T2 mapping evaluation of changes in cartilage matrix after PRP and HA injection therapy in knee osteoarthritis: a prospective, randomized, double blind, placebo controlled study

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Research article

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Abstract

Background

In this study we focused on evaluating the effect of intra-articular platelet-rich plasma (PRP) and hyaluronic acid (HA) on the qualitative and quantitative properties of the articular cartilage in patients with knee osteoarthritis (OA).

Methods

We evaluated 264 patients undergoing treatment of moderate knee OA. Patients aged between 40 and 70 years were included with articular K-L stage ≤ 2. Patients were randomized into three groups and treated with three doses of intra-articular PRP, HA, or placebo injection. Patients were evaluated clinically and by using T2 mapping.

Results

Both PRP (619.05 ± 243 ms; $p = 2.7 \times 10^{-5}$) and HA (637.12 ± 273 ms; $p = 1.\times10^{-4}$) group showed statistically significant lower post-application T2 relaxation times in comparison to the placebo group (859.80 ± 406 ms).

Cartilage thickness increased significantly after PRP (2.41±0.87 vs. 2.58±0.97 mm, p=0.033) and HA (2.28±0.81 vs. 2.80±1.00 mm, p=1.8×10) applications. There was a significant decrease in WOMAC pain score by 30% (p=0,001) and the overall WOMAC score by 27 $p=1.9\times10^{-4}$%) in PRP group. The decrease in WOMAC pain score and the overall WOMAC score in the placebo group was similar to the results observed in the PRP group. In the HA group a significant decrease in WOMAC pain score by 14% (p=0,005) was observed only at the first follow-up, whereas no difference was observed at the second follow-up.

Conclusions

T2 mapping of cartilage tissue may aid to monitor its properties after the intra-articular therapies in knee OA. However, there is a discrepancy between clinical findings and the results of T2 mapping, suggesting questionable grounds for applying intra-articular therapy.

Background

Knee Osteoarthrosis (OA) is a clinically important syndrome presented with pain, functional limitations, and decreased life quality. Osteoarthrosis is pathomorphologically characterized by the degeneration and loss of cartilage, bone remodeling, subchondral sclerosis and inflammation [1]. Since knee OA is a progressive disease, it is treated symptomatically with physical therapy and non-steroid anti-inflammatory drugs (NSADs) in early stages, followed by intraarticular injections of hyaluronic acid (HA)

and platelet-rich plasma (PRP) in moderate cases; however, it can also lead to severe disability and joint replacement [2].

PRP is plasma prepared from patients' own blood and has a higher concentration of platelets than normal plasma. Platelets are applied intraarticularly with injection. Growth factors are released from platelets and after stimulation are said to modulate biological processes such as cartilage healing and inflammation, and consequently improve the symptoms of OA [3].

HA is a polysaccharide compound containing glucuronic acid and acetyl glucosamine. As the concentration and molecular weight of hyaluronic acid are reduced in OA, intraarticular injections of HA are a therapeutic option. HA provides viscoelasticity of synovial fluid and stimulates the formation of endogenous hyaluronic acid [4, 5]. In addition, HA can be also effective with the stimulation and accumulation of proteoglycan, inhibition of inflammatory mediators and analgesic effect [5, 6].

The effects of intraarticular applications of HA and PRP has been studied in multiple trials in symptomatic OA patients with a focus on the knee function, pain, and quality of life [7, 8]; however, all these trials provide limited data based on qualitative and quantitative changes of articular cartilage after therapeutic applications.

In this randomized, double-blind, placebo-controlled study, we evaluated the impact of intraarticular administration of PRP and HA in patients with knee OA. Our research was mainly focused T2 mapping, the quantitative biochemical MRI technique, proven sensitive in measuring biomechanical and biochemical properties of cartilage such as collagen, glycosaminoglycan and water content and collagen orientation [9, 10]. The usefulness of T2 mapping was already demonstrated in different clinical settings e.g. in the diagnosis of early cartilage degeneration [11, 12], in the effect of loading on articular cartilage [13], in pre-surgical planning [14] and in the evaluation of successful treatment of cartilage lesions [15–17]. Focal increases in T2 relaxation times within cartilage have been associated with matrix damage, loss of collagen integrity and an increase in water content [9, 10, 18]. To the best of our knowledge, this is the first study that applies the T2 imaging to evaluate the efficacy of intraarticular application of PRP and HA in OA knee.

Methods

Patients (selection, inclusion, intervention)

The prospective double-blind parallel randomized controlled trial was approved by the institutional ethical committee. 264 patients were randomly assigned into three groups (intra-articular placebo, PRP, and HA injection) and evaluated at 0, 2 and 6 months of follow-up. The inclusion and exclusion criteria are listed in Table 1. Patients were prospectively evaluated at 0, 2 and 6 moths of follow-up using the WOMAC score. Additionally, range of motion (ROM) and trans-patellar circumference of both knees was measured and patient satisfaction as well as any adverse event were recorded. To ensure the blinding, all patients enrolled in the study underwent blood harvesting in order to obtain PRP for further knee injections

performed only in one third of them following the randomized selection. The randomized list of all patients was provided by an independent statistician and the injection solution (PRP, HA or saline solution) was assigned to the patients just before the application itself. Three injection applications were performed at weekly intervals. In addition, all clinical evaluations were performed by an independent medical member to keep the study double blinded.

