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REVIEW ARTICLE

A Systematic Review of the Novel Compound Arthrosamid Polyacrylamide (PAAG) Hydrogel for Treatment of Knee Osteoarthritis

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ABSTRACT

Background: Polyacrylamide (PAAG) hydrogel is a novel compound that has recently become available in the UK market under the name Arthrosamid to treat osteoarthritis (OA). It adheres to and bulks up the synovial membrane and acts as a scaffold to treat the synovium. The purpose of this systematic review was to explore all available patient reported outcome measures (PROMs) and adverse events of this novel compound for a management option for knee OA.

Study Design & Methods: We undertook a comprehensive literature review of PubMed, OVID, and MEDLINE databases up until April 2022 for reports of outcomes of PAAG and OA. Using keywords: ("Polyacrylamide" OR "PAAG" OR "Arthrosamid") AND ("Osteoarthritis" OR "OA"). Study participants were those that had PAAG hydrogel intraarticular injection for knee OA. All results were screened, and relevant papers reviewed in full. This review was performed in accordance with the Preferred Reporting Items of Systematic reviews and Meta-analysis (PRISMA) 2020 statement.

Results: A total combined number of 463 patients' outcomes were reported and assessed. Statistically significant data was identified in two studies at both 52 weeks and 13 months. Indicating the efficacy of PAAG hydrogel at one year post injection. Further continuation of one of these studies provided statistically significant results at 2 years. In a Randomised Control Trial (RCT) numerically superior data was identified compared to hyaluronic acid. Injection of PAAG hydrogel intraarticularly into the knee has been shown to be safe with no long-lasting adverse events reported.

Conclusion: From the literature this PAAG hydrogel seems to be an efficacious and safe treatment option for knee OA and provides positive results for at least 2 years.

Introduction:

Osteoarthritis (OA) or arthrosis is a common condition affecting more than 8.5 million people across the United Kingdom, with a total financial burden of £250 million yearly on community services[1]. Knee OA has the highest prevalence in the UK[2]. It is a chronic condition characterised by pain, swelling and ultimately physical disability. Mainstay treatment options include lifestyle changes and pain management. With treatment for end-stage disease being total knee arthroplasty. One option for pain control is injectable therapy such as hyaluronic acid, corticosteroids, and Platelet Rich Plasma. The most popular of these, corticosteroids, has not been shown to have impactful long-term outcomes[3]. Evidence has shown that corticosteroid injections can also be toxic to the knee cartilage[4]. This leaves room for an evidence-based treatment that provides adequate symptomatic improvement over a significantly longer period.

Our paper explores the novel compound polyacrylamide hydrogel (PAAG), an injectable solution of 2.5% cross-linked polyacrylamide and 97.5% non-pyrogenic water, marketed by Contura international as Arthrosamid®. PAAG hydrogel is a non-toxic[5], inert[6] and non- biodegradable synthetic product[7], that allows normal exchange of water with surrounding tissues due to its unique molecular structure[8]. PAAG hydrogel has been used safely in humans for many years as soft tissue augmentation in the face[9] and used for symptom management in female stress incontinence[10]. This paper, to our knowledge, will be the first systematic review of its use for knee OA.

Proposed Method of Action of PAAG hydrogel in knee OA

PAAG hydrogel has shown a novel method of action different to other currently used viscosupplements. Existing options typically have a short-acting effect, with Hyaluronic acid exhibiting a lifespan of three weeks in cartilage in the knee. In contrast, PAAG has more chronic long-acting effects that involve adherence to the synovial membrane, where it acts as a physical buffer and scaffold, allowing integration of a *de novo* layer of infiltrating synovial lining cells[11,12]. This layer also acts as a scaffold allowing integration into the synovial membrane forming a de novo layer of infiltrating synovial lining cells[13]. Histopathological results show angiogenesis and increased cartilage and synovial cell numbers[14] within the PAAG hydrogel.

Inflammatory cascade products such as cytokines have been shown to be increased in joints with OA[15]. The PAAG hydrogel layer acts as a 'shield' by increasing synovial membrane size and may lead to effective pain relief, reducing both inflammatory cascade products passing into the joint and number of penetrating nerve fibre endings[16].

One study showed initial distribution of the PAAG hydrogel upon weight bearing, 50% of the gel is shown to had moved to between the Patellofemoral joint[17]. The distribution of gel within the joint could also explain how PAAG can help with patients' pain, as 39% of symptomatic knee OA also have evidence of patellofemoral OA[18]. All these differing methods of actions may provide symptomatic relief for patients and for a longer period than existing options.

