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Research Article

Hyaluronic Acid Injections in Patients with Hip Osteoarthritis: A Systematic Review

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Abstract

Osteoarthritis (OA) is a major cause of pain and disability characterized by continual loss of cartilage, osteophyte formation, synovitis, and possible soft tissue damage. Intra-articular injections of corticosteroids or Hyaluronic Acid (HA) are used as an intervention when symptoms are refractory to other medical management options, or to delay a total hip replacement operation. HA is conceptually superior compared to other intra-articular injections as it is not suspected to expedite cartilage breakdown with serial injections and could potentially have a longer lasting therapeutic benefit than corticosteroids. Intra-articular injection of HA for symptom management of OA has the potential to increase viscosity of synovial fluid and provide pain relief to patients. Currently there is inconclusive evidence on the benefit of HA in patients with hip OA. Given the need for consensus, this systematic review evaluated the current literature to determine the benefit of HA injections in the hip. A review of databases including EMBASE, Pubmed, MEDLINE, and Cochrane Clinical Trial Register was conducted and two authors independently assessed all of the studies. Inclusion criteria dictated that only five randomized controlled trials involving the treatment of hip OA with HA compared to a control injection were considered. Five studies satisfied the inclusion criteria, and were subsequently used for analysis. Two out of four papers demonstrated significant improvement in outcome scores when HA was compared to placebo or local anesthetic injections. Two out of three papers showed no difference in outcome scores between HA and Corticosteroid injections. The third study that compared HA and Corticosteroids showed greater improvement for corticosteroid injected patients in early follow-up, but HA was shown to be superior in patients with high-grade disease in later follow-up. Given these results, it may be important to focus on patients with a higher grade of OA who may be more likely to benefit from HA injections in the hip in future research. Our recommendations for future research would be to continue evaluation of HA in the form of randomized controlled trials.

Keywords: Hyaluronic acid; Hip; Osteoarthritis

Background

Osteoarthritis (OA) is a chronic disease accompanied by increasing pain and is characterized by the continual degradation of cartilage, formation of osteophytes, presence of synovitis, and possible soft tissue damage. OA affects multiple domains of a patient's health, including physical function, social activities, relationships, socioeconomic status, emotional well being, and body image [1]. The prevalence of knee and hip joint OA is 9% in the general population [2].

Current Osteoarthritis Research Society International (OARSI) guidelines for hip OA were last published in 2008 and include non-pharmacologic recommendations for the management of OA such as education, exercise, weight loss if overweight, and walking aids [3]. If these methods failed there are limited pharmacologic interventions available for patients, which include acetaminophen/paracetamol and NSAIDS, and finally intra-articular injections hyaluronic acid or corticosteroids. If all these interventions fail to alleviate the symptoms of OA, joint replacement can be considered in appropriate patients [3]. The American College of Rheumatology (ACR) guidelines do not currently recommend intra-articular HA injections, duloxetine, or topical NSAIDs due to a lack of evidence [4].

Although current guidelines show conflicting recommendations, several intra-articular injections are currently successfully used in patients who are refractive to other methods of intervention in clinical practice [5,6]. However, intra-articular injections of hyaluronans, glucosamine/chondroitin, and corticosteroids remain controversial [7,8].

Intra-articular injection of Hyaluronic Acid (HA) is currently used as one option for conservative treatment of OA in the hip. HA is an organic polysaccharide produced by chondrocytes, synoviocytes, and fibroblasts. HA forms parts of connective, epithelial, and neural tissues and is necessary in maintaining the viscosity of the synovial fluid and protect the joint from inflammation and degradation [9]. Beyond the viscosity effects of HA in synovial fluid, HA also has a role in preventing fibronectin fragment mediated cartilage injury by coating the articular surface [10], providing chondroprotective effects on joint cells chondrocytes and synoviocytes [11], and reducing nociceptive activity [12]. The concentration of HA in joints decreases

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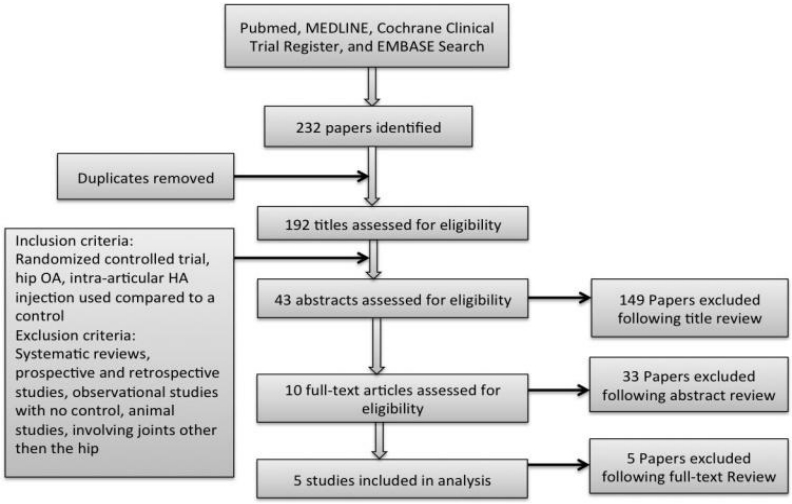