Table 1
Inclusion and exclusion criteria

Inclusion criteria
40–70 years old
History of knee pain and/or swelling in last 4 months
Kallgren, Lawrence score 2 or 3
Exclusion criteria
Older than 70 years
Kallgren, Lawrence higher than 3
Systemic disease
BMI > 35
Hematologic conditions (anemia, coagulopathies)
Inflammatory disease
Immunosuppressive therapy
Axial knee deformity (valgus/varus > 5 degrees)
Allergies

PRP was prepared using Arthrex ACP kit (Arthrex, Naples, US). 15 mL of venous blood was drawn and then centrifuged at 1500 rpm for 10 minutes. Plasma was removed using a double syringe system, leaving the final product 5 mL of PRP. Anticoagulants were not used as PRP was utilized within 15 minutes.

In the HA group, Suplasyn (Mylan) was used at 3 weekly intervals, each 2 mL syringe containing 20 mL of sodium hyaluronate with molecular weight of 500–730 kDa.

Outcome measures

Questionnaire and MRI-based findings were used as outcome measures. Our primary outcome measure was qualitative assessment of cartilage using T2 maps, and the secondary outcome measure the change in cartilage thickness 6 months after the applications. Tertiary outcomes were pain as a subscore of

WOMAC and overall WOMAC score. The WOMAC scoring was performed at three different time points: (1) before applications, (2) 2 months after the last application and (3) 6 months after the last application.

MRI protocol

Of the initial 264 patients, 204 of them performed both MRI examinations, the first before the application and the second 6 months after the last application. All MRI examinations were performed using 3-Tesla MRI (General Electrics Signa Excite xt) using an eight-channel knee coil. Coil and system QA were performed daily prior to any examination. Knee joint was fixed at 15°flexion. The MR images of T 2 mapping and 3D gradient-echo sequences with pre-pulse fat-saturation (3DGRE FAT-SAT) were obtained. Before carrying out the investigation, all patients performed a 10-minute walk in the hall after initial 30-minute rest to control the pre-loading of cartilage.

MRI analysis

To achieve adequate comparison of pre- and post-application MR images, two images were aligned by specially designed software. Methodology, used in this study, consisted of image registration, definition of cross-section, and extraction of image intensity profiles [19]. During image registration, two images are transformed by aligning their resolution, position, and rotation in order to achieve spatial matching of key points, defined by distinct image features like sharp edges. Such alignment allows for direct comparison of pre-application and post-application MR images (ROI positioning) and comparison of spatial frequencies of intensity values in arbitrary direction for purpose of cartilage thickness assessment.

All MRI evaluations were performed by a blinded musculoskeletal radiologist. *Functool* application was used on an ADW 4.4 workstation to make measurements on T2 quantitative mappings. Articular cartilage evaluations were performed on regions of interests (ROIs) set on the medial femoral weight bearing condyle on an area directly above the anterior meniscus horn in sagittal slice. The cartilage was divided into two zones according to its thickness, one being closer to the bony side (ROI 1) and the second being closer to the articular side (ROI 2) as shown in Fig. 1.

3DGRE FAT-SAT pulse rate was used for cartilage thickness measurements. 1.8 mm slice depth was used with 0.9 mm layover, thus enabling 3D visualization of cartilage. After aligning two images (pre-application and post-application), as described above, a user-defined line of cartilage cross-section was rasterized [19] and intensity values of obtained voxels from multiple images plotted on a single graph for comparison, as seen in Fig. 2. Finally, pixels were calculated into millimeters to express the cartilage thickness.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 25.0 (IBM Inc., Armonk, New York, USA), R 3.5.3 (www.r-project.org, R Core Team (2017), Vienna, Austria) and GPower 3.1 (G*Power, Kiel, Germany). Comparisons of continuous variables across nominal groups were carried out using Mann-Whitney U-Test or pairwise

Kruskal-Wallis H-Test after Kolmogorov-Smirnov test of normality. Paired samples were analyzed using the Wilcoxon signed-rank test. Statistical power was calculated by means of post hoc Wilcoxon-Mann-Whitney test or Wilcoxon signed-rank test for paired samples. Effect sizes were determined for each statistical analysis separately. The Spearman's correlation between paired groups was determined where needed. Alpha was set to 5% ($\alpha = 0.05$). P value < 0.05 and Power > 80% was considered statistically significant.

Results

Qualitative cartilage assessment: T2 mapping

Baseline characteristic between groups were similar as there were no statistically significant differences between them. The overall mean values of T2 relaxation times of ROI 1 and ROI 2 before applications are listed in Table 2.