Administration of PAAG hydrogel

PAAG hydrogel is an injectable treatment option of knee OA. The injection is given with local anaesthetic into the knee using ultrasound (US) guidance. If there is a joint effusion present, this should be removed first. Use of US guidance for knee injections has been shown to help with greater accuracy of delivering the injection[19], ensuring it is correctly placed within the joint cavity. The same needle should stay in situ throughout the whole procedure, and antibiotics should be given prophylactically to reduce risk of infection. The total volume of PAAG injected is up to 6ml, based on results up to 26 weeks[20].

Methods

This systematic review was performed in accordance with the Preferred Reporting Items of Systematic reviews and Meta-analysis (PRISMA) 2020 statement[21]. Using the PRISMA statement and checklist as guidance allows for reviews to have higher transparency and prevent poor quality reporting of reviews. This review protocol was not registered.

Protocol Setting

Comparative prospective and retrospective observational studies alongside randomised control trials (RCT's) and cohort studies were included in the search. Inclusion criteria were studies that recorded our primary outcome- patient reported outcome measures (PROMs) of patients who received PAAG hydrogel injection for treatment of Knee OA, with follow up and change in PROMS score recorded. PROMS scoring system to be assessed will be the WOMAC score. The Western Ontario and McMaster Universities Osteoarthritis Index. The WOMAC score it is reported as WOMAC pain, WOMAC stiffness, WOMAC functional and WOMAC total,

numerically higher scores show worse severity for the patient. Where reported we will also have secondary outcomes of any adverse effects experienced because of the PAAG hydrogel intraarticular injection.

A thorough literature search was carried out for articles relevant to PAAG hydrogel treatment for Knee OA. Key terms used for the search were ("PAAG" or "Polyacrylamide" or "Arthrosamid®") AND ("osteoarthritis" or "OA") in the search of databases for articles. PubMed was used as a primary database; OVID was also used to search for relevant literature. Arthrosamids'® website was also used for search of studies. Exclusion criteria were those that were animal studies, or any that referenced PAAG hydrogel use for anything other than knee OA, and any studies without an English translation.

The online tool 'Rayyan' was used for helping to screen articles found on search of databases[22]. All papers were reviewed and screened by author AC, RM and PL. Firstly by title and abstract and then screened by further full text review if not previously excluded.

Data Extraction and synthesis

Data was extracted from included studies using a standardised proforma. Data extracted from each study included: number of participants, follow up length, PROMs pre and post injection if reported and any adverse events reported. Data extracted from all studies will be shown in a table.

Risk of Bias Assessment

All included studies will undergo a risk of bias assessment. Using Cochrane Risk of Bias tool 2.0 (ROB 2) for RCT and Cochrane Robin-I tool for retrospective studies[23].

Results

Identification of Studies

On initial search of PubMed, OVID, and MEDLINE, 253 articles were found as of April 2022. The Arthrosamid's ® website also listed two further studies, Bliddal et al 2021, the "IDA study" and Bliddal et al 2022, the "ROSA study". Data from these, as well as an additional subgroup study- Bliddal et al 2022 RCT, were received following correspondence with the global brand manager of Arthrosamid®. After checking for duplicates 10 further studies were removed. 11 studies lacked an English translation and were removed. Of the remaining 235 studies and reports that were screened, five studies were included in the final systematic review. The total of 5 studies included from the 235 identified, all met the inclusion criteria, of being human studies of results post injection of PAAG hydrogel for treatment of knee OA which included data for primary or secondary outcomes of our study. 230 studies that were originally identified did not meet the inclusion criteria, reasons for exclusion include being animal studies, not including primary or secondary outcome data or being studies not deemed relevant for this systematic review. Table 1 provides a summary of each of the studies including study size, type, duration, and brief results, whilst Table 2 details the full results. Figure 1 shows the PRISMA flow diagram of screened and reviewed articles created using "estech.shinyapps.io", a tool used for creating PRISMA compliant flow diagrams[24].

