GF, vascular endothelial GF, insulin-like GF-1, fibroblastic GF, and epidermal GF. Dense granules contain regenerative molecules for damaged tissues, such as adenosine diphosphate, adenosine triphosphate, calcium, histamine, serotonin, and dopamine [12–14].

The comparison of the effects of intra-articular PRP and HA is controversial in knee OA [12, 15–17]. Because of the different results related with the hyaluronic acid and PRP, clinicians are seeking for new treatment methods. Natural peptides are polymers formed by linking alpha amino acids that were first used as a medicine in the early 1960s [18]. There are many different types of synthetic peptide polymers. "CG-Inflendin" and "CG-Flatin" is to stop the inflammation cycle by blocking the binding of TNFα binding to its receptor. CG-Seperin is MMP blocker. It downregulates LMWHA (low-molecular-weight hyaluronic acid) and keeps the HA to have higher molecular weight, as the LMWHA may cause inflammation by stimulating synthesis of inflammatory cytokines. "CG-Bonade" and "CG-Dentide" are binding with BMPR to stimulate the osteoblast differentiation. When the osteoblast is stimulated, at the same time, the osteoclast is inhibited as per the function of antagonism [18, 19].

However, peptides have been considered to have limited treatment potential due to various disadvantages including molecular instability, short plasma half life, lack of specificity, and poor oral bioavailability. The introduction of systems facilitating increased bioavailability and persistence in the recent years has shown particular promise for the treatment of various conditions, especially OA [18]. An intra-articular peptide product containing sodium hyaluronate (1.5%), oligopeptide-92, nanopeptide-25, octapeptide-11, heptapeptide-16, and decapeptide-23 is available in Turkey under the trademark Prostrolane® produced by CAREGEN Co. Ltd. Several intra-articular injections are frequently used in daily practice. And there are few studies for comparing intra-articular injections [4, 12, 15–17]. So for that reason, the aim of this study is to compare the efficacy of intra-articular injections in terms of pain intensity and functional status in knee OA.

Participants and methods

Fifty-four patients were included in this prospective randomized study. Patients were selected from 120 patients who admitted to the outpatient clinic of a hospital with symptomatic knee osteoarthritis between January 2018 and June 2018. Flow chart according to the Consort diagram [20] is shown in Fig. 1.

The knee roentgenograms (weight-bearing anteroposterior, lateral and Merchant's radiographs of both knees) of all patients were evaluated by the same physician. The inclusion criteria were having symptomatic chronic knee OA > 1 year, being radiologically Kellgren–Lawrence Grade 2–4 [21], 18 years of age and older, ability to provide informed consent, body mass index (BMI) < 30, stable knees without malalignment, and normal blood results and coagulation profiles. The patients with radiologically grade 4 knee osteoarthritis who did not want surgical treatment were included in the study. Exclusion criteria were having intra-articular effusion, knee instability, major axial deviation; systemic disorders such as diabetes, rheumatoid arthritis, coagulopathies, severe cardiovascular diseases, infections, or immune deficiency; current use of anticoagulant medications or NSAIDs used in the 5 days before blood test; history of known anemia; recent trauma; severe hip OA; invasive procedures to the knee; intra-articular steroids or any intra-articular injections to the knee within the previous 12 months, infection in knee; pregnancy; and psychiatric disease.

The patients were randomly assigned into three groups using a computer-based protocol for the three kinds of single-dose intra-articular injection. All the products were provided free of charge by Intraline Company. The patients were called to the clinic for intra-articular injections: Group 1 (peptide group, $n = 18$) received peptide, Group 2 received (hyaluronic acid group, $n = 18$) HA, and Group 3 received (PRP group, $n = 18$) PRP. The injections were performed when the patient is laying in supine position with the knee in semi-flexion. Peptide, HA, or PRP injections were administered under sterile conditions using a needle via the classic suprapatellar approach for intra-articular injection. All patients were prohibited from using NSAIDs or corticosteroids. Paracetamol was permitted three times a day, along with the application of an ice pack for pain at the injection site in all groups.

