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ORTHOPAEDIC SURGERY

What is the evidence for viscosupplementation in the treatment of patients with hip osteoarthritis? Systematic review of the literature

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Abstract
Introduction Osteoarthritis (OA) is a disease of the synovial joints and is the most common cause of chronic pain in the elderly. One of the treatment modalities for OA of the hip is viscosupplementation (VS). Today there are several different formulations of viscosupplements produced by different manufactures of different molecular weights. The objective of this review is to asses the efficacy of VS treatment of hip OA osteoarthritis in the current literature.
Material and methods The following databases were searched: Medline (period 1966 to November 2006), Cochrane Database of Systematic Reviews (1988 to November 2006), Cochrane Clinical Trial Register (1988 to November 2006), Database of Abstracts on Reviews and Effectiveness, Current Controlled Trials, National Research Register and Embase (January 1988 to November 2006). The search terms [osteoarthritis, hip (joint), viscosupplementation, hyaluronic acid, hyaluronan, sodium hyaluronate and trade names] were applied to identify all studies relating to the use of VS therapy for OA of the hip joint.
Results Sixteen articles concerning the efficacy of a total of 509 patients undergoing VS treatment for hip OA were included. Twelve European studies, three Turkish studies and one American study with Levels of Evidence ranging from I to IV evaluated the following products: Hylan G-F 20, Hyalgan®, Ostenil®, Durolane®, Fermatron® and Orthovisc®. Heterogeneity of included studies did not allow pooled analysis of data.
Discussion Despite the relatively low Level of Evidence of the included studies, VS performed under fluoroscopic or ultrasound guidance seems an effective treatment and may be an alternative treatment of hip OA. Intra-articular injection of (derivatives of) HA into the hip joint appears to be safe and well tolerated. However, VS cannot be recommended as standard therapy in hip OA for wider populations, and therefore the indications remain a highly individualised matter.

Keywords Review · Osteoarthritis · Hip joint · Viscosupplementation · Hyaluronan · Hyaluronic acid

Abbreviations

AAOS	American Association Orthopaedic Surgeons
CEBM	Centre for Evidence Based Medicine
HA	Hyaluronic acid
IA	Intra-articular
MDa	Million Daltons
MW	Molecular weight
NASHA	Non-animal stabilised hyaluronic acid
NSAID	Non-steroidal anti inflammatory drug
OA	Osteo-arthritis
PAS	Pain analogue scale
RCT	Randomised controlled trial

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THA	Total hip arthroplasty
VAS	Visual analogue scale
VS	Viscosupplementation
WOMAC	Western Ontario and McMaster Universities osteoarthritis index
OMERACT	Outcome measures in rheumatology

Introduction

Osteoarthritis (OA) is a disease of the synovial joints in which cartilage is lost, subchondral bone alters, and new bone is formed around the joint and is the most common cause of chronic pain in the elderly [42]. In OA the molecular weight and concentration of hyaluronan in synovial fluid is diminished. The hip is a frequent site of OA and the prevalence ranges from 7 to 25% in the Caucasian European population older than 55 years [17, 24, 41]. With the increasing longevity of the general population, OA adds to the enormous health care costs involved [29]. With the total joint replacement generally reserved for severe arthritis, there are several options available for the non-operative treatment of hip OA: re-education/counselling of patients, weight loss, physiotherapy, occupational therapy, ambulatory aids, orthotics, simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroid intra-articular (IA) injections and glucocorticoids [20]. None of them has shown to slow disease progression or reverse joint damage in humans [27].

The principle of viscosupplementation (VS) was pioneered by Balazs [3] Nowadays, there are several different formulations of viscosupplements produced by different manufactures and of different molecular weights. VS using intra-articular hyaluronic acid injections may possibly benefit the hip by the following mechanisms [30]: restoration of elastic and viscous properties of the synovial fluid; anti-inflammatory effects; anti-nociceptive effects; and normalisation of hyaluronan synthesis by synoviocytes. There have been reports of effective treatment of several joints with VS. Most studies discuss the treatment of OA of the knee with VS [5] VS is an effective agent for the treatment of pain and peri-arthritis of the shoulder [21, 25]. Some authors report good results of VS treatment for temporo-mandibular disorders [8, 23] or even foot and ankle disorders [47]. The objective of this review is to assess the efficacy of VS treatment of hip OA osteoarthritis in the current literature.