Table 1 *Summary of all relevant studies found on PAAG hydrogels for Knee OA*

Study	Study Type	Results
Henrikson et al, 2018[25]	Observational proof-of-concept cohort study. Cohort size of 84 patients (48 female). With data input at 4 months, 7 months, and 13 months, 62, 59 and 56 patients respectively continuing with the study.	Statistically significant results with use of PAAG hydrogels after 13 months.
Bliddal et al, 2021[26]	Prospective study with 49 participants (31 female). With a follow up initially over 6 months, 1 year and then extended to 2 years. 46, 46 and 35 participants continued at corresponding time points.	Statistically significant and clinically significant results at 12 weeks continued to 52 weeks based on WOMAC pain scale.
Bliddal et al, 2022	Randomised Control Trial of PAAG hydrogel vs Hyaluronic acid- one year performance RCT. 239 participants, randomised in a 1:1 fashion between PAAG hydrogel and hyaluronic acid, 119 and 120 participants respectively.	At 26 weeks PAAG was non-inferior to hyaluronic acid based on WOMAC pain scale at 52 weeks the PAAG was numerically superior to hyaluronic acid

		but with non-statistically significant results.
Bliddal et al, 2022 (subgroup of above trial)	Randomised Control Trial of PAAG hydrogel vs Hyaluronic acid in age, BMI (Body Mass Index) and Kellgren-Lawrence subgroups (KL)- Subgroup analysis of a randomised control trial. 239 participants, randomised in a 1:1 fashion between PAAG hydrogel and hyaluronic acid, 119 and 120 participants respectively.	PAAG hydrogel was numerically better in all subgroups except for KL group 4. Statistically significant evidence for normal BMI (18.5-24.9) and those <70 years old.
Overgaard et al, 2018[27]	Safety of Intra-articular Polyacrylamide Hydrogel for the Treatment of Knee OA symptoms: a retrospective case series. 91 participants reporting any adverse events.	Majority of cohort 66 reported no adverse effects. 15 reported a sensation of distension. 14 of these patients reported this leaving within days to weeks. 2 participants sought medical attention after PAAG hydrogel injection. No allergic reactions were reported.

Table 2 summary of results from each study assessed

Study	Mean change from baseline PROMs reported by study	Adverse Events reported in study
Henrikson et al, 2018 N=84 original participants	4 Months: (n=62) -WOMAC Pain= -14.6 (95% CI -18.9 to -10.2, p<0.0001) -WOMAC Stiffness= -12.3 (95% CI -17.7 to -6.9, p<0.0001) -WOMAC Function= -13.1 (95% CI -17.4 to -8.7, p <0.0001) -WOMAC Total= -13.4 (95% CI -17.5 to -9.2, p<0.0001) 7Months- (n=59) -WOMAC Pain= -16.0 (95% CI -20.4 to -11.6, p<0.0001) -WOMAC Stiffness= -13.3 (95% CI -18.8 to -7.8, p<0.0001) -WOMAC Function= -12.2 (95% CI -16.6 to -7.8, p<0.0001) -WOMAC Total= -13.1 (95% CI -17.3 to -8.8, p<0.0001) 13 Months- (n=56) -WOMAC Pain= -15.7 (95% CI -20.2 to -11.2, p<0.0001) -WOMAC Stiffness= -16.0 (95% CI -17.8 to -6.4, p<0.0001) -WOMAC Function= -9.4 (95% CI -14.0 to -4.9, p<0.0001) -WOMAC Total= -10.9 (95% CI –15.2to -6.6, p<0.0001)	Not reported
Bliddal et al 2021	4 weeks (n=49) WOMAC pain subscale= -15.4 (95% CI -19.7 to -11.2) WOMAC stiffness subscale= -11.4 (95% CI -16.2 to -6.6) WOMAC Physical Function subscale= -13.2 (-16.9 to -9.6) 13 weeks (n=48) WOMAC pain subscale= -18.3 (95% CI -23.4 to -13.3) WOMAC stiffness subscale= -21.0 (95% CI -26.4 to -15.7) WOMAC Physical function subscale= -17.2 (95% CI -21.5 to -13.1) 26 weeks (n=46) WOMAC pain subscale= -20.8 (95% CI -26.3 to -15.3) WOMAC stiffness subscale= -17.5 (95% CI -23.3 to -11.8) WOMAC Physical Function subscale= -18.0 (95% CI -23.0 to -13.1) 52 weeks (n=46)	MSK and connective tissue(26 weeks) Arthralgia- N=8, E=8 Joint swelling- N=3, E=3 Synovial cyst- N=2, E=2 Back pain- N=1, E=1 Bursitis- N=1, E=1 Joint effusion- N=1, E=1 Pain in extremity- N=1, E=1 GI disorders(26 weeks) Abdominal pain- N=1 E=1 GORD- N=1, E=1

