Intra-Articular Polyacrylamide Hydrogel Injections Improve Pain and Function in Knee Osteoarthritis: A Multicenter Retrospective Study

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Research Article

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Abstract

Objective

To evaluate the real-world effectiveness of intra-articular (IA) 2.5% polyacrylamide hydrogel (iPAAG) injections in reducing pain and improving function in patients with knee osteoarthritis (KOA).

Design:

This multicenter retrospective study analyzed outcomes from 387 patients (593 knees) treated with IA 2.5% iPAAG hydrogel. Patient-reported outcomes were assessed over 12 months. Pain was measured using the Visual Analogue Scale (VAS), and function was evaluated with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Results

At 12 months post-injection, mean VAS scores decreased by 2.5 points, mean total WOMAC scores decreased by 13.4 points, and the WOMAC function subscale decreased by 7.0 points. Improvements were consistent across age, sex, and BMI categories. Patients with Kellgren-Lawrence Grade 2 KOA demonstrated greater benefit compared to those with Grades 3 and 4. No unexpected safety concerns were reported.

Conclusions

IA 2.5% iPAAG injections significantly reduced pain and improved function in KOA patients in a real-world setting. These findings support its role as a non-surgical treatment option for symptomatic KOA, particularly in earlier disease stages.

Background

Osteoarthritis (OA) affects 15% of the global population over the age of 30 [1]. The disease progresses through a cycle of inflammation, degeneration and regeneration in the joints and surrounding tissues and is clinically characterized by pain, disability, co-morbidity and high mortality rates [2]. According to a population-based study published in February 2025, knee osteoarthritis (KOA) is one of the most prevalent chronic diseases, with an estimated incidence rate of 354 per 100,000 people and a prevalence rate of 4,294 per 100,000 people worldwide [3]. The economic burden is increasing in aging societies, particularly among women [4]. In 2019, the loss of healthy life in Western Europe was calculated as approximately two million years [4]. In 2021, the disease was represented by 12.0 million disability-adjusted life years [Rate: 138/100,000] [3]. Pain and loss of function reduce the quality of life and worsen mental health [5]. This situation negatively affects social well-being and increases the indirect economic

cost. The direct and indirect costs of OA due to loss of productivity are 7.2 billion and 4.6 billion, respectively [4].

Despite its prevalence, no curative treatment for KOA currently exists. Symptomatic and regenerative treatment methods such as disease-modifying intra-articular (IA) injections and cellular therapies are recently in demand [6, 7]. Among these, injectable polyacrylamide hydrogel (2.5% iPAAG) constitutes an option [8–11]. 2.5% iPAAG is a novel IA injectable composed of 2.5% cross-linked polyacrylamide and 97.5% non-pyrogenic water. It is a biocompatible and non-degradable gel, which is naturally integrated in the synovial membrane after IA injection. PAAG is applied in many countries in Europe, including the United Kingdom, for the symptomatic treatment of KOA. An overview of effectiveness data on IA PAAG from published articles is presented in Table 1. The first KOA case report of PAAG hydrogel was published in 2016 [12]. This patient underwent meniscus surgery in the ninth month after treatment, during which a synovial tissue sample was obtained and examined histologically. Findings revealed that the PAAG hydrogel had integrated into the synovium and stabilized the tissue. A proof-of-concept study later showed that pain, joint stiffness and function had significantly improved at four months after injection in 62 patients and that the improvement was sustained throughout the observation period of 13 months [8]. In a subsequent retrospective safety assessment, no significant incidence of adverse events related to the PAAG hydrogel treatment was observed. However, 16% of 91 IA PAAG hydrogel-injected patients had undergone knee replacement surgery at an average follow-up of 24 months [range: 4 to 87 months] [9]. Similar to the earlier findings, a recently published open-label study showed significant decreases in the mean Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain, stiffness and physical function subscale scores at 52 weeks after IA PAAG hydrogel application in 46 patients [11]. A randomized controlled study, comparing the efficacy and safety of the IA PAAG hydrogel injection with IA hyaluronan (HA) injection, similarly found significant decreases in the WOMAC pain, stiffness and function subscale scores in the IA PAAG hydrogel group that consisted of 106 patients at 12 months [13]. Interestingly, all IA PAAG hydrogel WOMAC subscale scores were numerically better than the HA scores at both 26 and 52 weeks. However, they were not significantly different.