Table 2
ROI 1 and ROI 2 baseline values across groups

	Control (n = 51)	PRP (n = 75)	HA (n = 78)	P value
ROI 1	603 ± 198	548 ± 255	545 ± 186	0.090
ROI 2	711 ± 270	756 ± 324	722 ± 302	0.905

There were no statistically significant differences between pre- and post-application in ROI 1 relaxation times in any of the groups. However, some differences were noted in ROI 1 post-application between PRP and placebo (502.87 ± 189 vs. 668.84 ± 278, p = 0.005, power = 96%) and between the HA and placebo group (531.18 ± 219 vs. 668.84 ± 278, p = 0.026, power = 83%), and no statistically significant differences between PRP and HA (Fig. 3). In the PRP group, a significant decrease in T2 relaxation times in ROI 2 was observed 6 months after the application (619 ± 243; $p = 2.1 \times 10^{-4}$, power = 100%) when compared to the pre-application (756.14 ± 323). A similar statistically suggestive decrease was observed in the HA group (637.12 ± 273 vs. 722.14 ± 302, p = 0.002, power = 56%). On the contrary, a statistically suggestive increase in post-application ROI 2 relaxation times was observed in the placebo group (859.80 ± 406 vs. 711.08 ± 269, p = 0.029, power = 72%). Subsequently, a comparison of post-application T2 ROI 2 relaxation times was performed between the groups. Both, PRP (619.05 ± 243; $p = 2.7 \times 10^{-5}$, power = 97%) and HA (637.12 ± 273; $p = 1.\times10^{-4}$, power = 93%) groups showed statistically significant lower ROI2 post-application relaxation times in comparison to the placebo (859.80 ± 406) post-application relaxation times.

Assessment of cartilage morphology: thickness

No statistically significant difference was observed in cartilage thickness between groups at pre-application (p = 0.352). The evaluation of cartilage thickness pre- vs. post-application showed no

statistically significant difference in the placebo group (Fig. 4). On the other hand, a tendency for increase in cartilage thickness was observed 6 months after the application in the PRP group (2.41 ± 0.87 vs. 2.58 ± 0.97, p = 0.033, power = 55%), whereas in the HA group, a statistically significant increase of cartilage thickness was observed (2.80 ± 1.00, $p = 1.8 \times 10^{-5}$, power = 100%) when compared to pre-application (2.28 ± 0.81).

WOMAC: pain and overall score

Baseline characteristic between the groups were similar as there were no statistically significant differences between them. The overall mean values are listed in Table 3. There were no statistically significant differences between the groups at any time point observed; however, we noticed significant changes between time points within each group. In the PRP group, a significant decrease in WOMAC pain score was observed in both 2 months after (7.36 ± 4.21; $p = 2.1 \times 10^{-5}$, power = 99.8%) and 6 months after the applications (6.50 ± 4.30; p = 0.001, power = 100%) when compared to pre-application (9.37 ± 3.87) (Fig. 5). Similarly, a decrease in overall WOMAC score was observed both after the first (44.46 ± 19.06; $p = 2.3 \times 10^{-5}$, power = 96.4%) and second post-application visit (36.35 ± 21.04; $p = 1.9 \times 10^{-4}$, power = 100%) when compared to pre-application (50.04 ± 19.52) (Fig. 6).

Table 3
Baseline values across groups

	Control (n = 66)	PRP (n = 87)	HA (n = 87)	P value
WOMAC pain	9.55 ± 3.53	9.37 ± 3.9	8.86 ± 3.72	0.575
WOMAC overall	50.45 ± 18.92	50.04 ± 19.52	48.24 ± 16.44	0.552

In placebo group a similar trend was observed. Statistically significant decrease of WOMAC pain score was observed 2 months after (7.80 ± 3.43; p = 0.001, power = 98.45%) and 6 months after the application (7.06 ± 4.39; $p = 5.3 \times 10^{-5}$, power = 100%) when compared to pre-application (9.55 ± 3.53). Similar, a decrease in overall WOMAC score was observed, but only after the second post-application visit (39.29 ± 20.77; p = 0.001, power = 100%) in comparison to pre-application (50.45 ± 18.92).

In the HA group, a statistically significant decrease in WOMAC pain score was observed 2 months after the application (7.61 ± 4.01; p = 0.005, power = 88.9%) when compared to pre-application (8.86 ± 3.72). A decrease trend in WOMAC pain score was also observed 6 months after application (8.21 ± 3.95; p = 0.008, power = 47%) when compared to pre-application (8.86 ± 3.72), but was not considered statistically significant due to low power. A statistically significant decrease was also observed for overall WOMAC score after first application (40.50 ± 18.72; $p = 7.9 \times 10^{-5}$, power = 99.89%) when compared to pre-application (48.24 ± 16.44). At the second post-application visit, only suggestive statistical significance was observed (43.67 ± 18.42; p = 0.016, power = 77.73%).

Discussion

Quantitative MRI *T2 mapping* techniques have been used as a non-invasive biomarker of early degenerative changes in knee OA [11, 12, 20]. MRI relaxation times are translated into quantitative values of tissues [21] in order to show subtle changes in cartilage composition in the early stages [9, 10]. In this randomized, double-blind, placebo-controlled study T2 mapping was used specifically to detect any changes in the cartilage tissue after intraarticular treatment with PRP and HA in patients with knee OA. Specially designed software and methodology was utilized in order to generate T2 relaxation times in the region of interest (ROI) [19]. Since research in this field has mainly focused on the clinical outcome by monitoring various subjective questionnaires and clinical measurements [7, 8, 22] the T2 mapping represents a novelty in this research field.

