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Intra-articular 2.5% polyacrylamide hydrogel for the treatment of knee osteoarthritis: an observational proof-of-concept cohort study

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ABSTRACT

Objective. *There is a drought of effective treatments of knee osteoarthritis (OA) and new therapies are needed. The present study has been conducted to establish an initial estimate of effectiveness of intra-articular (IA) injection of a proprietary 2.5% cross-linked polyacrylamide hydrogel (PAAG) for the treatment of knee OA symptoms and signs.*

Methods. *Patients with knee OA were invited into a prospective open-label cohort study. The patients received up to two IA injections of 3 ml of PAAG 1 month apart. The WOMAC questionnaire was used to estimate effectiveness, and was collected at baseline and after 4, 7 and 13 months. Primary outcome was change from baseline for the WOMAC pain subscale after 4 months (Normalised to 0–100 points; 100 worst). Data was analysed using a mixed-effect model without imputation of missing data.*

Results. *84 patients (48 females) received IA PAAG. Of these WOMAC data were available from 62 after 4 months, 59 after 7 months, and 56 after 13 months. There were statistically and clinically significant reductions in WOMAC pain after 4 months (mean change -14.6 points [95% CI: -18.9 to -10.2]; p<.0001). Similar results were found in WOMAC stiffness, physical function, and WOMAC total. The improvement was sustained throughout the observation period.*

Conclusion. *These results suggest beneficial effects of IA injection of PAAG on knee OA symptoms, even in the long term (1 year). This initial estimation of effectiveness is promising but needs to be confirmed in a randomised study with adequate measures taken to reduce risk of bias.*

Background

Osteoarthritis (OA) of the knee is very common and characterised by pain and physical disability. Due to the pivotal role of the knee in basic mobility and locomotion, knee OA is associated with significant impairments and limitations in basic activities of daily living, such as walking and moving around, self-care, and housekeeping activities as well as participation in community life and recreational activities – all contributing to reduced quality of life and needs for assistance.

There is a drought in available effective non-surgical treatments for knee OA with long-lasting interventions needed as the available options only provide short term small to moderate effects (1). However, new therapeutics and devices are being introduced, such as polyacrylamide gels. Polyacrylamide hydrogels are non-toxic (2), non-degradable synthetic products, used for years in the augmentation of soft tissues (3-5). Tissue compatibility has been tested and found excellent and it has been demonstrated that the gel retains its volume after seven months (6). Histopathological observations have verified that the hydrogel supports cellular growth and proliferation allowing vessel in-growth *in vivo* (7) forming a thin vessel-bearing network inside the gel. Animal studies have shown that intra-articular (IA) injection of a proprietary 2.5% cross-linked polyacrylamide gel (PAAG) significantly alleviates lameness and joint effusion over 2 years among horses with OA without adverse effects observed (8). Thus, IA injection of PAAG may be a promising treatment for knee OA in humans, albeit with a need for further scientific evaluation of effectiveness and safety.

The present observational study has been conducted to establish an initial estimate of effectiveness of intra-articular injection of PAAG for the treatment of pain and other symptoms in OA of the knee.

Methods

This study is an observational study of the effectiveness of intra-articular (IA) injection of PAAG with data collected from March 2010 to October 2017. Inclusion criteria were adults with a clinical diagnosis of OA of the knee according to the American College of Rheumatology who gave informed consent to follow-up visits after the IA injection of PAAG and a valid WOMAC questionnaire at baseline. Exclusion criteria were: Contra indications to IA injection (*e.g.* skin disease as judged by the treating rheumatolo-

gist) and other types of arthritis (*e.g.* rheumatoid arthritis). The protocol for this study was submitted to the local Health Research Ethics committee (ref.no: H-15006426) and the Danish Health and Medicines Authority before any study related activities. All patients gave informed consent prior to participation, and the study was conducted according to the principles of good clinical practice.

The patients received up to two treatments within one month and attended clinical follow-up visits 4, 7 and 13 months after the initial treatment. There were no restrictions regarding analgesics (*e.g.* paracetamol or NSAIDs).

Table I. Patient characteristics and baseline WOMAC scores.

n=84	Mean (SD)	Range
Age, years	68.9 (10.0)	36-91
Females, n (%)	48 (57%)	-
Height, cm	172.5 (9.3)	150.0-197.0
Weight, kg	80.2 (16.7)	53-154
BMI kg/m*m	26.9 (4.8)	17.8-50.8
Kellgren-Lawrence grade, n (%)		
1	3 (4%)	-
2	20 (24%)	-
3	39 (46%)	-
4	22 (26%)	-
WOMAC, 0–100		
WOMAC pain	44.3 (17.2)	5.0-75.0
WOMAC stiffness	44.9 (22.0)	0-87.5
WOMAC function	42.2 (20.7)	0-88.2
WOMAC total	42.8 (18.6)	0-84.4

Treatments administered

In this study, a proprietary 2.5% cross-linked polyacrylamide gel (PAAG) manufactured by Contura International A/S was used. 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, stable, and sterile.