Materials and methods

Inclusion criteria

The search of the literature performed in this study was limited to published original studies including male and/or female patients with a diagnosis of hip OA. The diagnosis of OA was made on the basis of detailed clinical and/or radiographic information. All VS products used for the treatment of hip OA in human were included. All different hyaluronan and hylan derivates of different MW and formulation were included. Studies comparing different types of HA, treatments such as placebo (saline, arthrocentesis) and other active treatments (corticosteroids, NSAID, glucocorticoids) were included. The OMERACT III [6] core set of outcome measures was considered for analysis; pain, physical function, patient global assessment and joint imaging (for studies of $\geq$1 year). The minimum criterion for inclusion of the trial in the review was the adequate reporting of at least one of the outcome variables. Information regarding other outcome measures and adverse events was extracted and analysed when feasible. Abstracts from scientific meetings and review articles were excluded.

Search strategy

The following databases were searched: Medline (period 1966–January 2006), Cochrane Database of Systematic Reviews (1988 to November 2006), Cochrane Clinical Trial Register (1988 to November 2006), Database of Abstracts on Reviews and Effectiveness, Current Controlled Trials, National Research Register and Embase (January 1988 to November 2006 to identify all studies relating to the use of VS therapy for OA of the hip joint. The applied search terms were: osteoarthritis, hip (joint), viscosupplementation, hyaluronic acid, hyaluronan, sodium hyaluronate and the trade names (Adant®, Arthrum®, Artz®, Biohy®, Durolane®, Fermatron®, Go-On®, Hylan G-F 20, Hyalgan®, NRD-101®, Orthovisc®, Ostenil®, Replasyn, ® SLM-10®, Suplasyn®, Synject®, Zeel Compositum®). Two authors independently performed the search strategy comparing results afterwards. Furthermore, the lists of references of retrieved publications were manually checked for additional studies potentially meeting the inclusion criteria and not found by the electronic search. There were no language restrictions, except for studies in Arabic script. Potentially, eligible non-English studies were translated.

Methods of the review

Selection of trials

From the literature search the title and abstract of potentially relevant articles were assessed. The full article was retrieved when the title or abstract revealed insufficient information to determine appropriateness for inclusion. All identified studies were assessed independently by two authors (M.v.d.B. and B.L.) for inclusion using the mentioned criteria. Disagreement was resolved by group discussion with arbitration by a third author (M.M.) where differences remained.

Data collection

The data from the included studies were extracted using a pre-piloted data extraction-tool (M.v.d.B.), and were verified by a second author (B.L.). Disagreement was resolved in a consensus meeting or by third party adjudication (M.M.) when necessary. Studies were not blinded for author, affiliation and source [22, 40, 46]. If necessary, authors were contacted in order to complete this and for further information on methodology.

Assessment of methodological quality

Methodological quality of included studies was assessed by assigning Levels of Evidence as previously defined by the Center for Evidence Based Medicine (CEBM) [18]. In short, for studies on therapy or prognosis, Level I is attributed to well designed and performed randomised controlled trials, Level II are cohort studies, Level III are case–control studies, Level IV are case series and Level V are expert opinion articles.

Results

We found 16 articles concerning the efficacy of 509 patients with VS treatment for their hip OA (Table 1) [7, 9–11, 13, 31–34, 36, 37, 39, 43–45]. Twelve studies were performed in European countries [7, 9, 10, 13, 31–34, 36, 37, 39], three studies in Turkey [11, 38, 43] and one in the US [44]. Two original Italian manuscripts were translated into English [36, 37]. The Levels of Evidence ranged from I to IV. The products that have been studied are: Hylan G-F 20 [10, 11, 13, 32–34, 36, 37, 43–45], Hyalgan® [9, 31, 39], Ostenil® [38, 43], Durolane® [7], Fermatron® [45] and Orthovisc® [45].

