Research Article

Polyacrylamide Hydrogel Injection for Knee Osteoarthritis: A 6 Months Prospective Study

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Abstract

Objective: Intra-Articular (IA) injection of polyacrylamide hydrogel (PAAG) is a possible treatment for symptomatic Osteoarthritis (OA) of the knee. This study evaluated the efficacy and safety of a single injection of 6 ml intra-articular PAAG over 26 weeks.

Methods: Open-label study in patients with symptomatic and radiographically confirmed knee OA . Primary outcome was change in WOMAC pain after 13 weeks. Secondary outcomes were WOMAC stiffness and function subscales, Patient Global Assessment of disease impact (PGA) and proportion of OMERACT-OARSI responders. Follow-up time points were 4, 13 and 26 weeks.

Results: 49 patients (31 females) received PAAG, with 48 patients completing the 13 and 46 the 26 weeks assessments. Mean change in WOMAC pain after 13 weeks was -18.3 points [95% CI-23.4 to -13.3]; P<.0001 and at 26 weeks -20.8 points [95% CI -26.3 to -15.3]; P<0.0001 with similar benefits for WOMAC stiffness, physical function, and PGA. After 13 weeks 64.6% were OMERACT-OARSI responders and this was maintained at 26 weeks.. During the 13 weeks, 18 patients reported 23 adverse events, 13 of which were related to PAAG, none severe. Two serious adverse events, atrial fibrillation and gastrointestinal pain, were assessed as 'not related' to PAAG.

Conclusions: PAAG can be delivered in a single 6 ml injection and this non-randomized trial in patients with knee OA demonstrated beneficial clinical effects at 13 and 26 weeks. No serious adverse events were seen with PAAG. These encouraging results need to be confirmed in controlled studies.

Keywords: Intra-articular treatment; Osteoarthritis

Background

Osteoarthritis (OA) is the most common arthritis, characterised by pain and physical disability [1]. More than 10% of persons 55 years of age or older have symptomatic OA, primarily involving the knees [2]. Although several treatment options for OA in the knee are available, non-pharmacological treatments (e.g. exercise, weight loss if overweight) are often underutilised, analgesics have limited benefits, and joint replacement surgery is limited to end-stage disease. New treatment options are therefore warranted in order to improve the care of people with OA. Recently,

Intra-Articular (IA) injection of polyacrylamide gel (PAAG) has been suggested as a possible treatment for symptomatic OA. PAAG is a proprietary 2.5% cross-linked polyacrylamide hydrogel, manufactured by Contura International A/S. PAAG contains 2.5% polyacrylamide and 97.5% non-pyrogenic water, with a unique molecular structure that allows normal water exchange with the surrounding tissue without losing shape. PAAG is biocompatible, non-absorbable, non-biodegradable, and structurally stable. For more than 20 years, PAAG has been used for various indications such as bulking for stress urinary incontinence and soft tissue augmentation. PAAG is classified as a Class IIb device under the European Council Directive 93/42/EEC on medical devices.

PAAG has been extensively tested in horses with OA with pain relief observed within a month, with the majority of the horses no longer being lame after 24-months [3]. An observational study in patients with knee OA reported that IA PAAG delivered as two injections of 3 ml separated by 1 month provided symptomatic relief up to 13 months [4]. If 6 ml can be delivered in one treatment session, this would improve patient acceptability, feasibility of treatment and reduce the risk of potential side effects related to repeated injections. The objectives of this study were to evaluate the efficacy and safety of one injection of 6 ml IA PAAG on knee pain in patients with moderate to severe knee OA.