The most important finding in the present study was a substantial focal decrease in T2 relaxation time after HA applications ($p = 0.002$, power = 56%) and a statistically significant decrease after PRP applications in patients with knee OA. The focal change in T2 relaxation times within each group was observed at the articular side of the cartilage (ROI 2), whereas there were no differences observed in the subchondral cartilage layer (ROI 1). These results indirectly suggest that the target location of intraarticular application is mainly on the articular side of the cartilage. On the contrary, T2 relaxation times in placebo group substantially increased ($p = 0.029$, power = 72%). There were no differences in cartilage thickness at follow-up in the placebo group, whereas the thickness of articular cartilage substantially increased in PRP group ($p = 0.033$, power = 55%) and significantly increased in HA group. This may in turn indicate a modification in the cartilage microstructure, collagen orientation, and water content after intraarticular PRP and HA applications (5,6), possibly to prevent further deterioration of OA by restoring cartilage tissue [9, 10, 18]. Furthermore, T2 relaxation times were significantly lower in both ROI 1 and 2 after PRP and HA applications compared to the placebo group at follow-up. Therefore, PRP and HA applications might provide some sort of protective effect even in the deeper cartilage layer.

On the other hand, the differences in T2 relaxation times might be due to the altered loading of articular cartilage as a consequence of intraarticular applications [13]. Different volumes of intraarticular applications (5 ml in PRP and 2 ml in HA) and extraarticular (subcutaneous) administration of saline solution in placebo group might have influenced the results of T2 relaxation times. A similar impact on T2 relaxation times were demonstrated in surgical treatments of cartilage lesions, especially in matrix autologous chondrocyte implantation (MACI) [16, 17]. Since this is the first study using T2 mapping to evaluate a potential cartilage repair after intraarticular administration of PRP or HA, there is a lack of evidence regarding the interpretation of the T2 relaxation time of potentially “recovered” cartilage. Nevertheless, several parameters clearly indicate that there were some favourable changes in articular cartilage after intraarticular applications of HA and PRP compared to the placebo group at follow-up. Other factors that may affect T2 relaxation times, such as gender and age [12, 23, 24], BMI and daily activity [25], and time after loading [13, 26] were excluded by providing homogenous groups and using the pre-loading protocol.

The other objective of this study was to evaluate the effect of intraarticular applications of PRP and HA on knee function, pain, and quality of life by using WOMAC questionnaires and clinical examination. The

positive effect of intraarticular applications in treatment of symptomatic knee OA was well documented in the literature [7, 8, 22]. The results of this study showed significant decrease in WOMAC pain score and overall WOMAC score in the PRP group at follow-ups, which is consistent with the literature [27, 28]. This, in combination with the results of T2 mapping, seems to be in favour of improving cartilage properties (5,6). On the other hand, the results in the placebo group are surprising as the significant decrease in WOMAC scores was similar to the PRP group despite the deterioration of cartilage characteristics based on T2 mapping [9, 10, 18]. The opposite proved to be the case for the HA group since a significant decrease in WOMAC pain score was observed only at the first follow-up at 2 months, whereas no difference was observed at the second follow-up at 6 months. Similarly, mixed clinical outcomes were demonstrated in randomized controlled trials when the effect of intraarticular HA administration was compared to PRP in knee OA treatment [2, 29, 30].

Finally, the results of T2 mapping seem to match the clinical findings and patients' satisfaction only in the PRP group, whereas this was not observed in the HA or placebo group. Namely, patients in the placebo group showed the same level of satisfaction (according to WOMAC score) compared to the PRP group, while in the HA group the level of satisfaction no longer improved over time. Thus, the actual significance of the observed changes in cartilage T2 mapping is questionable since it does not match the clinical findings. Although the results of T2 mapping indicated improving cartilage properties after receiving PRP or HA, there was no overall superior clinical improvement compared to the placebo group. Therefore, further research needs to be conducted in order to successfully validate the actual relevance of T2 mapping after administration of intraarticular therapy, possibly with concurrent histological analysis and clinical data. In addition, the long-lasting effect of T2 changes and overall cost benefit ratio of intraarticular therapy in knee OA should also be re-evaluated.

In conclusion, T2 mapping of cartilage tissue may aid in monitoring cartilage improvement or deterioration after the administration of intraarticular therapy in knee OA. However, clinical data seem not to match the results of T2 mapping in all cases. Therefore, the actual significance of T2 mapping in this clinical setting should be further investigated. Intraarticular therapy did not demonstrate any superior effect on patient's satisfaction and level of pain compared to placebo group. Thus, the effectiveness of intraarticular therapy with PRP or HA in knee OA needs to be reassessed in placebo-controlled trials.