Table 1

Effectiveness results from published articles on intra-articular PAAG hydrogel applied in knee osteoarthritis patients.* VAS: Visual Analogue Scale; WOMAC: The Western Ontario and McMaster Universities Arthritis Index.

Year	Author	Patients (n)	Follow-Up	VAS (change from baseline) (10 to 0)	WOMAC score (change from baseline) (99 to 0)	Notes
2016	Christensen [12]	1	9m	(-)	(-)	PAAG Synovial Tissue Integration. Synovial Biopsy at 9m.
2018	Henriksen [8]	62	4m	(-)	-13.4	
		59	7m	(-)	-13.1	
		56	13m	(-)	-10.9	
2021	Bliddal [10]	49	4w	(-)	Pain subscale: -15.4 Stiffness subscale: -11.5 Physical function subscale: -13.2	
		48	13w	(-)	Pain subscale: -18.0 Stiffness subscale: -20.8 Physical function subscale: -17.1	
		46	26w	(-)	Pain subscale: -21.7	

*Reviews and abstracts were excluded.

Year	Author	Patients (n)	Follow-Up	VAS (change from baseline) (10 to 0)	WOMAC score (change from baseline) (99 to 0)	Notes
					Stiffness subscale: -17.9 Physical function subscale: -18.4	
2022	Maulana [18]	1	4m	(-)	(-)	15 points increase in Oxford Knee Score and 45 points increase in Lysholm Knee Score. Reduction in patellofemoral bone marrow lesion after injection observed in MRI.
2024	Bliddal [11]	49	52w	(-)	Pain subscale: -17.7 Stiffness subscale: -11.0 Physical function subscale: -14.9	Extension of the Bliddal 2021 article.
2024	Bliddal [13]	115	26w	(-)	Pain subscale: -18.5 Stiffness subscale: -18.4 Physical function subscale: -18.9	

*Reviews and abstracts were excluded.

Year	Author	Patients (n)	Follow-Up	VAS (change from baseline) (10 to 0)	WOMAC score (change from baseline) (99 to 0)	Notes
		106	52w	(-)	Pain subscale: -17.6 Stiffness subscale: -17.5 Physical function subscale: -17.5	
*Reviews and abstracts were excluded.						

Although the therapeutic effect of IA PAAG hydrogel is consistent across studies, most published data are derived from small cohorts or single-center studies, and there remains a need for large-scale, real-world evidence to validate its clinical utility. This multicenter retrospective study aims to evaluate the effectiveness of 2.5% iPAAG in improving pain and functional outcomes in KOA patients over a 12-month period. Patient-reported outcome measures (PROMs), including the Visual Analogue Scale (VAS) for pain and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for function, were assessed. Additionally, the study explores whether demographic and clinical factors—age, sex, body mass index (BMI) and radiographic Kellgren-Lawrence (KL) grade—are associated with treatment response.

Methods

Design

This was a retrospective case series of consecutive KOA patients with at least 12 months follow-up after the treatment with IA PAAG hydrogel (Arthrosamid, Contura, Denmark) injection. A three-center clinical study collecting real-world data was designed. Ethical approval was obtained from the Bursa City Hospital Non-Invasive Clinical Research Ethics Committee (Approval Date: 06.08.2025; Approval No: 2025-14/3). The trial was registered at ClinicalTrials.gov (Identifier: NCT07193368; registration date: September 25, 2025; URL: https://clinicaltrials.gov/study/NCT07193368?cond=NCT07193368&rank=1). The study was conducted in accordance with the principles of the Declaration of Helsinki. Given the retrospective nature of the study, informed consent was waived by the ethics committee. Joint pain and function data including VAS, WOMAC as well as baseline X-Ray pictures of the IA PAAG-injected KOA