Methods

This study was an open label, 26-week observational study of the efficacy and safety of intra-articular (IA) injection of PAAG with data collected from August 2019 to April 2020 at three clinical sites in Denmark. The protocol for this study was approved by the local Health Research Ethics committee (ref.no: H-19031685), the Danish Health authorities, and was registered at www.clinicaltrials.gov (NCT04179552) before any study related activities. Patients gave informed consent prior to participation, and the study was conducted according to the principles of good clinical practice. Inclusion criteria were: adults with a clinical diagnosis of knee OA according to the American College of Rheumatology, definite radiographic OA in the target knee (Kellgren-Lawrence grade 2-4) (locally read), score of ≥2 (on 0-4 scale) on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) question related to pain while walking on a flat surface, a body mass index (BMI) <35 kg/m², and, if patients were taking oral analgesics, they needed to have been on a stable dose for at least 4 weeks prior to inclusion. Exclusion criteria included: previous IA PAAG treatment, IA hyaluronic acid or its derivatives in target knee within prior 6 months, IA corticosteroids within 3 months, skin disease in the injection area, and surgery in the treatment knee within 6 months.

The patients received one treatment of 6 ml PAAG and attended clinical follow-up visits after 4, 13, and 26 weeks.

Treatments Administered

PAAG was provided in sterile, pre-filled 1 ml sealed syringes to be injected IA with a sterile 21G x 2-inch (0.8 x 50 mm) needle. Each patient received one IA injection of PAAG (6ml) under ultrasound guidance to ensure proper placement of the bolus inside the joint cavity. Prior to the injection, prophylactic antibiotics were given and topical anaesthetics were applied. Once the needle was inserted, the prefilled 1 ml PAAG syringes were changed via the Luer lock system to reach a total of 6 ml of PAAG with the needle remaining in place. Analgesic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol was allowed during the trial, but not exceeding the recommended dosage (e.g. paracetamol up to 4000 mg/day and ibuprofen 1200 mg/day), but not allowed within 48 hours prior to a study visit. Non-pharmacological therapy was allowed if kept stable during the study. All concomitant therapies and treatments were recorded.

Outcomes

The primary outcome measure was change from baseline in the pain subscale of the WOMAC at 13 weeks. Secondary outcome measures were changes in baseline in the physical function and stiffness subscales of WOMAC, Patient's Global Assessment (PGA) of OA impact, and the proportion of positive responders to the OMERACT-OARSI response criteria [5]. Data were collected at baseline, and after 4, 13, and 26 weeks. In this study, the Danish WOMAC was used in the 5-point Likert format with scores ranging from 0 (indicating no pain, stiffness, or difficulty) to 4 (indicating extreme pain, stiffness, or difficulty). The three WOMAC subscale scores were normalised to a 0-100 scale with 0 indicating best outcome and 100 indicating worst outcome. The PGA was based on responses to the question "How much does the knee osteoarthritis (treatment knee) as a whole affect your life at present?" indicated on a 100 mm Visual Analogue Scale (VAS) with anchors 0 = "Not at all" and 100 = "The worst imaginable". OMERACT-OARSI response was defined as either (1) improvement in WOMAC pain or physical function ≥50% and an absolute change ≥20 normalised units (0-100); or (2) ≥20% improvement and an absolute change ≥10 points two of the three categories: WOMAC pain, WOMAC physical function, and PGA.

Statistical Methods

The sample size was calculated to detect a change of at least 12 points on the WOMAC pain subscale (0-100 points) using a one-sample t-test and a statistical significance level of 0.05, assuming a common standard deviation of 22 points. To obtain 90% power a sample size of 38 was required. The analyses of the primary outcome were performed by using a repeated measures mixed linear model with a restricted maximum likelihood based approach and carried out on the full analyses set population defined as patients who received study treatment as per the protocol and who had a valid recording of the WOMAC pain subscale at baseline. Missing data were not imputed but handled implicitly by the repeated measures mixed linear model. The analyses of the secondary outcomes were performed using the same statistical model as for the primary outcome applied to the same population defined as all allocated subjects who received study treatment. The proportion of positive responders to the OMERACT-OARSI criteria at time points 4 weeks, 13 weeks, and 26 weeks were summarised including exact Clopper-Pearson 95% confidence intervals. Internationally applicable estimates of minimal clinically important improvements (MCII) of the WOMAC scores on the 0-100 scale have been suggested for individuals with knee OA in a 4-week study of nonsteroidal anti-inflammatory drugs [6]. For the WOMAC pain subscale the MCII is 9 points; for the stiffness

subscale MCII it is 7 points; and for the function subscale MCII it is 6 points. For transformed WOMAC pain, stiffness and physical function subscales the proportion of subjects fulfilling the MCII criteria at week 26 were summarised including exact Clopper-Pearson 95% confidence intervals.