PAAG was provided in sterile, pre-filled 1 ml sealed syringes to be injected intra-articularly with a sterile 21G x 2 inch (0.8x50 mm) needle. PAAG is classified as a Class IIb device under Council Directive 93/42/EEC on medical devices. Each patient received up to two intra-articular injections of PAAG (3 ml) approximately one month apart (±2 weeks).

Outcomes

The primary outcome measure was change from baseline in the pain subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire (9) at 4 months. Secondary outcome measures were changes in baseline in the physical function and stiffness subscales of WOMAC as well as the total WOMAC score. WOMAC scores were collected 4, 7, and 13 months after the first treatment (±2 weeks).

The WOMAC is a self-reported questionnaire with a total of 24 items used to assess three knee OA related health concepts, pain (5 items), stiffness (2 items), and physical function (17 items). In this study, the Danish WOMAC was used in its Likert format, and all 24 items were rated by the subject on a 5 point Likert scale with scores ranging from 0 (indicating no pain, stiffness, or difficulty) to 4 (indicating extreme pain, stiffness, or difficulty). The three WOMAC subscales and the total WOMAC score were normalised to a 0–100 scale with 0 indicating best and 100 worst.

The WOMAC referred to the treated knee. In case of bilateral symptoms, the most symptomatic knee was chosen as the target of this investigation.

Internationally applicable estimates of minimal clinically important improvements (MCII) of the WOMAC scores on the 0–100 scale have been established for patients with knee OA in a 4-week study of non-steroidal anti-inflammatory drugs (10). For the WOMAC pain subscale the MCII is 9 points; for the stiffness subscale MCII it is 7 points; for the function subscale MCII it is 6 points; and for the total WOMAC the MCII it is 7.

Statistical methods

This was a proof-of-concept study and no *a priori* sample sizes were calculated as there were no prior data available in this population to inform a calculation. However, to detect a MCID of 9 points on the WOMAC pain subscale with a conservatively set standard deviation of 25 points using a one sample analysis, a sample size of 63 would give a statistical power of 80.3%.

The main analyses were performed on the patients, who had records of WOMAC questionnaire at baseline as well as at follow up (the as-observed (AO) population), *i.e.* without imputation of missing data. Instead, we used repeated measures mixed linear models to analyse the change from baseline with adjustment for the baseline value, patients as a random factor, and time (in months from baseline) as a fixed factor.

Sensitivity analyses were done on the intention-to-treat (ITT) population that included all patients using baseline observation carried forward (BOCF) imputation of missing observations.

Results

122 knee OA patients received IA treatment of 3 ml PAAG, of which 38 did not return a baseline WOMAC questionnaire, resulting in 84 patients with pre-treatment WOMAC scores. 75 patients attended the second treatment visit, of which 72 patients received a second IA injection of 3 ml of PAAG (3 patients did not attend the second treatment visit, but continued participation). At the 4, 7, and 13 months follow-up visit WOMAC data were available from 62, 59, and 56 patients, respectively. Baseline characteristics are presented in Table I.

Table II shows the results from the main analyses and the sensitivity analyses. At the 4 months follow-up there was a statistically and clinically sig-

Table II. Results of main and sensitivity analyses. Changes from baseline in WOMAC scores after 4, 7, and 13 months.
Top: Estimates based on the as-observed data set, *i.e.* no imputation of missing observations.
Bottom: Estimates based on the intention-to-treat data set, *i.e.* with baseline observation carried forward imputation of missing observations.