patients were retrospectively evaluated. Missing data were addressed by excluding patients with incomplete follow-up records from the analysis; no data imputation was performed. The study included archive data of male and female patients over the age of 40 years diagnosed with KL grade 2 to 4 KOA who had received intra-articular PAAG injections. Patients were excluded if they had a history of knee surgery prior to receiving PAAG injections, malignancy, local infection or septic arthritis, or inflammatory diseases such as rheumatoid arthritis. Additional exclusion criteria included pregnancy, avascular necrosis and the presence of advanced varus or valgus knee deformities. Patients did not receive any concomitant intra-articular injections or surgical procedures during the follow-up period; however, those who had received other treatments prior to the 2.5% iPAAG injection were not excluded. None of the patients received more than one 2.5% iPAAG injection within the follow-up period. Patients lost to follow-up or lacking complete outcome data were excluded from the final analysis.

Variables

Independent variables were the IA PAAG-injected KOA patients and their follow-up period. Dependent variables were (1) sex, (2) age, (3) BMI (kg/m^2), (4) VAS pain score, (5) WOMAC score and (6) KL score on X-ray pictures. Improvement of pain and function before and after injections were evaluated. The follow-up period was determined as twelve months. Injections were carried out between 11 February 2023 and 24 June 2024.

Radiological Quantification and Treatment

Classification was undertaken according to the Kellgren-Lawrence (KL) system [14] from standing bilateral anteroposterior knee radiographs of the patients.

Injections were performed under local anesthesia and ultrasound guidance according to the manufacturer’s instructions.

Outcome Measures

Pain was assessed using the VAS scale [15] ranging between 0 and 10, with 0 being no pain and 10 being worst pain.

Functional level was evaluated using the total WOMAC and physical function subscale scores [16].

Assessments were performed at baseline and at 12 months post-injection.

Statistics

The study used real-world data to analyze changes in pain and function scores after treatment with IA PAAG. The data were analyzed using IBM SPSS Statistics version 29 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as means ± standard deviations. Differences in VAS, total WOMAC and WOMAC function scores pre- and post-injection were evaluated using paired-samples t-tests. Comparisons between categorical subgroups (sex, age groups, BMI categories and Kellgren–Lawrence grades) were performed using one-way ANOVA or independent-samples t-tests. Interaction trends between sex and BMI on clinical outcomes were explored using subgroup analyses. A two-tailed p-value of less than 0.05 was considered statistically significant.

The probability of correctly detecting meaningful difference between before and after injection in the VAS, WOMAC and WOMAC FUNCTION scores are greater than 0.999.

Results

Participants

Archive data of 342 (86.8%) women and 52 (13.2%) men with primary and secondary KOA who received IA PAAG hydrogel injections were evaluated at twelve months. Seven patients were lost to follow-up and excluded from the final analysis, resulting in a dataset 593 knees of 387 patients for outcome evaluation. Demographic data of the patients are presented in Table 2.

Table 2
Demographic data of patients.

IA PAAG-hydrogel injected patients (n)	**387**
Female sex (n [%])	337 (87.08)
Age (years) (mean, standard deviation and range)	68.4 ± 8.44 [Range 42.0–93.0]
Left (n)	95
Right (n)	86
Bilateral (n)	206
Body mass index (kg/m^2) (mean, standard deviation and range)	32.6 ± 5.4 [Range 19.0-52.9]
Kellgren-Lawrence score) (mean, standard deviation and range)	3.3 ± 0.7 [Range 1.0–4.0]

Pain Outcomes (VAS)

At 12 months post-injection, VAS scores decreased in 326 (84.2%) patients, remained unchanged in 34 (8.8%) patients and increased in, and 27 (7.0%) patients. The largest individual changes were 6-point reductions (from 8 to 2 in one and 9 to 3 points in another patient) while the largest increase was 2 points (Fig. 1). The mean VAS score significantly decreased from 7.6 ± 1.1 at baseline to 5.1 ± 2.0 at 12 months after treatment($p < 0.001$) (Table 3).

Table 3
Baseline and 12-month scores of VAS and WOMAC (total and function) with mean differences and 95% confidence intervals.