Declarations

Ethics approval and consent to participate

Th study was approved by the ethic committee of University Medical Center Maribor, Slovenia (Ref. Nr. IRP-2016/02-05)

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on request

Competing interest

None

Funding

None

Authors' contributions

MV – conception, study design, data collection, article drafting, critical revision of article, final approval of article to be published

JN – data interpretation, article drafting

TB – data collection

MG – data analysis and interpretation

DM – software developmentment, data analysis

RP – data collection

IM – data collection

RK - data interpretation, article drafting

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Figures

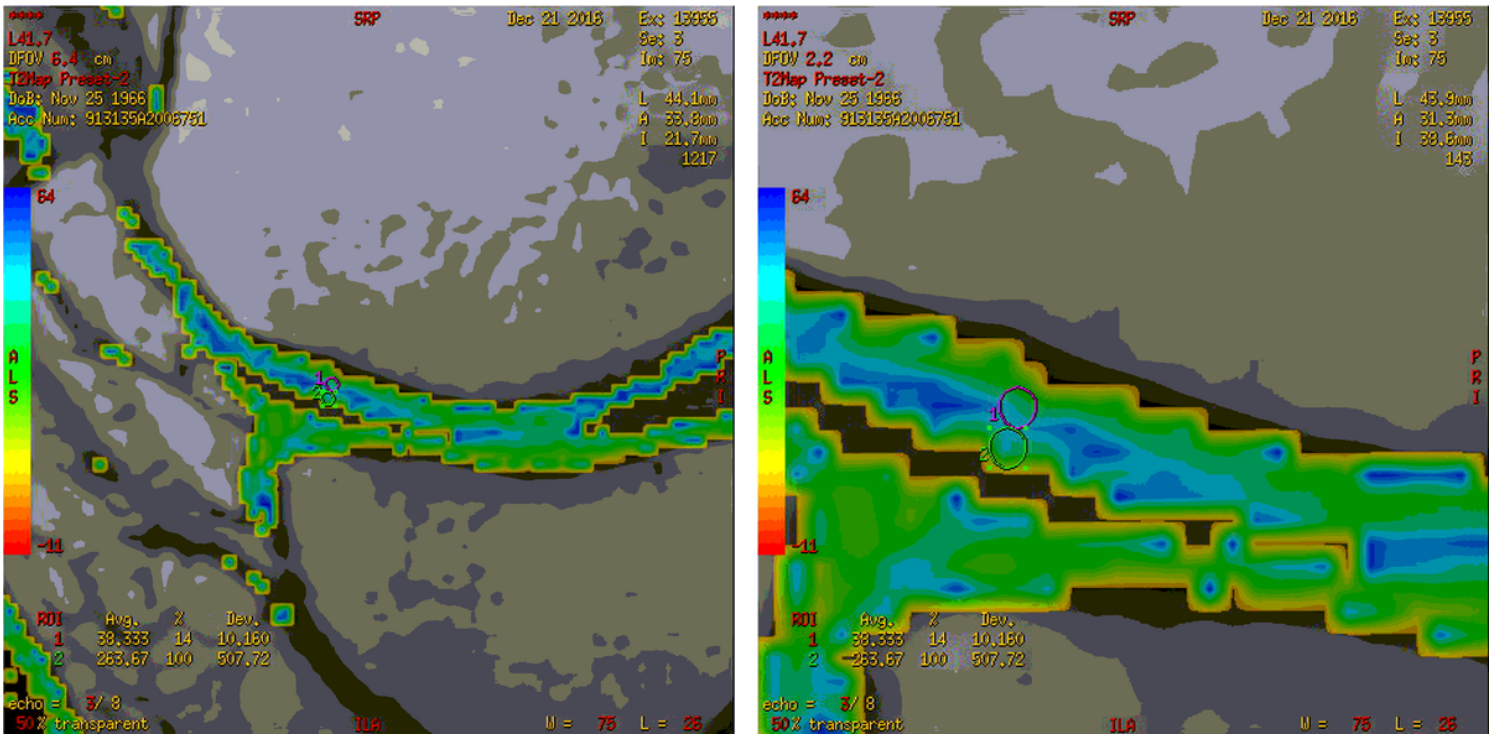

Figure 1

T2 mapping of articular cartilage. ROI 1 (deep layer, purple circle) and ROI 2 (superficial layer, green circle) set on the medial femoral condyle at the are above the anterior meniscus horn.