Group 1 received peptide injections with the Prostrolane® trademark which is produced by Caregen Co. Ltd. This product is available as a 2-ml vial and includes sodium hyaluronate (1.5%), oligopeptide-92, nanopeptide-25, octapeptide-11, heptapeptide-16, and decapeptide-23, which is also available in a pre-filled syringe.

Group 2 received hyaluronic acid injections. Biometics® is a solution containing linear macromolecular mucopolysaccharide hyaluronate consisting of disaccharide units of glucuronic

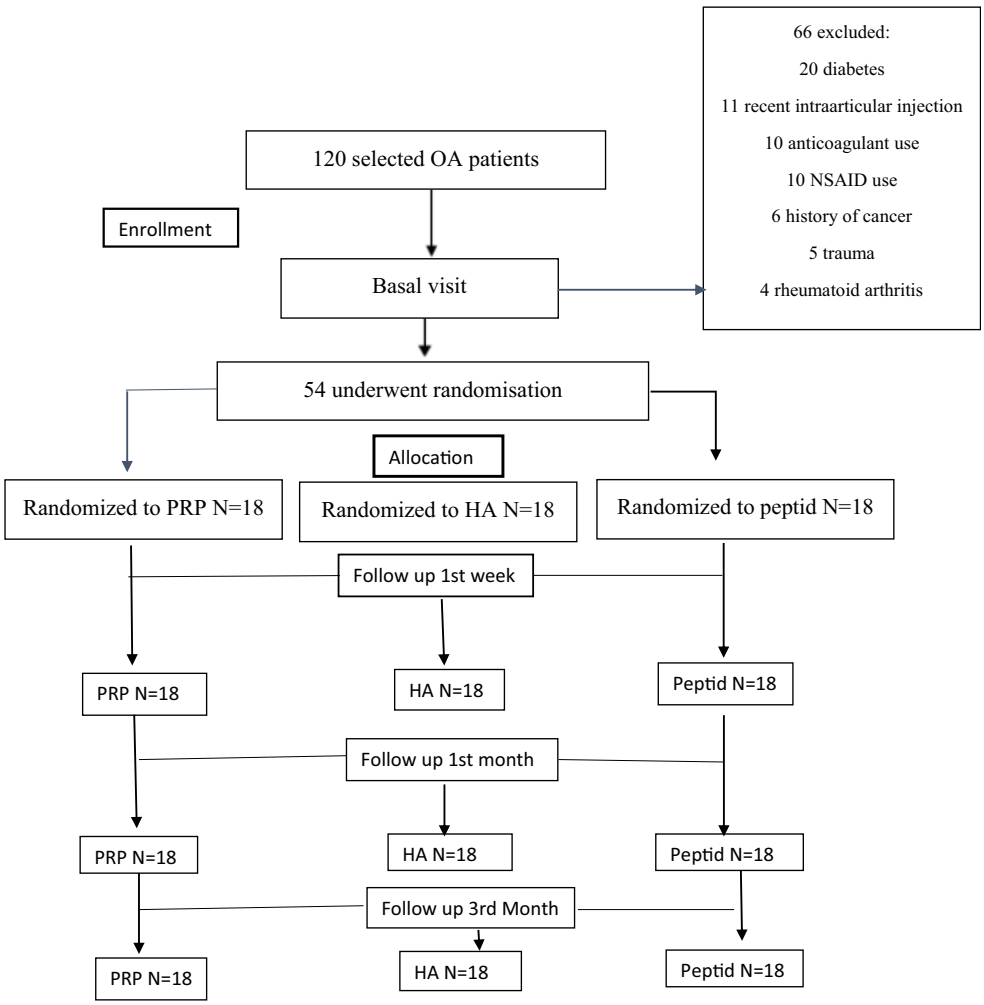

Fig. 1 Flow diagram of the study. *N* number of patients, OA osteoarthritis, PRP platelet-rich plasma, HA hyaluronic acid and peptid

acid and *N*-acetyl glucosamine in phosphate-buffered saline, which is available in a pre-filled syringe. The molecular weight of the product is between 1,700,000 and 2,100,000 kDa.