O	Baseline score	12 months	Mean difference	95% CI of the difference	
				Lower	Upper
VAS (0–10)	7.61 (1.12) N = 387	5.13 (1.97) N = 387	2.48	2.27	2.68
WOMAC total (0-100)	58.03 (10.10) N = 387	47.76 (13.43) N = 387	10.27	9.26	11.27
WOMAC function (0–68)	41.13 (7.36) N = 386	34.11 (10.15) N = 386	7.02	6.26	7.79
All numbers are mean (standard deviation) unless otherwise stated					

Functional Outcomes (WOMAC)

The total WOMAC score decreased, remained unchanged and increased in 317 (81.9%), 9 (2.3%) and 61 (15.8%) patients, respectively. The mean WOMAC score improved from 58.0 ± 10.1 to 47.8 ± 13.4 in 12 months ($p < 0.001$) (Fig. 2, Table 3). The largest individual increase was 12 points in a patient who had experienced arthroscopic debridement twice previously. This patient needed additional interventions after IA PAAG injections.

The WOMAC physical function subscale score decreased, remained unchanged and increased in 319 (82.6%), 4 (1.0%) and 63 (16.3%) patients, respectively. The mean WOMAC function score improved from 41.1 ± 7.4 to 34.1 ± 10.1, in 12 months ($p < 0.001$) (Fig. 3, Table 3).

Sex-Based Comparison of Clinical Outcomes

There were no statistically significant differences between men and women in the changes from baseline for the VAS, WOMAC and WOMAC function scores ($p = 0.562$, $p = 0.793$, and $p = 0.872$, respectively) (Table 4).

Table 4
Changes in VAS and WOMAC (function and total) scores from baseline to 12 months after intra-articular PAAG hydrogel injection, shown separately for men and women. Data are presented as mean ± SD, along with mean differences and 95% CI.

	Baseline score	12 months	Mean difference	95% CI of the difference	
				Lower	Upper
VAS					
Men	7.46 (1.23) N = 50	5.14 (1.80) N = 50	2.32	1.84	2.80
Women	7.64 (1.10) N = 337	5.13 (1.99) N = 337	2.50	2.27	2.73
WOMAC Function					
Men	39.40 (7.56) N = 50	32.54 (9.76) N = 50	6.86	4.71	9.01
Women	41.39 (7.31) N = 336	34.34 (10.20) N = 336	7.05	6.23	7.87
WOMAC Total					
Men	55.78 (11.04) N = 50	45.86 (13.39) N = 50	9.92	7.10	12.74
Women	58.36 (9.94) N = 337	48.04 (13.43) N = 337	10.32	9.23	11.40

Age-Based Comparison of Clinical Outcomes

When stratified by age groups (40–54, 55–64, 65–74 and ≥ 75 years), no significant differences were observed in the changes from baseline for the VAS, WOMAC and WOMAC function scores ($p = 0.129$, $p = 0.566$, and $p = 0.889$, respectively) .

Radiographic Severity and Clinical Outcomes

A significant change from baseline was observed for the VAS score across Kellgren Lawrence (KL) grades ($p = 0.039$), while changes from baseline for the WOMAC and WOMAC function scores did not differ significantly ($p = 0.347$ and $p = 0.25$, respectively) (Table 5). Patients with KL Grade 2 had significantly greater improvements in VAS scores compared to those with Grade 3 ($p = 0.038$) and Grade 4 ($p = 0.011$). No significant difference was found between Grade 3 and 4 ($p = 0.484$) patients.

Table 5
Changes in VAS and WOMAC (function and total) scores from baseline to 12 months after intra-articular PAAG hydrogel injection, presented according to Kellgren–Lawrence (KL) grades 2, 3, and 4. Data are expressed as mean ± SD, along with mean differences and 95% CI.