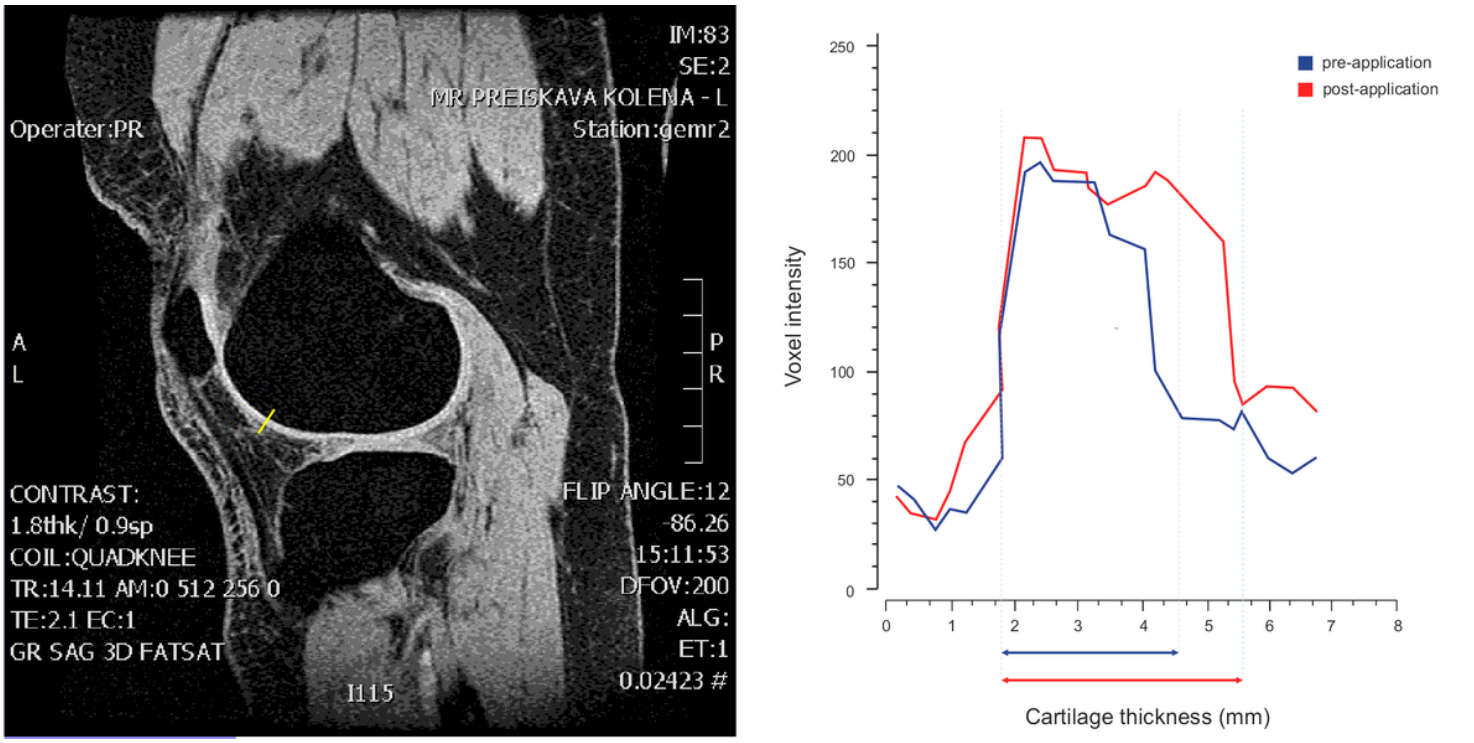

Figure 2

Articular cartilage thickness. After aligning pre- and post-application images, a line over the cartilage was defined, the cross-section rasterized and intensity values of voxels plotted on a graph for comparison. A sharp increase in intensity defines the edge of the cartilage (next to subchondral bone), whereas the drop represents its edge of the cartilage.

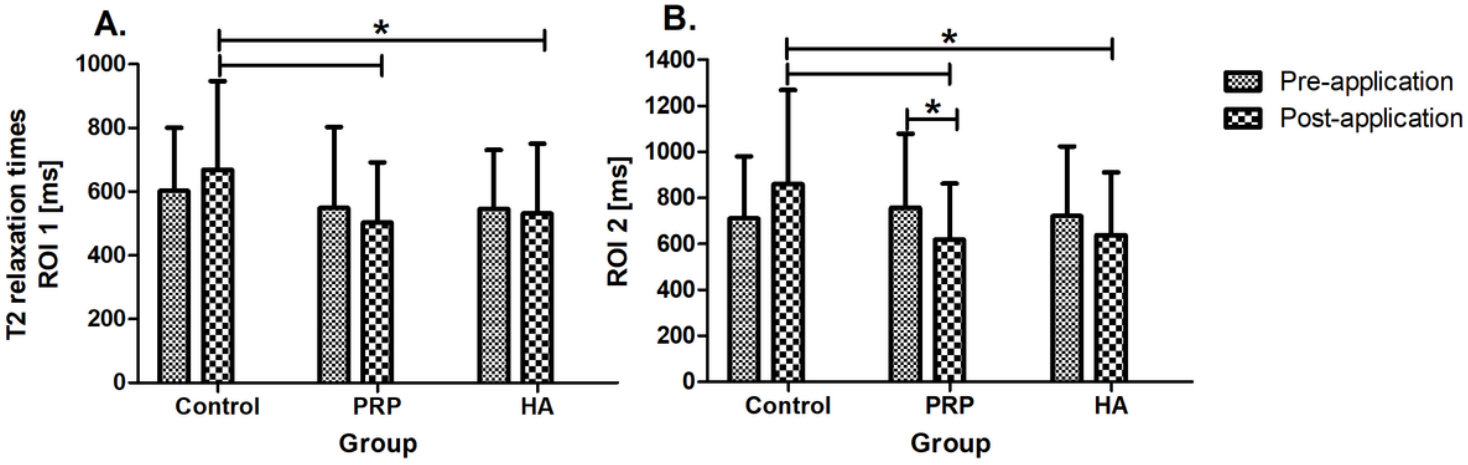

Figure 3

Comparison of T2 relaxation times at ROI 1 and ROI 2 between groups before the application and 6 months after the application. Data are presented as mean values±SD. Statistically significant differences between pre- and post-application were determined using the Wilcoxon signed-rank test and in comparison, for control the Mann-Whitney U-test (*P≤0.05).