Group 3 received the PRP injection. I-Stem® was used as a PRP kit. 21-gauge needles were used to prevent rupture of erythrocytes. For PRP preparation, 2.2 cc anticoagulant + 17 cc blood is taken for women, and 2.2 cc anticoagulant + 16 cc blood is taken for men. An air hole is opened with a 90-mm needle (moved to the left and right). Blood is injected into the kit with a 90-mm-long needle. The solution is then centrifuged at 3000 RPM in fixed-angle centrifuges and 3400 RPM in swing-rotor centrifuges for 6–7 min by placing it opposite the balance kit. After centrifugation, the kit is removed without shaking. Using a 2–3 cc injector, the buffy coat layer immediately above the erythrocytes is first taken using the tornado technique with the tip of a 50-mm needle, and 2–3 cc is then taken with the plasma injector. In this way, 2–3 ml PRP containing the buffy coat is obtained.

Clinical parameters were recorded. Primary outcome of the study was the pain severity as measured by the visual analogue scale (VAS) rest and movement scores. Knee pain was evaluated with the 10-cm horizontal VAS (on a scale of 0–10, where 0 = no pain and 10 = worst pain). Secondary outcome measures were Western Ontario and McMaster Universities Arthritis Index (WOMAC) [22], Lequesne Index [23], and the Health Assessment Questionnaire (HAQ) [24]. The WOMAC consists of three components: pain, stiffness, and physical function. WOMAC scores were recorded on a Likert scale from 0 to 4 (0 = no pain/restriction, 1 = mild pain/restriction, 2 = moderate pain/restriction, 3 = severe pain/restriction, 4 = very severe pain/restriction). Lequesne Index is a measure consisting of 3 parts: pain/discomfort, daily living activities, and maximum walking distance. HAQ is used to evaluate activities of daily living consisting by 20 items in eight parts. Each item is scored from 0 to 3 (0: I do it without any difficulty; 1: I do it with some difficulty; 2: I do it very hardly; 3: I cannot do it).

All the measurements were performed by blind clinicians at the baseline, at the end of the 1st week after injection, first and third month follow-up to all groups.

Written informed consent was obtained from all the participants. The ethics committee of Kanuni Sultan Suleyman EAH, University of Health Sciences, Turkey, and health authority approved the study protocol.

Statistical analysis

The SPSS version 10.0 software program was used for the statistical analyses. Average, standard deviation, median lowest, highest, frequency, and ratio values were used for the descriptive statistics of the data. The distributions of the variables were measured with the Kolmogorov Smirnov test. The Kruskal-Wallis and Mann-Whitney *U* tests were used to analyze quantitative independent data. The Wilcoxon test was used for the analysis of the dependent quantitative data. The chi-square test was used to analyze qualitative independent data, and Fischer's test was used when the chi-square test conditions were not met. In all analyses, a value of $p < 0.05$ was accepted as statistically significant.

Results

Mean age was 55.8 ± 8.9 years. Forty-four were women. Clinical characteristics are shown in Table 1. There were no statistically significant differences among the variables of groups except age ($p > 0.05$). The mean age in the peptide group was significantly higher ($p < 0.05$) than that of the PRP group.

There is no warmth, joint deformity, neurologic deficit at baseline examination in all groups, and ACL and Apley tests were negative in all patients at baseline.

VAS resting scores were significantly improved both 1 week and a month after treatment in all the groups ($p < 0.05$). VAS resting scores improved significantly in the groups except HA group, in the third month. VAS resting scores in the peptide group showed a statistically significant improvement compared to those of the other groups at 3 months control ($p < 0.05$) (Table 2).

WOMAC pain scores improved significantly in the groups after treatment in all the control visits ($p < 0.05$). WOMAC pain score was significantly lower in the peptide group compared to the HA and PRP groups at 3 months control ($p < 0.05$) (Table 2). There were no significant differences among the groups in WOMAC stiffness, WOMAC physical function, and WOMAC total score at baseline or in the follow-up measurements ($p > 0.05$) (Table 2).

Lequesne Knee Pain Function scores improved significantly in all the groups ($p < 0.05$). There was no significant difference in terms of the Lequesne Knee Pain Function scores between the groups ($p > 0.05$) (Table 3).