	Baseline score	12 months	Mean difference	95% CI of the difference	
				Lower	Upper
VAS					
KL grade 2	7.02(1.22) N = 48	3.87(2.02) N = 48	3.15	2.35	3.95
KL grade 3	7.33(0.99) N = 165	4.89(1.75) N = 165	2.44	2.13	2.75
KL grade 4	8.07(1.03) N = 174	5.79(1.90) N = 174	2.28	2.00	2.56
WOMAC Function					
KL grade 2	36.00(5.65) N = 48	27.37(9.07) N = 48	8.63	5.80	11.45
KL grade 3	39.30(6.81) N = 165	32.74(9.21) N = 165	6.56	5.45	7.70
KL grade 4	44.38(6.89) N = 174	37.64(9.85) N = 174	6.74	5.65	7.83
WOMAC Total					
KL grade 2	49.93(7.13) N = 48	37.78(7.78) N = 48	12.15	8.55	15.74
KL grade 3	55.51(8.92) N = 165	45.62(11.82) N = 165	9.89	8.34	11.44
KL grade 4	62.92(9.50) N = 174	53.11(12.85) N = 174	9.81	8.39	11.23

BMI and Clinical Outcomes

When BMI was categorized into three groups (≤ 24.9, 25.0–29.9, and ≥ 30.0), no significant differences were found in the changes from baseline for VAS ($p = 0.864$), WOMAC ($p = 0.82$), or WOMAC function ($p = 0.832$) scores between the groups.

Although not statistically significant, a sex-specific trend was observed: in men, higher BMI was associated with greater improvement, whereas in women, less improvement was observed with increasing BMI.

Discussion

Intra-articular PAAG hydrogel injections represent a promising non-surgical treatment option for symptom relief in patients with KOA. This study is the first to evaluate the real-world effectiveness of IA PAAG on a larger scale, encompassing 593 knees of 387 KOA patients, with a follow-up period of 12 months. The results revealed clinically relevant and statistically significant improvements in both pain and physical function, reinforcing the therapeutic potential of PAAG hydrogel in routine clinical practice.

Patients in this cohort experienced a mean reduction of 2.5 points in pain, as assessed by VAS (0–10). This exceeds the pain reductions reported in previous studies, which ranged from approximately 1.6 to 1.8 points when converted from the normalized WOMAC pain subscale (0–100) to a comparable 0–10 scale [8, 11, 13]. Similarly, the mean reduction in total WOMAC score was 10.3 points on a 0–96 scale, closely aligning with the 10.5-point reduction reported by Henriksen et al. [8]. The observed improvement in WOMAC physical function score (7.0 points on a 0–68 scale) also compares favorably with prior findings, exceeding the 6.4-point reduction reported by Henriksen et al., though remaining slightly below the 10.1 and 11.9-point reductions reported in other studies [11, 13].

Importantly, the improvements in pain and physical function were consistent across sex, age, and BMI categories, suggesting that IA PAAG hydrogel may be broadly effective across diverse patient subgroups. While not statistically significant, a trend was noted in which higher BMI in men was associated with greater improvement, whereas women with higher BMI tended to experience less benefit. These observations may reflect underlying sex-specific biomechanical or inflammatory differences [17] and warrant further investigation.

Patients with KL Grade 2 KOA demonstrated greater improvement in VAS scores compared to those with Grades 3 and 4, indicating that earlier stages of joint degeneration may be more responsive to PAAG hydrogel treatment. This finding highlights the importance of timely intervention in the disease course.

The results of this study have several important implications for clinical decision-making and future research. First, the demonstrated effectiveness of PAAG hydrogel across a large, real-world cohort supports its use as a viable non-surgical treatment option for KOA, particularly for patients who are not candidates for joint replacement surgery. This includes individuals who decline surgery despite medical advice, as well as those with severe comorbidities that pose significant risks during anesthesia.

Second, the favorable outcomes in patients with KL Grade 2 disease suggest that PAAG hydrogel may be most beneficial when administered during the earlier stages of KOA. This underscores the need for early diagnosis and intervention, which could potentially delay disease progression and reduce the need for surgical intervention.

Third, the lack of significant influence from demographic factors such as age, sex, and BMI suggests that PAAG hydrogel may be broadly applicable, simplifying patient selection and expanding access to treatment.