	WOMAC pain subscale= -18.3 (95% CI -23.3 to -13.3, p=<0.0001) 2 years (n=32) WOMAC pain subscale= -19.2 (95% CI -25.8 to 12.7, p=<0.0001) WOMAC stiffness subscale= -16.9 (95% CI -24.4 to -9.5, p=<0.0001) WOMAC physical function subscale= -19.1 (95% CI -24.6 to -13.7, p=0.0001)	Infections(26 weeks) Nasopharyngitis- N=1, E=1 Skin infections- N=1, E=1 Cardiac Disorders(26 weeks) AF- N=1, E=1 Injury, poisoning, and procedural complaints(26 weeks) Upper limb fracture- N=1, E=1 Metabolism and Nutrtition Disorder(26 weeks) Diabetes Mellitus- N=1, E=1 Not coded-N=1,E=1 Total= N=20, E=27 Serious AE's= N=2, E=2 Found not to be due to device or injection
Bliddal et al, 2022	Synvisc-One- n=120 Arthrosamid- n=119 WOMAC pain subscale (26 weeks) -Synvisc-One= -14.8 (95% CI -17.9 to -11.7, p= noninferior) -Arthrosamid= -18.4 (95% CI -21.5 to -15.3, p=noninferior) -Treatment difference= 3.6 (95% CI -0.9 to 8.1) WOMAC pain subscale (52 weeks) -Synvisc-One= -13.3 (95% CI -16.7 to -10.0, p=0.0572) -Arthrosamid= -17.9 (95% CI -21.3 to -14.6, p=0.0572) - Treatment difference= 4.6 (95% CI -0.1 to 9.4) WOMAC stiffness subscale (52 weeks) -Synvisc-One= -12.9 ((95% CI -17.2 to -8.6, p=0.1080) -Arthrosamid= -17.9 (95% CI -22.2 to -13.5, p=0.1080) - Treatment difference= 5.0 (95% CI -1.1 to 11.1) WOMAC Physical Function subscale (52 weeks) -Synvisc-One= -15.2 (95% CI -18.6 to -11.8, p=0.3006) -Arthrosamid= -17.7 (95% CI -21.2 to -14.3, p=0.3006) -Treatment difference= 2.5 (95% CI -2.3 to 7.4) Patient Global assessment (52 weeks) -Synvisc-One= -13.5 (95% CI -18.1 to -8.9, p=0.2275) -Arthrosamid= -17.5 (95% CI -22.2 to -12.9, p=0.2275) - Treatment difference= 4.0 (95% CI -2.5 to 10.6)	Not reported

Bliddal et al 2022, Subgroup Data- all at 52 weeks	WOMAC pain subscale Age <70 -Synvisc-One (n=62) = -14.0 (95% CI -18.3 to -9.6, p=0.0195) -Arthrosamid (n-63) = -21.3 (95%CI -25.5 to -17.0, p=0.0195) -Treatment difference= 7.3 (95% CI 1.2 to 13.4) Age >70 -Synvisc-one (n=47) = -12.5 (95% CI -17.6 to -7.4, p=0.7970) -Arthrosmaid (n=44) = -13.4 (95% CI -18.7 to -8.2, p=0.7970) -Treatment difference= 1.0 (95% CI -6.3 to 8.2) Normal BMI (18.5-24.9Kg/m2) -Synvisc-One (n=35) = -10.6 (95% CI -15.8 to -5.3, p=0.0110) -Arthrosamid (n=24) = -21.4 (95% CI -21.0 to -11.3, p=0.0110) -Treatment difference= 10.9 (95% CI 2.6 to 19.1) Overweight (25-29.9Kg/m2) -Synvisc-One (n=51) = -14.2 (95% CI –19.5 to -9.2, p=0.6114) -Arthrosamid (n=57) = -16.1 (95% CI -21.0to -11.7, p=0.6114) -Treatment difference= 1.8(95% CI 5.3 to 8.9) Obese (>30kg/m2) -Synvisc-One (n=23) = -14.5 (95% CI -22.7to -6.2, p=0.5565) -Arthrosamid (n=26) = -17.8 (95% CI -25.6 to -10.0, p=0.5565) -Treatment difference= 3.3 (95% CI -8.0 to 14.7) Kellgren-Lawrence Grade 2 -Synvisc-One (n=54) = -15.3 (95% CI -20.4 to -10.3, p=0.3305) -Arthrosamid (n=61) = -18.8 (95% CI -23.5 to -14.1 p=0.3305) -Treatment difference= 3.5 (95% CI -3.6 to 10.0) Kellgren-Lawrence Grade 3 Synvisc-One (n=40) = -11.0 (95% CI -16.5 to -5.5, p=0.0.0722) -Arthrosamid (n=35) = -18.4 (95% CI -24.3 to -12.5p=0.0722) -Treatment difference= 7.4 (95% CI -0.7 to 15.5) Kellgren-Lawrence Grade 4 Synvisc-One (n=15) = -13.1 (95% CI -21.9 to -4.3, p=0.0572) -Arthrosamid (n=11) = -10.3 (95% CI -20.6 to 0.0 p=0.0572) -Treatment difference= -2.8 (95% CI -0.1 to 9.4)	Not reported
Overgaard et al, 2018	Not reported	Soreness= n=3 (7.3%) Burning sensation n=1 (2.4%) Sensation of distension n=15 (36.6%) Skin or joint pricking sensation n=3 (7.3%) Numbness n=1 (2.4%) Cold sensation n=1 (2.4%) Heat sensation n=1 (2.4%) Reduced range of motion n=4 (9.8%) Stiffness n=2 (4.9%) Total 41 100%