Hyalgan® (low MW (500–730 kDa) HA) versus methylprednisolone versus lidocaine

Qvistgaard et al. [39] performed a randomised, double blind, placebo controlled trial of 101 patients with hip OA. The study was designed with a three-armed parallel-group (Hyalgan versus methylprednisolone versus lidocaine). Three ultrasound-guided, intra-articular injections with Hyalgan were given at 14 days interval. The primary outcome measure was "pain on walking", registered on a visual analogue scale (VAS). Secondary outcome measures were "pain at rest" on a VAS, Lequesne score, WOMAC total osteoarthritis index, and "patient global assessment" on a VAS. Evaluation was performed at baseline and after 14, 28 and 90 days. There was only one patient lost to follow-up. There was no statistically significant effect between the three products on any outcome measure including the primary outcome measure, i.e. "Pain on walking", at 3 months of follow-up. Patients treated with corticosteroids experienced significant improvement during the 3 months of intervention, with an effect size indicating a moderate clinical effect. Although a similar significant result following treatment with HA could not be shown, the effect size indicated a small clinical improvement. A subgroup analysis was made on base of the presence of joint effusion but these groups were too small to analyze the differences. Beside this, there was no information given of these subgroups. Due to this, we scored only placebo controlled study as a level I study.

Hylan G-F 20 (high MW HA) versus Ostenil® (low MW HA)

Tikiz et al. [43] performed a randomised controlled double blind trial in which the efficacy of IA injections of a 1.2 MDa HA (Ostenil®) versus hylan G-F 20 (Synvisc®) in 43 patients (56 hips) with hip OA was compared. The IA injections produced a significant reduction in pain VAS, Womac, and Lequesne index scores in both groups (Ostenil and Synvisc). The percentage reduction was 38 and 40% ($P < 0.001$) in VAS pain score, 43 and 40% in WOMAC ($P < 0.001$), and 47 and 49% in Lequesne index ($P < 0.001$) in the LMW HA and Hylan G-F groups at the sixth month, respectively. After three injections, improvement was prominent at the first month and maintained for 6 months in both groups. However, there were no significant differences in outcome between any of the measurements at the first, third and sixth month between the two products ($P < 0.05$). No systemic AE was recorded. Local AE consisting of pain and/or swelling were noted in 3 of 32 hips (9%) injected with LMW HA and in 3 of 24 hip (12.5%) injected with hylan G-F 20. Although the method of randomization was not mentioned, we scored this study as a level I study.

Synvisc® versus Fermatron® versus Orthovisc®

Van den Bekerom et al. [45] studied 60 patients who received VS with Orthovisc® (MW: 1.0–2.9 MDa and extracted from rooster combs), Synvisc® (Hylan GF 20 with an average MW 6.0 MDa) or Fermatron® (synthetically HA analogue). All patients were candidate for surgical treatment with a THA. Overall mean VAS score (maximum 100-point VAS) decreased from 66.3 to 49.3, 6 weeks after the last infiltration. Prior to VS, 39/60 patients (65%) needed daily analgesics and/or NSAIDs. Six weeks after the last infiltration this number decreased to 16 patients, representing a decline of 59% of the patients who needed daily analgesics. Six months after the third infiltration, 27/60 patients (45%) were not operated. No differences in

Table 1 Overview of studies concerning viscosupplementation treatment of hip osteoarthritis