Results

50 subjects (31 females, mean age 70 SD 9 years) were screened and 49 enrolled in the study (Table 1). One subject received only approximately 5 ml of PAAG due to a user error; thus, the full analysis set consisted of 48 subjects. All 48 subjects completed the 4 and 13 week assessments, and 46 completed the week 26 assessment.

Table 2 shows the results from the main analyses. At the 13 weeks follow-up there was a decrease in the WOMAC pain score of -18.3 points (95% CI -23.3 to -13.3; P<.0001). This was further improved at 26 weeks to -20.8 (95% CI -26.2 to -15.3; P<.0001). Similar results were found for the WOMAC stiffness and function subscales, which improved at the 4, 13 and 26 week assessments. WOMAC pain, stiffness and function subscales data at the 26-week assessment are provided in Figure 1. At 4, 13 and 26 weeks, the PGA had decreased by -13.4 mm (95% CI -19.5 to -7.3; P<.0001); -18.7 mm (95% CI -25.3 to -12.1; P<.0001), and -15.4 mm (-23.5 to -7.6; P=0.0003), respectively.

	PAAG-OA N (%)
Screened subjects	50
Screening failures	1
ITT analysis set	49 (100.0)
Full analysis set	48 (98.0)
Per protocol analysis set	41 (83.7)
Withdrawn until 26 weeks	3 (6.1)
Adverse event	1 (33.3)
Withdrawal by subject	2 (66.7)
Completers of 26 weeks	46 (93.9)
N: Number of subjects; %: Percentage of subjects	

Table 1: Subject disposition.

	WOMAC Pain subscale		WOMAC Stiffness subscale		WOMAC Physical function subscale	
	Actual values	**Change from baseline**	**Actual values**	**Change from baseline**	**Actual values**	**Change from baseline**
Full analysis set (N,%)	49 (100.0)					
Baseline						
N	49		49		49	
Mean (SD)	50.3 (11.8)		55.6 (17.5)		46.6 (16.1)	
Median	50.0		62.5		45.6	
Min - Max	20 - 75		0 - 88		9 - 87	
Week 4						
N	49	49	49	49	49	49
Mean (SD)	34.9 (16.4)	-15.4 (15.3)	44.1 (20.6)	-11.5 (17.3)	33.4 (16.7)	-13.2 (13.8)
LSMean	-15.4		-11.4		-13.2	
95% CI	(-19.7; -11.2)		(-16.2; -6.6)		(-16.9; -9.6)	
Median	35.0	-15.0	50.0	-12.5	35.3	-10.3

	WOMAC Pain subscale		WOMAC Stiffness subscale		WOMAC Physical function subscale	
	Actual values	**Change from baseline**	**Actual values**	**Change from baseline**	**Actual values**	**Change from baseline**
Min - Max	0 - 75	-50 - 15	0 - 88	-50 - 38	1 - 63	-38 - 22
Week 13						
N	48	48	48	48	48	48
Mean (SD)	32.1 (18.2)	-18.0 (18.5)	34.6 (21.0)	-20.8 (19.9)	29.4 (18.0)	-17.1 (16.1)
LSMean	-18.3		-21.0		-17.2	
95% CI	(-23.4; -13.3)		(-26.4; -15.7)		(-21.5; -12.9)	
Median	35.0	-20.0	25.0	-25.0	28.7	-19.8
Min - Max	0 - 75	-55 - 35	0 - 75	-63 - 38	0 - 60	-44 - 25
Week 26						
N	46	46	46	46	46	46
Mean (SD)	28.9 (18.6)	-21.7 (19.6)	37.2 (21.5)	-17.9 (21.2)	28.6 (20.3)	-18.4 (17.0)
LSMean	-20.8		-17.5		-18.0	
95% CI	(-26.3; -15.3)		(-23.3; -11.8)		(-23.0; -13.1)	
Median	30.0	-22.5	31.3	-18.8	28.7	-20.6
Min - Max	0 - 70	-60 - 25	0 - 75	-50 - 50	0 - 62	-47 - 21
N: Number of subjects, SD: Standard deviation; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index						