A key limitation of this study is the absence of a control group, which restricts the ability to draw comparative conclusions. Additionally, in cases of bilateral intra-articular injections, VAS and WOMAC scores were recorded at the patient level rather than per knee, and a single KL grade was assigned per patient. This may have obscured side-specific differences in disease severity and treatment response.

Despite these limitations, the relatively large number of patients and long follow-up period are notable strengths. Future studies should consider even longer-term follow-up to assess the long-term durability of treatment effects. Investigating the biological mechanisms underlying differential responses by BMI and KL grade may also yield insights that inform personalized treatment strategies.

Abbreviations

OA
Osteoarthritis
KOA
Knee Osteoarthritis
IA
Intra-articular
VAS
Visual Analog Scale
WOMAC
Western Ontario and McMaster Universities Osteoarthritis Index
BMI
Body Mass Index
KL
Kellgren–Lawrence
PAAG
Polyacrylamide Hydrogel
iPAAG
Injectable Polyacrylamide Hydrogel.

Declarations

- **Ethics approval and consent to participate**
  This study was approved by the Bursa City Hospital Non-Invasive Clinical Research Ethics Committee (Approval Date: 06.08.2025; Approval No: 2025-14/3). The study complied with the Declaration of Helsinki. Informed consent was waived due to the retrospective study design.

- **Consent for publication**
  Not applicable.
- **Availability of data and materials**
  All data generated or analyzed during this study are included in this published article. Additional data are available from the corresponding author upon reasonable request.
- **Competing Interests**
  Feza Korkusuz, MD, is a member of the Academic Advisory Board of Contura International A/S, Copenhagen, Denmark, and an active member of the Turkish Academy of Sciences (TÜBA). The authors declare no other competing interests.
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- **Authors' contributions**
  Bilal Aykaç, Özgür Oktay Nar, and Feza Korkusuz contributed to the conception and design of the study. Bilal Aykaç, Gülce Naz Ünsal, and Selin Demirel performed data acquisition and analysis. All authors participated in interpretation, manuscript drafting, and critical revision. All approved the final manuscript.
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Figures

Figure 1:

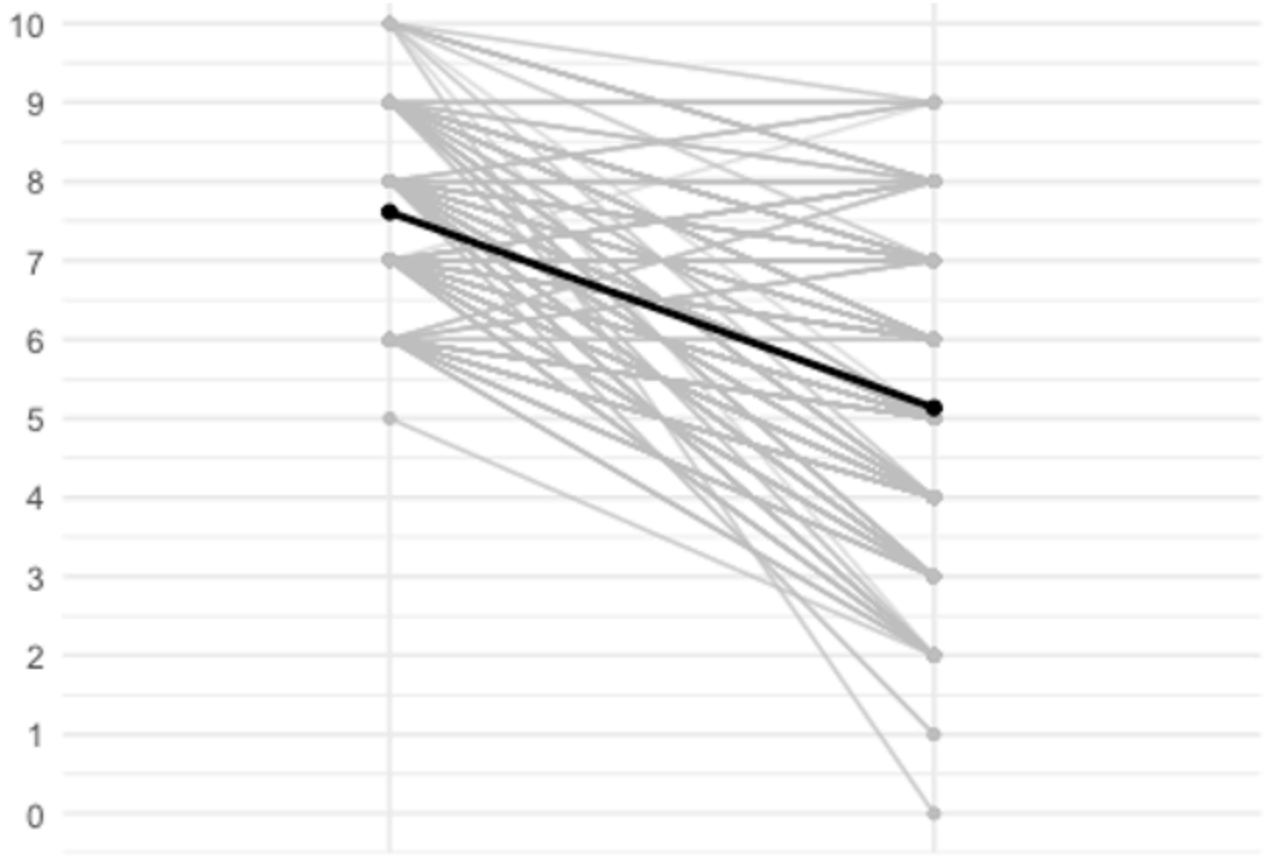

Figure 1

Overall VAS score changes in 387 KOA patients that received IA PAAG. The average VAS decrease (bold black line) was from 7.6 ± 1.1 to 5.1 ± 2.0 in twelve months ($p<0.001$).

Figure 2:

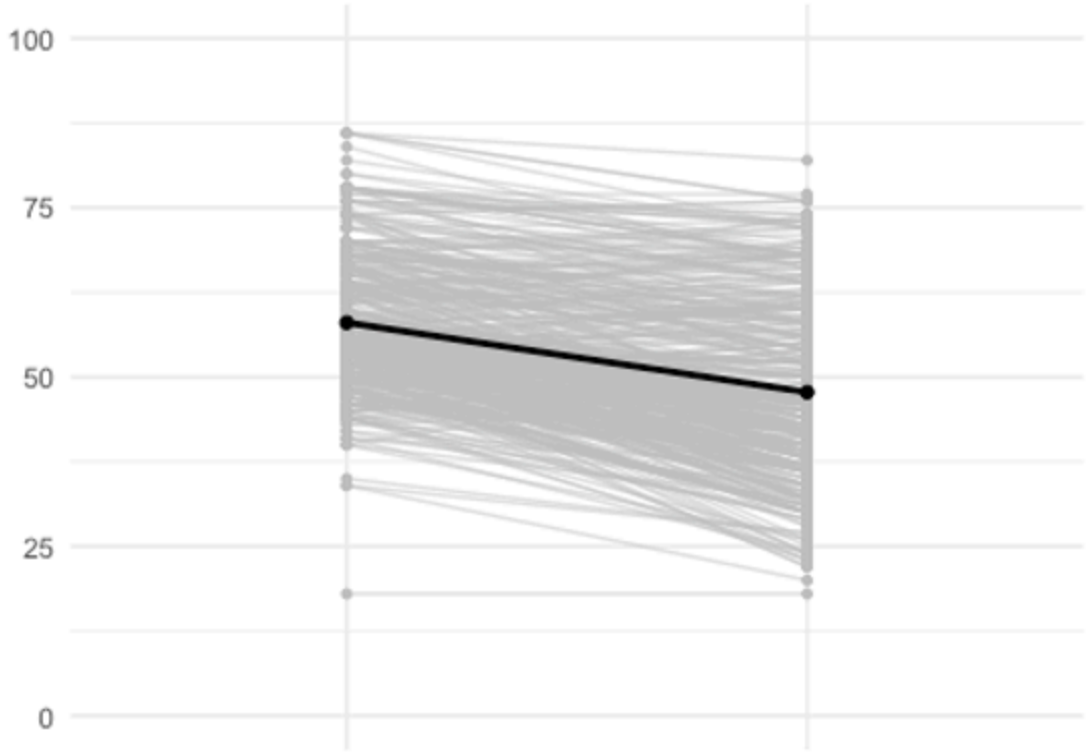

Figure 2

Overall WOMAC score changes in 387 KOA patients that received IA PAAG. The average WOMAC decrease (bold black line) was from 58.0 ± 10.1 to 47.8 ± 13.4 (p<0,001)in twelve months.