Demographics of Studies

Five studies were included in the final systematic review, two published papers and three reports, with a combined total of 463 patients. The sample size of the studies ranged from 49 to 239. Follow up post injection of PAAG hydrogel ranged from 4 weeks to 2 years, with all studies reporting data at either 13 months or 52 weeks. There were no noticed differences in studies between mean age of patients.

PROM's

PROMs data was included in four of the five studies with the exception being the retrospective study from Overgaard et al [27]which only detailed adverse events (Table 2). The WOMAC stiffness and WOMAC physical function scores were reported alongside WOMAC pain subscale in each of the four studies apart from the Bliddal et al 2022 subgroup data which only detailed the latter. Table 2 presents a summary of full PROMs scores reported. All studies demonstrated a numerical mean reduction in WOMAC pain, stiffness, and physical function from the pre-injection PROMs. No studies demonstrated a worsening of patients PROMs scores.

Henrikson et al, 2018[25] and Bliddal et al[26], 2021 demonstrated statistically significant reduction in WOMAC pain, stiffness and physical function scores post PAAG injection, at 13 months and 2 years respectively. WOMAC pain subscale demonstrated results of -15.7 (95% CI -20.2 to -11.2, p<0.0001) in Henrikson et al[25] and -19.2 (95% CI -25.8 to 12.7, p=<0.0001) in Bliddal et al, 2021[26]. WOMAC stiffness demonstrated -16.0 (95% CI -17.8 to -6.4, p<0.0001) and -16.9 (95% CI -24.4 to -9.5, p=<0.0001) respectively. WOMAC Physical function demonstrated in Henrikson et al[25], -9.4 (95% CI -14.0 to -4.9, p<0.0001) and in Bliddal et al -19.1 (95% CI -24.6 to -13.7, p=0.0001). This demonstrates that PAAG hydrogel when injected intra-articularly in those with Knee OA, has a positive effect on PROMs.

Bliddal et al, 2022 RCT demonstrated numerically superior results without statistical significance in WOMAC pain, stiffness and physical function compared to Hyaluronic acid treatment option at 52 weeks. WOMAC pain, stiffness, and physical function results were -17.9 (95% CI -21.3 to -14.6, p=0.0572), -17.9 (95% CI -22.2 to -13.5, p=0.1080), -17.7 (95% CI -21.2 to -14.3, p=0.3006) for PAAG hydrogel. Hyaluronic acid demonstrated the following results -13.3 (95% CI -16.7 to -10.0, p=0.0572), -12.9 ((95% CI -17.2 to -8.6, p=0.1080), -15.2 (95% CI -18.6 to -11.8, p=0.3006). Treatment difference when comparing mean change in baseline WOMAC scores show a larger difference and superiority of PAAG hydrogel to that of Hyaluronic acid at 52 weeks, treatment difference= 4.6 (95% CI -0.1 to 9.4), compared to the 26-week results, treatment difference 3.6 (95% CI -0.9 to 8.1).