Table 2: Summary of transformed WOMAC pain subscale (0-100) - 26 weeks ITT analysis set.
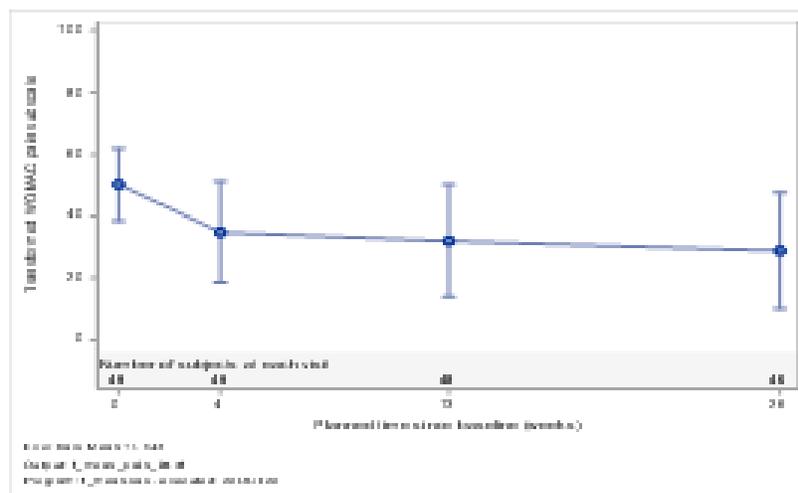

Figure 1: Mean plot of transformed WOMAC pain subscale (0-100) - 26 weeks - ITT analysis set.

The proportion of OMERACT-OARSI responders at the 4, 13 and 26 week assessments were 53.1%; (95% CI 38.3 to 67.5); 64.6% (95% CI 49.5 to; 77.8), and 67.4% (95% CI 51.98 to 80.47), respectively. The proportion of patients with a response larger than the MCII in the transformed WOMAC subscales at week 26 was highest for the WOMAC pain subscale (78%) but was greater than 70% for all 3 subscales (Table 3).

	N	n (%)	(95% CI)
ITT analysis set	49		
Transformed WOMAC pain subscale	46	36 (78.3)	(63.6 ; 89.1)
Transformed WOMAC stiffness subscale	46	34 (73.9)	(58.9 ; 85.7)
Transformed WOMAC physical function subscale	46	34 (73.9)	(58.9 ; 85.7)
N: Number of subjects, n: number of subjects achieving the minimal clinically important improvements (MCII) on the WOMAC subscales			
MCII: Change in WOMAC pain ≤ -9, Change in WOMAC stiffness ≤ -7, Change in WOMAC physical function ≤ -6			
CI: Clopper-Pearson exact confidence interval for the proportion			

Table 3: Summary of minimal clinically important improvements for WOMAC subscales - 26 weeks.

Safety

Twenty-one participants reported a total of 31 adverse events (AEs) during the 26-week study period, of which 14 events were assessed to be related to PAAG (Table 4). 12 events (in 11 patients) were musculoskeletal and connective tissue disorders with 11 events being in the treated knee. The most frequently treatment related AEs were arthralgia (7 events), joint swelling (3 events) and synovial cysts (2 events). Almost all treatment related AEs were mild, with 3 classified as moderate (Table 5). Two events were reported as serious adverse events (SAEs): 1 hospitalisation with atrial fibrillation and 1 hospitalisation with abdominal pain; neither were assessed as related to the device. No deaths were reported, and no AE led to withdrawal from the study (Figures 2,3).