Figure 3:

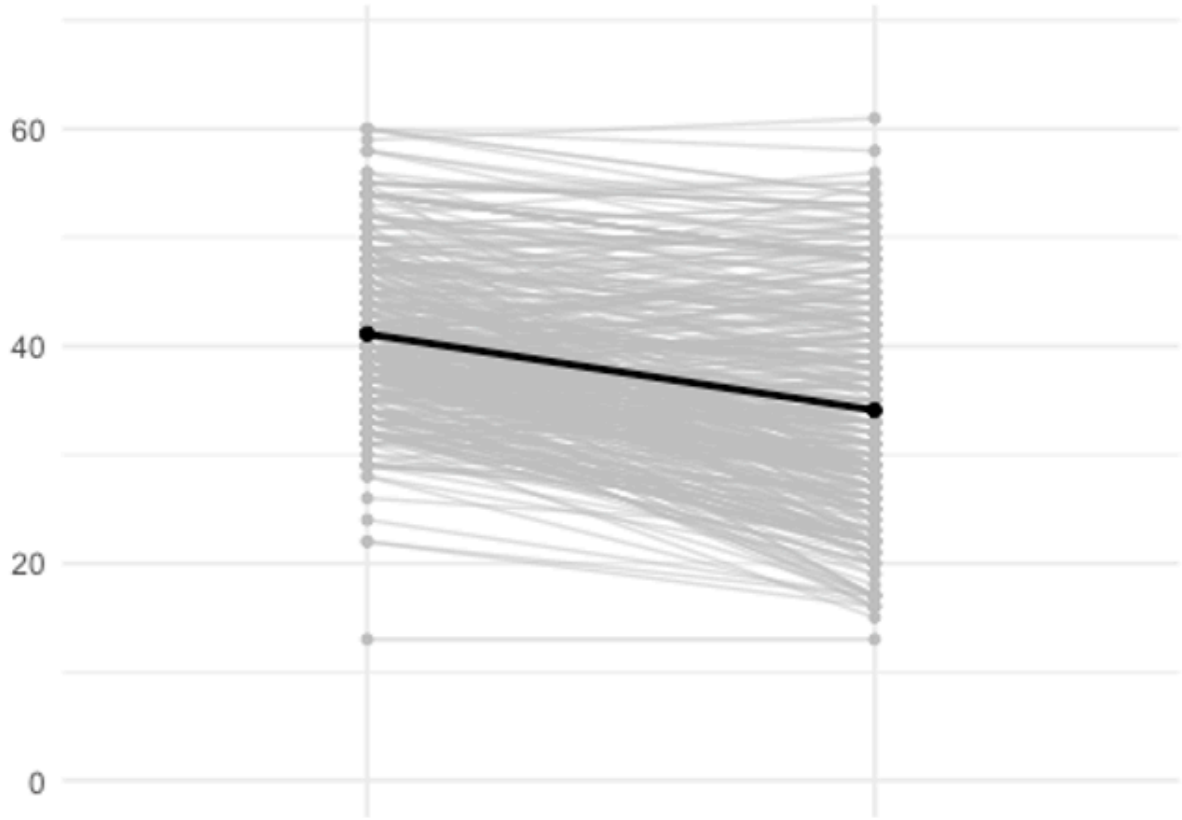

Figure 3

Overall WOMAC function score changes in 387 KOA patients that received IA PAAG. The average WOMAC function decrease (bold black line) was from 41.1 ± 7.4 to 34.1 ± 10.1 (p<0,001)in twelve months.

Supplementary Files

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- SuplementaryMaterial.docx