Bliddal et al, 2022 RCT subgroup study categorised results into groups of differing age, Body mass index (BMI) and Kellgren-Lawrence (KL) grade. Statistical significance was shown in groups of patients who were under the age of 70, and in those with normal BMI (18-24.9 kg/ m^2) who received PAAG hydrogel injection compared to those who had Hyaluronic acid. Numerically superior results were demonstrated in all other groups, other than KL grade 4 patients, where PAAG hydrogel was inferior to Hyaluronic acid. At KL grade 4 PAAG hydrogel still showed WOMAC pain subscale improvement from baseline.

Adverse Events

Adverse events data was reported in two studies of our systematic review. Overgaard et al, 2018 [27] and Bliddal et al 2021[26]. No long term significant adverse events were reported. A total of 41 adverse events were reported by Overgaard et al in 91 participants and 27 events in 20 patients in Bliddal et al, 2021. Overgaard reported 7 severe cases of patient reported severity, all had resolved within months. Bliddal et al 2021, had 0 severe reported cases of severity with 22 events being scored as mild by the participants. The most common adverse event reported was a sensation of distension with 15 patients (16.5%) reporting this in Overgaard et al, 2018[27]. A common adverse event reported in both studies was arthralgia with eight (40%) and two (2.2%) in Bliddal et al and Overgaard et al respectively. Arthralgia experienced had resolved between days and weeks all cases. Two Serious adverse events were reported by Bliddal et al, although both were found not to be related to the injection of PAAG hydrogel itself.

Risk Of Bias Assessment

For two of the studies which contained initial results, Bliddal et al, 2022, it was not possible to conduct risk of bias assessment with the information available. Risk of bias was assessed using the Cochrane Robin-I tool[23] for the three remaining studies (Henrikson et al, Bliddal et al 2021, and Overgaard et al). The results of risk of Bias assessment can be seen in *appendix 2*. Two papers identified a high risk of bias due to there being no control group in the study. Henrikson et al, as a

retrospective study identifies recall bias as a point to be taken into account.

Discussion

We have carried out a systematic review of five total studies investigating the effectiveness of the novel compound PAAG hydrogel as a treatment option for knee OA. Included studies all show a reduction in mean PROMs score post injection of PAAG hydrogel, supporting its use as a treatment for knee OA. All studies that included PROMs as an outcome used WOMAC meaning there was good homogeneity between studies. Studies by Henrikson and Bliddal both show statistically significant improvement for patients' pain, stiffness, and physical function post treatment with PAAG hydrogel. No studies reported any long term or serious adverse events post injection, adding to the already existing safety data for PAAG hydrogel when used for other therapeutic uses [9-10].

We included one RCT in this systematic review, Bliddal et al 2022 which compared novel PAAG hydrogel to an existing treatment option, Hyaluronic acid in 239 patients. At 52 weeks numerically superior data was shown by those who received the PAAG hydrogel injection in WOMAC pain, stiffness, and physical function. This study had a low risk of bias with it being a double-blind trial. Despite not being a statistically significant difference, the treatment difference between the reduction of mean WOMAC score increased between 26-52 weeks. As described above with PAAG hydrogels novel proposed method of action this is in keeping with it having a longer-term effect than currently available options. To confirm this hypothesis this RCT should be continued, and participants followed up for a longer period.

When comparing results from across the studies we identified, Bliddal et al 2021 and Henrikson et al 2018 reported the biggest difference of PROMS at time points throughout the study. At 4 months Henrikson et al showed a mean reduction of WOMAC pain subscale of -14.6 and Bliddal et al, 3-month data, showed a mean reduction of WOMAC pain subscale of -18.3. When we looked at the data for 13 months in Henrikson et al the mean WOMAC pain reduction was -15.7- and 12-month data for Bliddal et al showed a result of -18.3. Data was also reported at 2 years in Bliddal et al with a mean WOMAC reduction of -19.2, there was no comparable data in Henrikson et al. The average WOMAC pain subscale reduction between these two studies at both 3-4 months and 12-13 months was calculated, these values were respectively -16.45 and -17. When comparing the average of these studies this highlights the similarities among data reported in the studies rather than any obvious large differences. Bliddal et al 2021 data scores higher at all time points reported than Henrikson et al, but the data between studies has a trend of being more similar than it is different. The small variation of results between these two studies could be due to number of reasons such as differing patient reporting of PROM's as they are still open to a subjective report from patients. The data between the two studies being more similar could show that there is a consistency between the studies looking at the effect of PAAG hydrogels.