HAQ scores showed significant improvement in all the groups at the control visits ($p < 0.05$). No significant

Table 1 The sociodemographic and clinical characteristics

	Peptide Mean ± SD/*n*-%	Hyaluronic acid Mean ±.SD/*n*-% Med	PRP Mean ± SD/*n*-% Med	*P*
Age (years)	59.7 ± 6.8	55 1 ± 10.3	52. 7 ± 8.3	0.013*
Gender	14 77.8%	14 77.8%	16 88.9%	0.612
Female	4 22.2%	4 22.2%	2 11.1%	
Male				
BMI (kg/m^2)	31.5 ± 4.6	31 .0 ± 4.9	28.3 ± 4.4	0.052
Education	15 83.3%	13 72.2%	7 38.9%	0.118
Primary school	3 16.7%	2 11.1%	10 55.5%	
High school	0 0.0%	3 16.7%	1 5.6%	
University				
Job	4 22.2%	4 22.2%	2 11.1%	0.062
Retired	14 77.8%	11 61.1%	11 61.1%	
Housewife	0 0.0%	3 16.7%	5 27.8%	
Others				
Kelgren Lawrence	6 33.3%	5 27.8%	5 27.8%	0.987
II	7 38.9%	7 38.9%	8 44.4%	
III	5 27.8%	6 33.3%	5 27.8%	
IV				
ROM	103.9 ± 11.7	113.4 ± 11.9	108.3 ± 15.6	0.085
Knee circum.cm	42.2 ± 3.1	42.7 ± 6.0	44.5 ± 4.5	0.291
Knee 10 cm	47.9 ± 4.5	45.6 ± 7.2	47.6 ± 6.7	0.483
Crepitation	14 77.8%	15 83.3%	12 66.7%	0.492
Varus stress test	4 22.2%	2 11.1%	6 33.3%	0.276
Valgus stress test	14 77.8%	12 66.7%	13 72.2%	0.758
Mc Murray test	2 11.1%	0 0.0%	1 5.6%	0.06

Table 2 VAS rest pain and VAS movement pain scores and Western Ontario and McMaster Universities Arthritis Index (WOMAC) evaluations

	Peptide Mean ± SD Med	Hyaluronic acid Mean ± SD Med	PRP Mean ± SD Med	*P* (K)
VAS rest pain				
Baseline (B)	26.7 ± 29.7	25.0 ± 25.7	41.1 ± 22.2	0.141
1 week	5.0 ± 12.5p < 0.004*	11.8 ± 16.3	16.1 ± 21.2	0.199
B-1 week (W)		$p < 0.007$*	$p < 0.001$*	
1 month	3.9 ± 9.8	13.3 ± 16.4	15.0 ± 19.5	0.094
B-1 month (W)	$p < 0.005$*	$p < 0.04$*	$p < 0.001$*	
3 months	6.1 ± 10.9	15.6 ± 16.5	22.2 + 18.6	0.018**
B-3 months (W)	$p < 0.011$*	$p < 0.105$	$p < 0.001$*	
VAS movement pain				
Baseline (B)	81.1 ± 11.8	79.4 ± 8.0	82.2 ± 14.0	0.328
1 week	53.9 ± 20.3	52.4 ± 24.1	58.3 ± 20.4	0.703
B-1 week (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
1 month	47.8 + 16.6	40.0 ± 17.5	53.9 ± 18.8	0.052
B-1 month (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
3 months	46.1 ± 20.3	44.4 ± 20.9	53.3 ± 20.6	0.372
B-3 months (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
WOMAC pain				
Baseline (B)	8.8 ± 4.7	9.3 ± 3.0	12.4 ± 5.2	0.052
1 week	2.8 ± 1.9	3.1 ± 1.8	5.5 ± 5.8	0.551
B-1 week (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
1 month	2.9 ± 2.8	4.4 ± 3.3	5.3 ± 5.3	0.194
B-1 month (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
3 months	2.8 ± 1.4	4.9 ± 2.3	5.3 ± 4.0	0.013**
B-3 month (W)	$p < 0.001$*	$p < 0.002$*	$p < 0.001$*	
WOMAC stiffness				
Baseline (B)	3.4 ± 1.6	3.4 ± 1.1	4.5 ± 2.3	0.234
1 week	1.7 ± 1.0	1.2 ± 0.9	1.7 ± 2.3	0.360
B-1 week (W)	$p < 0.005$*	$p < 0.001$*	$p < 0.001$*	
1 month	0.8 ± 0.8	1.9 ± 1.4	1.7 ± 2.2	0.052
B-1 month (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
3 months	1.0 ± 1.0	1.8 + 0.9	1.7 ± 1.9	0.053
B-3 months (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
WOMAC function				
Baseline (B)	33.3 ± 14.5	30.1 ± 10.9	41.7 ± 18.6	0.054
1 week	16.4 ± 8.3	13.2 ± 8.2	20.6 ± 18.4	0.574
B-1 week (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
1 month	9.9 ± 7.2	15.0 ± 10.5	15.9 ± 17.4	0.313
B-1 month (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
3 months	13.4 ± 9.0	15.7 ± 10.2	16.9 ± 14.5	0.832
B-3 months (W)	$p < 0.001$*	$p < 0.003$*	$p < 0.001$*	
WOMAC Total				
Baseline (B)	47.6 ± 20.1	44.7 ± 150	61.0 ± 26.6	0.080
1 week	21.8 ± 10.9	18.2 ± 10.7	29.0 ± 27.6	0.722
B-1 week (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
1 month	14.2 ± 10.4	22.3 ± 15.1	24.0 ± 25.7	0.203
B-1 month (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
3 month	17.9 ± 11.4	23.2 ± 13.9	24.8 ± 21.1	0.555
B-3 months (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	