Main analysis (no imputation of missing data) (n=84 at baseline)						
Change from baseline in	4 months (n=62)		7 months (n=59)		13 months (n=56)	
	Mean (95% CI)	*p*-value	Mean (95% CI)	*p*-value	Mean (95% CI)	*p*-value
WOMAC pain	-14.6 (-18.9 to -10.2)	<0.0001	-16 (-20.4 to -11.6)	<0.0001	-15.7 (-20.2 to -11.2)	<0.0001
WOMAC stiffness	-12.3 (-17.7 to -6.9)	<0.0001	-13.3 (-18.8 to -7.8)	<0.0001	-12.1 (-17.8 to -6.4)	<0.0001
WOMAC function	-13.1 (-17.4 to -8.7)	<0.0001	-12.2 (-16.6 to -7.8)	<0.0001	-9.4 (-14 to -4.9)	<0.0001
WOMAC total	-13.4 (-17.5 to -9.2)	<0.0001	-13.1 (-17.3 to -8.8)	<0.0001	-10.9 (-15.2 to -6.6)	<0.0001
Results with BOCF imputation of missing data (n=84 at baseline)						
Change from baseline in	4 months (n=84)		7 months (n=84)		13 months (n=84)	
	Mean (95% CI)	*p*-value	Mean (95% CI)	*p*-value	Mean (95% CI)	*p*-value
WOMAC pain	-11.1 (-14.9 to -7.4)	<0.0001	-11.1 (-14.9 to -7.4)	<0.0001	-11.1 (-14.8 to -7.3)	<0.0001
WOMAC stiffness	-8.2 (-12.5 to -3.8)	0.0003	-8.8 (-13.1 to -4.4)	<0.0001	-10.0 (-14.3 to -5.6)	<0.0001
WOMAC function	-10.2 (-13.7 to -6.6)	<0.0001	-8.4 (-12 to -4.9)	<0.0001	-8.0 (-11.5 to -4.4)	<0.0001
WOMAC total	-10.2 (-13.6 to -6.8)	<0.0001	-9.0 (-12.4 to -5.6)	<0.0001	-8.8 (-12.2 to -5.4)	<0.0001

BOCF: Baseline observation carried forward. WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

nificant decrease in the WOMAC pain score of -14.6 points (95% CI -18.9 to -10.2; $p<.0001$). Similarly, there were stable and statistically significant changes on all WOMAC subscales and WOMAC total over the 13 months observation period (Table II). For all WOMAC subscales and WOMAC total all estimated mean changes were greater than the MCII, albeit the 95% confidence limits did not respect the MCII for the WOMAC stiffness (4 and 13 months), and WOMAC total (13 months). The results of the sensitivity analyses showed statistically significant but generally lower estimates of effects (mean changes from baseline), consistently above the MCII (Table II).

Discussion

This observational "proof-of-concept" cohort study showed a statistically significant improvement in the WOMAC pain subscale over 4, 7, and 13 months after receiving up to 2 intra-articular injections of PAAG within approximately 1 month.

The primary outcome (pain reduction after 4 months) exceeded the established MCII of 9 points corresponding to an improvement of approximately 30% of the baseline WOMAC pain scores. The pain reduction after 4 months was supported by the secondary endpoints of improvement in the other WOMAC domains (stiffness, function and total), indicating effectiveness of intra-articular PAAG on core OA outcomes. Further, the effect seemed to be long-term, with effectiveness maintained for up to 13 months with clinically important improvements in pain at all time points.

The results were, quite robust to the sensitivity ITT analyses that showed statistically and clinically significant improvements despite the very conservative BOCF imputation of missing observations. The substantial number of missing observations (28 out of 84 (=33%) at 13 months) explains the reduced estimates in the ITT analysis. As this was an observational study done in a clinical setting, the reasons for loss to follow-up were not recorded. Nevertheless, the effectiveness results on the imputed data set did exceed the MCII in the sensitivity analyses and thus confirmed a statistically significant and clinically relevant improvement.

The mechanism of action of PAAG for treatment of knee OA is not completely elucidated. However, several indications point to more than one mechanism of action:

Most other IA therapies, such as hyaluronic acid or corticosteroids, have biological components designed to interact with receptors to cause an effect. In contrast, PAAG is an inert biocompatible foreign component and thus must have different mechanisms of action than a direct interaction with receptors. PAAG integrates in the synovial membrane through a combination of cell infiltration, vessel in-growth, and molecular water exchange (11). The biocompatible features of PAAG; free influx and outflow of nutrients, cytokines and growth factors to and from the joint cavity (6, 12), possibly generate a proliferative environment. The integration with the synovial tissue could also be speculated to increase the distance or create a barrier between inflammatory active cells in the synovium, which could then encumber cell signalling and in turn lower inflammatory activity. Another possible mechanism could be that the gel reduces penetrability of the barrier between the inflamed synovium and the joint cavity.

This study has several inherent weaknesses. Firstly, the study was observational with no control group, which introduces a high risk of bias. Further, the reasons for the substantial amount of missing data were not documented. Also, information about the amount, type, dosage or frequency of analgesics taken by the participants during the observation period was not collected,

which could bias the results. Nevertheless, the results are encouraging as there are no treatments available with long lasting effects on knee OA symptoms as indicated in the present data.

Conclusion

These initial estimates of the effectiveness of IA injection of 2.5% cross-linked PAAG for treatment of symptomatic knee OA indicates that there may be clinical benefits associated with the treatment. The results suggest that IA injection of 2.5% cross-linked PAAG may yield clinical responses that exceed the minimal clinical important improvement (MCII) and that these responses may last for up to 13 months. This is promising as no other single non-surgical treatment has such prolonged effect. However effectiveness needs to be confirmed in a large randomised study with adequate measures taken to reduce risk of bias.

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