	PAAG-OA N (%) E
ITT analysis set	49
Adverse events (AEs)	20 (40.8) 27
Serious AEs	2 (4.1) 2
Non-serious AEs	20 (40.8) 25
Treatment emergent AEs (TEAEs)	20 (40.8) 27
Non-treatment emergent AEs	0
Adverse device effects (ADEs)	12 (24.5) 15
Serious ADEs (SADEs)	0
AEs leading to withdrawal from study	0

	PAAG-OA N (%) E
Severity	
Mild	17 (34.7) 22
Moderate	5 (10.2) 5
Severe	0
Outcome	
Recovered/resolved	12 (24.5) 14
Not yet recovered	0
Recovering/resolving	9 (18.4) 10
Not recovered/not resolved	3 (6.1) 3
Unknown	0
Relationship to medical device	
Not Related	9 (18.4) 12
Unlikely	5 (10.2) 6
Possibly	6 (12.2) 6
Probably	2 (4.1) 2
Related	1 (2.0) 1
N: Number of subjects experiencing the event at least once,	
%: Percentage of subjects	
E: Total number of reporting of the event	
Adverse events with start date no later than the visit 4 date or withdrawal date in case of withdrawal before visit 4 are included	

Table 4: Adverse events - 26 weeks.

System organ class Preferred term	PAAG-OA N (%) E
ITT analysis set (N %)	49 (100.0)
Any adverse events	20 (40.8) 27

Musculoskeletal and connective tissue disorders	15 (30.6) 17
Arthralgia	8 (16.3) 8
Joint swelling	3 (6.1) 3
Synovial cyst	2 (4.1) 2
Back pain	1 (2.0) 1
Bursitis	1 (2.0) 1
Joint effusion	1 (2.0) 1
Pain in extremity	1 (2.0) 1
Gastrointestinal disorders	2 (4.1) 2
Abdominal pain	1 (2.0) 1
Gastrooesophageal reflux disease	1 (2.0) 1
Infections and infestations	2 (4.1) 2
Nasopharyngitis	1 (2.0) 1
Skin infection	1 (2.0) 1
Cardiac disorders	1 (2.0) 1
Atrial fibrillation	1 (2.0) 1
Injury, poisoning and procedural complications	1 (2.0) 1
Upper limb fracture	1 (2.0) 1
Metabolism and nutrition disorders	1 (2.0) 1
Diabetes mellitus	1 (2.0) 1
Not coded	1 (2.0) 1
N: Number of subjects experiencing the event at least once,	
%: Percentage of subjects	
E: Total number of reporting of the event	
Adverse events with start date no later than the visit 4 date or	
withdrawal date in case of withdrawal before visit 4 are included	