Study	Year	L of E	Country	Patients	Mean age	Outcome measurements	Product	Infiltrations	Interval	Follow-up
Bragatini [9]	1994	IV+	Italy	44, 50 hips	57 ± 13	Pain VAS/joint mobility	Hyalgan	3–5	1 week	180 days
Berg [7]	2004	IV−	Sweden	31	60.0 ± 10.1	Womac/pain, stiffness physical function scores(NASHA)	Durolane	1	–	3 months
Conrozier [13]	2003	IV	France	57	59.8 ± 9.5	Pain VAS/Womac/global assessment	Hylan G-F 20	1–2	30 days	90 days
Vad [44]	2003	IV−	U.S.	22, 25 hips	56.4 (39–72)	Pain VAS/AAOS Lower Limb Core Scale	Hylan G-F 20	3	1 week	1 year
Brocq [10]	2001	IV−	France	22	54.7 ± 10.0	Lequesne/Pain VAS/NSAID, analgesics use	Hylan G-F 20	1–2	30 days	180 days
Caglar-Yagci [11]	2004	IV+	Turkey	14	65.4 ± 5.9	Lequesne/Pain VAS/15 meter walking time/ patients satisfaction/analgesic use	Hylan G-F 20	3	1 week	90 days
Tikiz [43]	2005	I	Turkey	43, 56 hips	58.8 ± 9.8 /60.4 ± 9.6	VAS/Womac/Lequesne	Hylan G-F 20/Ostenil	3	1 week	6 months
Bekerom [45]	2006	IV	Belgium	60	59 (52–68)	VAS/analgesic use/delay in need for arthroplasty	Orthovisc/Fermatron/ Hylan G-F 20	3	2 weeks	6 months
Migliore [33]	2005	IV	Italy	12	68.4 ± 11.9	Lequesne/Pain VAS/NSAID use	Hylan G-F 20	14/12	–	3 months
Migliore [37]	2005	IV	Italy	26	66 (55–78)	Lequesne/pain VAS/NSAID use	Hylan G-F 20	46/26	2 months	12 months
Migliore [31]	2003	IV	Italy	28	66 (55–78)	Lequesne/Pain VAS/NSAID use	Hylan G-F 20	78/28	2 weeks	–
Migliore [34]	2006	IV	Italy	30	70 (52–89)	Lequesne/pain VAS/NSAID use	Hylan G-F 20	55/30	1 month	6 months
Migliore [32]	2005	IV	Italy	14/19 hips	71.6 (±10.9)	Lequesne/pain VAS/NSAID use/ global assessment	Hyalgan	48/19	1 month	12 months
Migliore [36]	2006	IV	Italy	36	64.5 (37–82)	Womac/Pain VAS/NSAID use	Hylan G-F 20	1–2	3 months	18 months
Qvistgaard [39]	2006	II	Denmark	33	66(±12) (28–88)	Pain VAS (walking and at rest)/Lequesne/ Womac/Global assessment	Hyalgan	3	2 weeks	3 months
Pourbagher [38]	2005	IV−	Turkey	10	63.2 (27–80)	Pain VAS, WOMAC	Ostenil	3	1 week	6 months

efficacy were noted between the three products. Side effects of inflammatory origin were noted in five patients (8.3%). This was scored as a level IV study.

Hylan G-F 20

Eight studies evaluated the effect of Hylan G-F 20 without comparison to another product or to placebo [10, 11, 13, 33, 34, 36, 37, 44].

In the descriptive prospective pilot study without a control group (Case series) of Corozier et al. [13] 25 patients received 1 injection and 32 received 2 injections. The IA injection (2 ml) was performed under fluoroscopy, and follow-up visits were performed at day 7, 30, 60 and 90. The possibility of a second injection at day 30, 60 or 90 was considered if the reported pain level was equivalent to baseline. In the analysis, there was no difference made between the patients who received one or who received two injections. AEs, walking pain (VAS), WOMAC index and patient and physician's global assessment were recorded at each visit. Transient hip pain was reported following 10.1% of injections, but no patients withdrew from the study because of this. Two mild synovial fluid aseptic effusions occurred after the first injection. Walking pain decreased from 69.3 mm at entry to 39.5 mm at the end point ($P < 0.0001$). All other outcome measures decreased significantly. This was a level IV study.

Vad et al. [44] performed a prospective open label study on 25 patients to evaluate the efficacy of hylan G-F 20 in the treatment of hip OA. Each hip joint was injected with 2 ml of hylan G-F 20 at 2, 3 and 4 weeks and fluoroscopic lavage with 100 ml of normal saline at week 1. At 1 year follow-up, the AAOS Lower Limb Core Scale score improved from a pre-injection mean of 44.2 to a follow-up mean of 86.1 ($P < 0.05$). The mean VAS improved from a pre-injection mean of 8.7 (range 6.4–10) to a follow-up mean of 2.3 (range 0–7.2). The overall success rate was 84%. In patients with mild to moderate OA, the mean VAS decreased from a pre-injection value of 7.8 to a follow-up value of 1.7. The success rate was 90.5 in that subgroup. In patients with severe OA, the mean VAS decreased from a pre-injection value of 9.1 to a follow-up value of 3.8. The success rate was 50% in that subgroup. There were no treatment adverse events. There were two biases in this study: all patients received a hip exercise programme and all hip were lavaged at 1 week. The therapeutic effect of a hip lavage was described in the study of Egsmose [46]. Due to these biases we scored this study as a low-quality case-series (Level IV−).