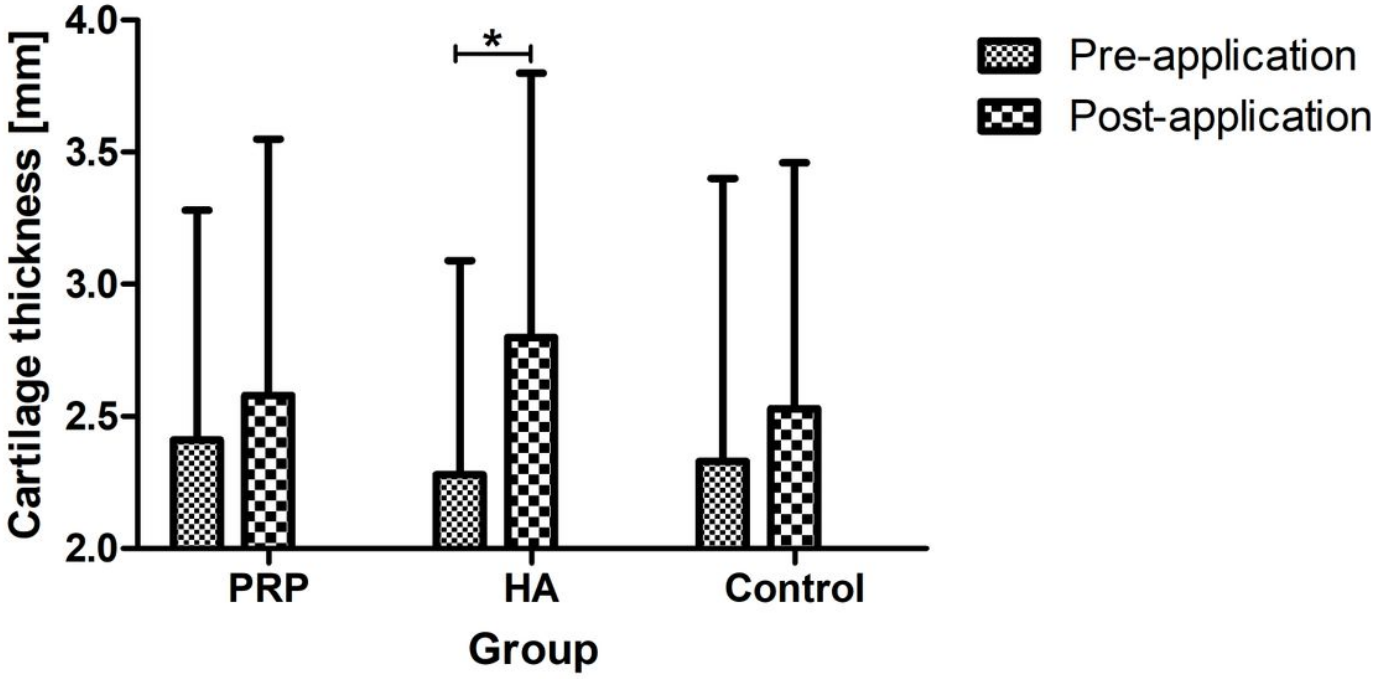

Figure 4

Comparison of cartilage thickness between groups pre-application and 6 months post-application. Data are presented as mean values±SD. Statistically significant differences between pre- and post-application were determined using the Wilcoxon signed-rank test (*P≤0.05).