Table 5: Treatment emergent adverse events by system organ class and preferred term -26 weeks - ITT analysis set.
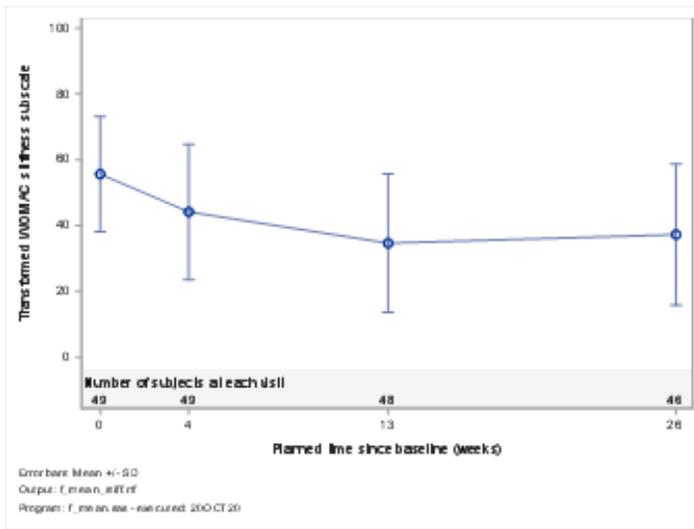
Figure 2: Mean plot of transformed WOMAC stiffness subscale (0-100) - 26 weeks - ITT analysis set.
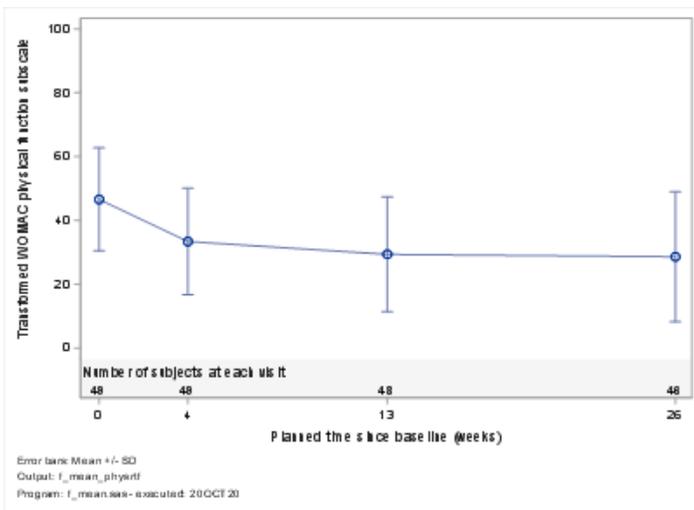

Figure 3: Mean plot of transformed WOMAC physical function subscale (0-100) - 26 weeks.

Discussion

This open label study in patients with knee OA who received 6 ml PAAG administered as one IA injection showed significant improvement in the WOMAC pain subscale at 4 and 13 weeks which were sustained at 26 weeks. A high percentage of patients achieved MCII at all time points. This was accompanied by improvements in the WOMAC stiffness and function, as well as in the PGA, and two thirds of patients were OMERACT-OARSI responders, demonstrating the efficacy of IA PAAG. PAAG has non-absorbable, non-biodegradable and non-migratory characteristics.

Upon injection into the joint cavity, the hydrogel integrates with synovial cells which then proliferate, ultimately re-establishing the synovial lining [7,8]. As the synovial membrane is highly innervated with nociceptive nerve fibres, this re-establishment of synovium may explain the beneficial effects on pain and other OA symptoms. Although speculative, the action on pain may be via an antiinflammatory effect on the synovium.

The 13 week efficacy outcomes of the single 6 ml injection in this study are similar to the 4 month outcomes of a previously reported observational study where 2 separate injections of 3 ml were tested [4]. Relatively few adverse events were reported in both studies, and all device related AEs were assessed as mild or moderate. In this series, no acute inflammatory adverse reactions was experienced to the injection. However, if such were to occur, the immediate treatment would follow the RICE prinicple (rest, ice, elevation) or, in case of excess joint fluid, aspiration. The 2 reported SAEs were assessed as not related to the device. Thus, the overall findings suggest that the clinical application of PAAG is safe and effective and can be conducted as a single injection, thereby simplifying the treatment strategy. This study is limited by the lack of a control group, which introduces a risk of bias to the results. However, it was designed to detect therapy effects as experienced by the patients and the results are indicative of a considerable benefit following treatment with PAAG, reflecting similar results seen in a previous study [4,9]. Nevertheless, a randomised, controlled study is needed to confirm the clinical efficacy and its role in managing patients with knee OA.

Conclusion

In conclusion, this study in patients with knee OA suggests that 6 ml PAAG can be delivered in a single session with good clinical effects at 26 weeks follow up with no safety concerns raised. The outcomes appear promising but need to be confirmed in a randomized, controlled study.

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