Brocq et al. [10] performed in an open label prospective study 30 injections in 22 patients. All patients had a hip OA with a pain VAS greater than 40/100 and a Lequesne index greater than 6. One or two IA hip injections were performed with of hylan G-F 20 under fluoroscopic guidance. The response rate (response is a 50% decrease in the Lequesne score after 1 month as compared to baseline) was 50% (11/22) after the first injection. Five of the 11 patients who failed to respond to the first injection received a second injection on day 30; two had a response, yielding a cumulative response rate of 13/22. In the six patients followed up for more than 6 months, the improvement was sustained. They noted a self-limited exacerbation of pain during the first few days in three patients. This study was scored as a level IV study because of the small number of patients (22 patients), patients received one or two injections and the short follow-up (only six patients with a follow-up of 6 months).

Caglar Yagci et al. [11] performed in an open label prospective study 3 hylan G-F injections each to 14 patients with hip OA. These injections were applied to the hip joint with the lateral approach and ultrasound guidance. Follow-up after 30 and 90 days of treatment showed a VAS, Lequesne hip OA severity index and 15-m walking time that were significantly lower than before the treatment ($P < 0.01$). This decrease continued after the 30th day. No side effects or complications were observed. This well performed case-series was scored as a level IV+ study.

Migliore et al. [31–34, 36, 37] published six articles concerning the ultrasound guided IA injection of HA in the treatment of symptomatic hip OA. These articles include 4 original articles [33, 34, 36, 37] and two letters to the editor [31, 32]. In the four prospective open uncontrolled studies with a follow-up of 3 [33], 6 [34], 12 [37] and 18 [36] months, Migliore found that after injecting 2 ml of Hylan G-F 20 into the hip joint, the Lequesne index/Womac index, VAS pain score and NSAID consumption showed a significant reduction comparing to the baseline. The original studies were well-described case-series with different follow-up (3, 6, 12 and 18 months). Altogether, there were 151 patients evaluated but there was no information if this was a cohort re-evaluated in the different studies. Migliore et al. [35] described only good results without adverse events. The letters to the editor (level V) were actually case series and therefore scored as level IV studies.

Ostenil® (low MW HA)

Pourbagher et al. [38] prospectively studied (only) ten patients who had the diagnosis of unilateral hip OA. Every subject received three injections of sodium hyaluronate with real-time sonographic monitoring, 1 per week for 3 consecutive weeks. Each patient's outcome was assessed on the basis of pain VAS and Womac scores that were recorded before the set of injections and 2, 4 and 6 months after the third injection. Computed tomography confirmed accurate placement in all 30 injections. The average VAS pain score before the set of injections was 8.3 and the average

VAS pain score 6 months after the last injection was 4.4 ($P < 0.05$). The average Womac score at baseline was 41.6 (38–45) and the corresponding value at 6 months was 20 (12–32) ($P < 0.05$). According to the Womac data, 20% had excellent results, 60% had good outcomes and 20% had fair outcomes. Pourbagher et al. [38] stated that sonographically guided intra-articular injection of sodium hyaluronate for patients with hip osteoarthritis is easy to perform and is a safe, economical and well-tolerated form of treatment. In contrast to fluoroscopic or computed tomographic guidance, the sonographic technique exposes neither the patient nor the physician to radiation. Since there were only ten patients included, this article was scored as a level IV study.

Durolane® (non-animal stabilised HA, NASHA)

Berg et al. [7] included 31 patients with symptomatic hip OA (Kellgren Lawrence) in his prospective open label study. These patients received an IA injection of 3 ml under fluoroscopy. A potential bias was that three patients were excluded because of the higher need for analgesics. Clinical assessment (Womac, patients' physical function scores) was made at baseline, 2 weeks and 3 months. Another potential bias was that only 18 patients who had an initial good response were evaluated from 6 to 11 months after injection. At 3 months, pain (Womac A) and disability (Womac C) were reduced by 50 and 44% respectively. Six–eleven months post-infiltration the results remain satisfactory (respectively a decrease of 42 and 39% compared to baseline). At the studies end-point 68% of the patients considered their condition to have improved. Only one patient considered his condition worsened. The only treatment related adverse events were exacerbation of pain and/or stiffness in the treated hip (nine patients). They all resolved without any treatment or with NSAIDs. Due to the biases, which were mentioned in their article, this study was scored as a level IV study.