Kruskal-Wallis (W) Wilcoxon test

*Significant difference ($p < 0.05$) when compared to the pre-injection evaluation of the same group; **significant difference ($p < 0.05$) when compared to the pre-injection evaluation between groups

difference was found in the groups at the control visits in terms of the HAQ scores ($p > 0.05$) (Table 4).

There were no side effects and no dropouts in the treatment groups.

Discussion

In this study, a single dose of intra-articular PRP, HA, or peptide injection provided satisfactory results in terms of pain and function in knee OA. The follow-up parameters were improved at the first week after treatment in all the groups. Pain and knee functions as measured by VAS, WOMAC, HAQ, and Lequesne Index were significantly improved after the treatment. This benefit was maintained up to the first 3 months. The only exception was that VAS resting scores in the 3 months were not significantly decreased in HA group. Pain severity as measured by VAS resting scores and WOMAC showed better improvement at 3 months control in the peptide group ($p < 0.05$).

There are previous studies comparing PRP, HA, or combined treatments in the literature [1, 4, 15–17, 25]; however, as per our knowledge, this is the first study that compares the efficacy of PRP, HA, and peptide products. Lana et al. concluded that the improvement in the VAS value was better in the PRP group than that in the HA groups at days 30, 90, and 180 after treatment [4]. However, in our study, both HA and PRP were useful in pain relief in our study; PRP was found more effective in pain relief than HA in that previous study. In the study of Lana et al., HMW HA was used and PRP was obtained by a similar method to ours. The discrepant outcome may be related with the differences in the stage of the OA and the frequency or number of PRP applications. In the study of Lana et al., PRP was administered at 1- or 2-week intervals. In our study, all three groups received a single injection to minimize variation in interpreting the results. Because there is no standardization regarding the kits as well as the number and quality of the obtained platelets used in PRP-related studies in the literature, it is not possible to describe the effectiveness of PRP in terms of standard data. A single dose of PRP may be as effective as double dose [26].