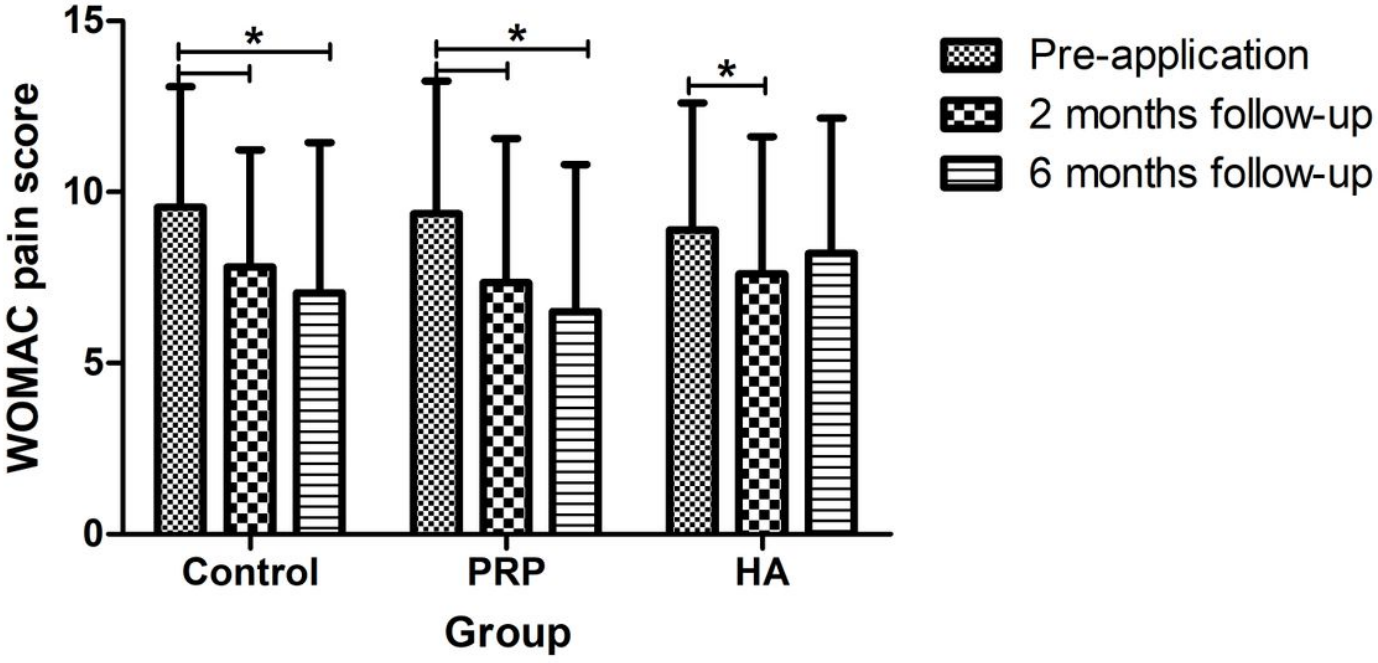

Figure 5

Comparison of pain (WOMAC) between groups at three time points. Data are presented as mean values±SD. Statistically significant differences between pre- and post-application were determined using the Wilcoxon signed-rank test and in comparison, for control the Mann-Whitney U-test (*P≤0.05).

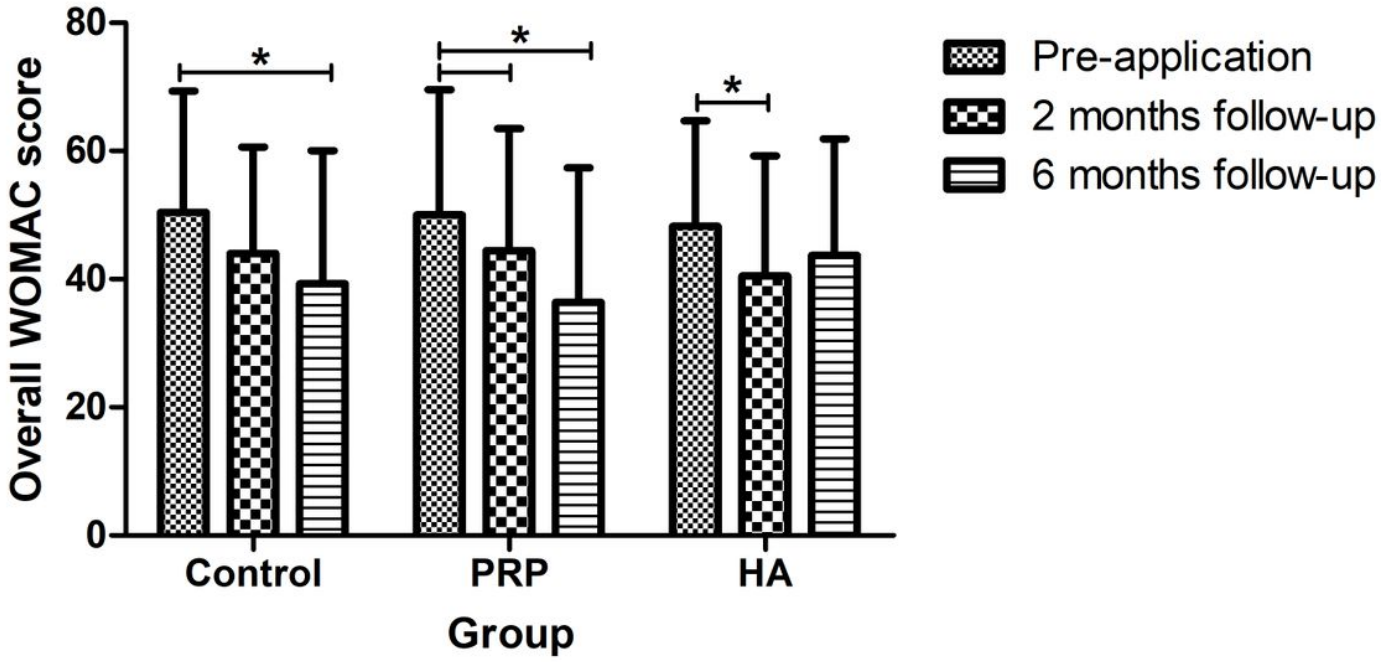

Figure 6

Comparison of WOMAC score between groups at three time points. Data are presented as mean values±SD. Statistically significant differences between pre- and post-application were determined using Wilcoxon signed-rank test and in comparison, for control the Mann-Whitney U-test (*P≤0.05).