Hyalgan® (low MW (500–730 kDa) HA)

Bragantini et al. [9] treated 50 hip joints with a total of 3–5 IA injections of 20 mg/2 ml Hyalgan. The improvement observed at the end of the treatment period (30th day) was significant, compared with baseline measures for pain and joint motion. This improvement continued to increase during the follow-up period up to the 60th day and was maintained up to the 180th day. Patients with mild to moderate disease and those receiving four injections experienced the greatest symptomatic improvement. This study was scored as a well-performed case-series (level IV+ study).

Migliore et al. [32] evaluates the efficacy of 4 ml Hyalgan® in a prospective open label study. Fourteen patients with 19 hips were evaluated at 3-month intervals. The patients receive two, three or four injections. Two patients were lost to follow-up. There were significant changes at the VAS and Lequesne index at all time points compared to baseline ($P < 0.05$); the decrease in pain VAS and Lequesne index at 12 months compared to baseline was 43 and 36%, respectively. Global patient evaluation and global physician evaluation significantly improved ($P < 0.05$). Without the drop-out the NSAID use diminished significantly compared with baseline ($P < 0.05$). Patients with grade 4 Kellgren Lawrence score had poor and short-lived benefit from the injection, both for pain evaluation and functional status. This study was scored as a level IV study.

Discussion

Due to the relatively low level of evidence [18] of the included studies/articles only some preliminary conclusions can be drawn and a lot of suggestions for further investigations/research can be made. VS performed under fluoroscopic or ultrasound guidance is an effective treatment and may be an alternative treatment compared to other methods of conservative treatment or to THA of hip OA [7, 9, 10, 13, 31–34, 37]. The colour Doppler vision allowed us to avoid injecting blood vessels [35]. Ultrasound guidance is more economic and faster in comparison to fluoroscopic guidance [35]. In contrast to fluoroscopic techniques, ultrasound does not require use of radiations or iodised contrast [35].

In contrary to the case series, Qvistgaard performed a RCT and opinionated that considering the costs and invasiveness of the procedures, injections cannot be recommended as standard therapy in hip OA for wider populations, and therefore the indications remain a highly individualised matter [39]. IA injection of HA or its derivates into the hip joint appears to be safe and well tolerated [14, 39]. Adverse events frequency ranged from 10 to 30% which is slightly higher than the rates reported in VS treatment of knee OA [14]. Repeated injections did not increase the risk of adverse events [14]. Some patients experienced transient hip pain after the infiltration but made a full recovery in the following days. They all resolved without any treatment or with NSAIDs [7]. Complications are rare but a single case of septic arthritis was reported after multiple injections of hyaluronate and glucocorticoid [12]. Gout, pseudogout and chondrocalcinosis have not been reported after hip infiltrations with HA.

Between the compared products there were no significant differences in outcome at follow-up [43, 45]. Patients with mild to moderate disease and those receiving four injections experienced the greatest symptomatic improvement

[9, 32, 44]. VS is not a replacement of surgery but could delay surgical intervention and therefore it may be useful in patients who do not want to be operated and/or patients who are inoperable, i.e. in cardiovascular or lung disease [45]. We believe that treatment decisions must be made on individual basis, carefully weighing the relative benefits and disadvantages of the treatment.

There was used a strict methodology for paper selection, focussing on the above mentioned measurements. It was the initial intention of the authors to evaluate the different randomised treatment products by pooling the results of the trials. This had to be abandoned because of the heterogeneity of study designs (number of infiltrations, injection technique, outcome measurements, follow-up). Only two randomised controlled double blind trials [39, 43] and 13 case series were found in the search of the literature. Due to this lack of evidence and heterogeneity a meta-analysis of the available literature was not possible.

The technique of VS has been in use for more then 25 years in the treatment of OA of several joints and appears to be effective but there is insufficient evidence available from randomised controlled trials (RCTs) to determine the exact value of VS in the treatment of OA of the hip. There is an urgent need for sufficiently powered, high quality and appropriately reported RCTs of the therapeutic effect of different types of HA products of different molecular weight versus other treatment modalities and versus placebo. The findings of these RCTs should help to inform the selection of patients who are eligible for VS treatment for hip OA. There is need for determination of a sub-group of patients who are candidates for VS treatment, and determinants of the response to VS treatment [39]. We should be aware of publication bias; trials with positive results have more chance to be published then trials with negative results [28]. As a result in this review VS could yield more positive results then in reality.