Both of intra-articular PRP and HA injections are thought to be effective for pain and quality of life in OA [9, 27–29]. In our study, patients' well-being status improved after PRP beginning from the first week till to the third month post-injection. Sampson et al. reported a significant improvement in pain and quality of life which continued a year after PRP injection in 14 patients with OA [30]. Sanchez et al. suggested that good health status rates as measured by pain severity and WOMAC scores were increased for 5 weeks after PRP in an observational cohort study [27]. We limited the follow-up duration by 3 months in our study due to small patient numbers and to limit the potential dropout rates due to the reasons such as transportation problems for some of our older patients. Kon et al. reported that intra-articular PRP was more effective than both low-molecular-weight and high-molecular-weight HA injections in terms of pain, quality of life, and patient satisfaction at 2 and 6 months after treatment in 150 patients with knee OA [15]. Filardo et al. reported significant improvements after PRP and HA injections along 12 months after treatment in OA, in a study in which PRP and HA injections were administered once a week for a total of three sessions. Moreover, no significant difference was reported in terms of the quality of life between the groups [28].

Intra-articular peptide injection is thought to inhibit cartilage degeneration in a mouse experimental knee OA model [29]. Additionally, peptides might stimulate differentiation as well as proliferation of chondrocytes [18, 29].

In our study, all the groups showed similar well-being in terms of VAS movement pain, HAQ, Lequesne and WOMAC scores except pain score, and no statistically significant differences were found among the groups. Peptide injection provided better results in terms of resting pain and WOMAC pain score at the 3 months control. Peptides may help better pain control, because of the different action mechanisms in the knee joint. However, we cannot declare these effects strongly

Table 3 Lequesne Knee Pain Function Index scores of groups

	Peptide Mean ± SD Med	Hyaluronic acid Mean ± SD Med	PRP Mean ± SD Med	*P* (K)
Lequesne Knee Pain Function Index				
Baseline (B)	9.0 ± 2.8	8.9 ± 2.6	11.7 ± 3.5	0.053
1 week	4.7 ± 2.4	4.7 ± 3.4	5.9 ± 5.6	0.949
B-1 week (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
1 month	4.3 ± 3.0	4.9 ± 3.1	5.6 ± 5.4	0.703
B-1 month (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
3 months	4.9 ± 2.6	5.6 ± 3.2	5.8 ± 5.4	0.794
B-3 months (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	

K Kruskal-Wallis (W) Wilcoxon test

*Significant difference ($p < 0.05$) when compared to the pre-injection evaluation of the same group

Table 4 Health Assessment Questionnaire scores of groups

	Peptide Mean ± SD Med	Hyaluronic acid Mean ± SD Med	PRP Mean ± SD Med	*P* (K)
Total HAQ scores				
Baseline(B) 12.5 ± 8.3		12.3 ± 5.7	18.9 ± 9.8	0.073
1 week	6.7 ± .5.0	5.1 ± 3.8	8.7 ± 8.4	0.498
B week (W)	$p < 0.004$*	$p < 0.001$*	$p < 0.001$*	
1 month	6.7 ± 7.1	4.9 ± 3.2	8.2 ± 8.3	0.602
B month (W)	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	
3 months	5.3 ± 4.3	6.4 ± 7.2	6.8 ± 8.6	0.993
B-3 month (W)	$p < 0.001$*	$p < 0.031$*	$p < 0.001$*	

K Kruskal–Wallis (W) Wilcoxon test

*Significant difference ($p < 0.05$) when compared to the pre-injection evaluation of the same group

due to the limited patient number and relatively short follow-up period in this study. Maybe, our study provides a basis for future studies comparing HA, PRP treatment, and peptides.

In this study, some of the patients had mild to moderate knee OA but some of them had severe OA radiologically. Also, the patients with advanced osteoarthritis who did not want surgical procedures were included in this study; however, we know that the intra-articular injections are more successful in patients with mild to moderate knee OA.

There are some limitations of this study. The first one is absence of a placebo group. Other limitations are small sample size of groups, failure to establish blindness, and the lack of imaging because of the relatively short follow up duration and biochemical cartilage morphology examinations. Future studies and comparing the clinical and histopathological features of the three injection groups may help to clarify our findings.

In conclusion, intra-articular HA, PRP, and peptide injections were found to be useful for pain relief and functional improvement in this study. Peptide injection might be an alternative in the patients with knee OA.

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Compliance with ethical standards

The ethic committee of Kanuni Sultan Suleyman EAH, University of Health Sciences Turkey approved the study (ID: KAEK/2018.4.6) and written consent was obtained from all participants before enrollment.

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