We identified the following limitations to our systematic review. One identified limitation was that of the study size, as a novel compound for knee OA there were not many available studies to include in this systematic review. The total combined patient cohort size of 439 despite being the first and largest of our knowledge to look at PAAG hydrogel for use in knee OA, can be considered a small cohort size for systematic review. The largest included study was Bliddal et al, 2022 with 239 participants and the smallest was Bliddal et al, 2021 with 49 participants.

The objective of our study was to review all current literature for PAAG hydrogel use in knee OA and assess its efficacy, safety, and longevity as a therapeutic choice. This has shown that PAAG hydrogels have numerically better efficacy as a treatment option compared to Hyaluronic acid and has shown no worrying adverse events when injected intra-articularly, with a reduction in mean patient PROMs being recordable at 2 years. We recommend for a further review of literature as more are completed on PAAG hydrogel for knee OA and for current studies to continue follow up to assess fully how long a reduction of mean WOMAC score is shown.

Conclusion

Following this systematic review of the current literature the available data shows that the PAAG hydrogels represent a good treatment option for those suffering with knee OA. All studies included show a reduction in mean WOMAC pain, stiffness, physical function score over all periods of time at follow up and show numerical superiority to current options such as hyaluronic acid in a randomised control trial. PAAG hydrogels have also been shown to be safe and have no long-term effect when injected into the knee[26,27].

For completeness we would recommend continuing follow up data on the RCT of PAAG hydrogel and Hyaluronic acid. We further

recommend a large RCT taking into account the following population subgroups BMI, Age and severity of OA to assess PAAG hydrogels effectiveness between different populations.

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Appendix 1

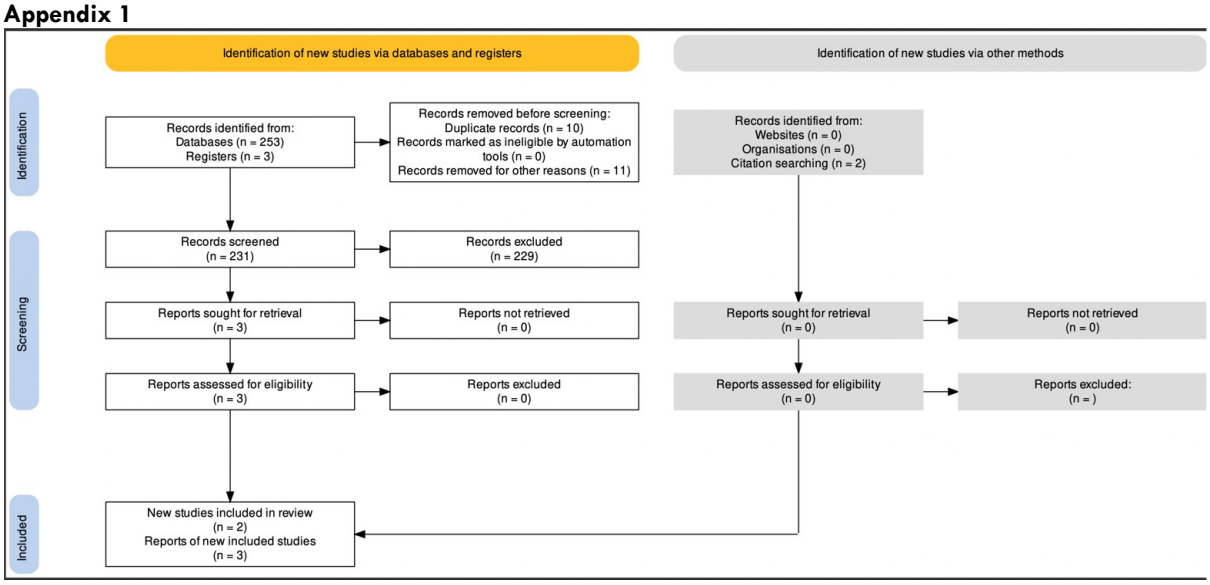

Figure 1 Flow diagram showing study selection

Appendix 2

Table showing risk of bias in each identified study

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall Bias
Henrikson et al, 2018	Low	Low	Low	Low	Low	Serious	Low	Moderate
Overgaard et al, 2018	Serious	Low	Low	Moderate	Critical	Low	Low	Serious
Bliddal et al, 2021	Moderate	No info	Low	Low	Low	Low	Moderate	Moderate