Future research should focus on obtaining sufficiently long-term follow-up (up to 1 year) on all patients using a systematic and prospective approach. Blinding of both, the patient and investigator is possible and is recommendable in future trials. The use of well-defined and validated functional outcome measures, including patient-derived quality of life measures, is preferable. The use of standardised outcome measures is encouraged to facilitate meta-analyses and between trial comparisons. OMERACT III outcome factors [16] should be used in future trials. Finally, the recording of all relevant cost outcomes would be useful. Due to the lack of strong evidence available, a prospective placebo-controlled double blind multicentre study has been initiated to evaluate the efficacy and safety of VS in the treatment of severe symptomatic OA of the hip.

Scores

Womac Index [4]: The Western Ontario and McMaster University Osteoarthritis Index is a disease-specific and self-administered health measure developed to study patients with OA in the hip or knee. The scoring system utilises pain (5 questions), stiffness (2 questions) and physical function (17 questions) domains. The 3 domains in the WOMAC can be analysed separately or combined in a single score. Each question has 5 alternative answers with a score of 0–4 points. Maximum scores are 20 points for pain, 8 for stiffness and 68 points for physical function.

Harris Hip Score [19]: The Harris Hip Score was first developed in 1967 and is one of the most frequently used hip instruments. It is a disease-specific staff administered scoring system which was introduced to provide an evaluation system for various hip disabilities and methods of treatment. This Score gives a maximum of 100 points, with domains for pain, function, deformity and motion. Pain and function were the two basic considerations and received the heaviest weighting (44 and 47 points, respectively). Range of motion and deformity are seldom of primary importance, and therefore received five and four points, respectively. Function was subdivided into activity of daily living (ADL, 14 points) and gait (33 points).

Lequesne Algofunctional Hip Score [26]: This hip score is intended to be of value in therapeutic trials of OA in weightbearing joints, as well as a measurable appraisal of patient status at different stages. This includes the measurement of pain (five questions), walking distance (one question) and activities of daily living (four questions), with versions available for the hip and knee. Scores of each question are added together to provide a combined disease severity score. Scores of 1–4 are classified as mild osteoarthritis, 5–7 moderate, 8–10 severe, 11–13 very severe and 14 as extremely severe osteoarthritis.

AAOS Lower Limb Core Scale [2]: Developed in 1998 by a cooperative group of orthopaedic associations and specialty organisations. General pain and disability of lower limbs, with specificity for hip problems and support documentation for joint replacement. General pain and disability of lower limbs, with specificity for hip problems and support documentation for joint replacement. Includes comorbidities, the SF-36, and satisfaction with symptoms items. Lower limb: physical pain and health scale, 29 items; core disability scale, 7 items.

VAS [15]: Patient self-assessment of variations in pain intensity, measured on a simple visual analogue scale, to assess the efficacy of treatment. VAS scales are included in a number of the instruments cited in this document. 100-mm-long continuous scale of absolutes ranging from “no pain” to “extreme or unbearable pain.” Percentage of pain is determined by physical measuring from the end of the

line to the patient mark on the pain scale, and divided by total length of the line. Change in pain is estimated indirectly by taking the difference between any two recordings of pain severity.

OMERACT III outcome measures [6]: Significant progress has been made in outcome measurement procedures for OA clinical trials, and guidelines have been established by the US Food and Drug Administration, European League Against Rheumatism, the World Health Organization/International League of Associations for Rheumatology and the Group for the Respect of Ethics and Excellence in Science. However, there remains a need for further international harmonisation of measurement procedures used to establish beneficial effects in Phase III clinical trials. A key objective of the OMERACT III conference was to establish a core set of outcome measures for future phase III clinical trials. During the conference, using a combination of discussion and polling procedures, a consensus was reached by at least 90% of participants that the following four domains should be evaluated in future phase III trials of knee, hip and hand OA: pain, physical function, patient global assessment, and, for studies of 1 year or longer, joint imaging (using standardised methods for taking and rating radiographs, or any demonstrably superior imaging technique). These evidence-based preferences, achieved with a high degree of consensus, establish an international standard for future phase III trials and will also facilitate meta-analysis and Cochrane Collaborative Project goals.

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