Figure 1: Flowchart summarizing the review process from the search strategy.

with age and a reduced concentration of HA has been seen in knees plagued with OA compared to normal knees [13]. Therefore, it is thought that intra-articular injection of HA into the joint affected by OA could increase the viscosity of synovial fluid, decrease inflammation, and decrease pain.

Intra -articular injections of HA have been used in clinical practice in spite of the fact that the therapeutic effect has not been extensively evaluated. Therefore, our goal was to perform a systematic review to evaluate the benefit of HA injections in the context of OA in the hip and to determine clinical situations in which this treatment would be most appropriate.

Methods

Search strategy

Our search identified randomized controlled trials that involved intra-articular treatment of OA in the hip using HA and a control. Our search included all HA products, types of administration, and grades of OA. We performed a comprehensive literature search that included all articles up until July 2014 using multiple databases including Pubmed, MEDLINE, Cochrane Clinical Trial Register, and EMBASE. The searches were independently performed and the results collected by two researchers. Using the following search terms: (Hyaluronic acid [MeSH] AND (hip osteoarthritis [MeSH] or hip arthritis) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] NOT (animals [mh], we found 192 papers.

Selection of studies

To select the appropriate studies, two researchers who met after each review to compare results conducted a review of the search results independently. First the title was reviewed, then the abstract, and finally the entire paper for inclusion or exclusion. Studies were included if they met the criteria of being a randomized controlled trial involving the treatment of hip OA with HA compared to a control injection group (for example saline, local anesthetic, or corticosteroid injections). The outcome of interest was pain and function at follow-up visits after receiving HA or control injection. We excluded studies involving joints other then the hip, systematic reviews, prospective and retrospective studies, observational studies with no control, and animal studies. All studies were independently assessed for inclusion based on our criteria and disagreement between reviewers was resolved by discussion.

Results

The initial search from all databases produced 192 studies. Following the title, abstract, and full text review five RCTs were deemed to be relevant and eligible for our review (Figure 1).

Study characteristics

Table 1 demonstrates the characteristics and patient demographics of the five randomized control trials that were selected for our systematic review analysis. Two studies compared HA to a placebo (either saline or local anesthetic), one study compared HA to corticosteroid, and two studies compared HA to corticosteroid and saline. The primary outcome measure selected for comparison amongst the studies was WOMAC or lequesne index and the secondary outcome measure was pain or patient global assessment. Baseline characteristics of patients including age, ratio of male to female, and disease severity were similar amongst all studies.

Outcomes

Table 2 displays whether or not a significant difference was found between the interventions compared for the primary and secondary outcomes measured. Qvistgaard et al. (2006), Atchia et al. (2011), and Spitzer et al. (2010) compared the effect of HA to corticosteroids. Qvistgaard et al. (2006) and Atchia et al. (2011) found no significant difference in outcome scores between HA and Corticosteroid injections. However, Spitzer et al. (2010) described improvements in WOMAC and PGA in both the corticosteroid group and the HA group with a greater improvement in the HA treated group in patients with a more severe OA. Spitzer et al. (2010) also showed that the improvement in outcome scores lasted 4 weeks for the patients injected with corticosteroid, while the patients injected with HA benefited from the injection for 26 weeks. Four studies, Qvistgaard et

Table 1: Randomized control trials of hyaluronic acid injection for osteoarthritis of the hip.

Study Author, Year of publication	Intervention	Sample Size	Mean age	% Female	KLG or Croft Stage (% of patients)
Richette et al., 2009	HA	42	60.8	64	KLG 2 (16.7%) KLG 3 (83.3%)
	Saline	43	59.5	53	KLG 2 (9.3%) KLG 3 (90.7%)
Migliore et al., 2009	HA	22	68	45	KLG 2 (4.5%) KLG 3 (95.5%)
	Local Anesthetic	20	67	50	KLG 2 (15%) KLG 3 (75%) KLG 4 (10%)
Qvistgaard et al., 2006	HA	33	65	61	Croft 1-2 (50%) Croft 3-4 (50%)
	Corticosteroids	32	69	72	Croft 1-2 (54%) Croft 3-4 (46%)
	Saline	36	64	61	Croft 1-2 (65%) Croft 3-4 (35%)
Atchia et al., 2011	HA	19	69	69	Croft 1-2(21.1%) Croft 3-4 (78.9%)
	Corticosteroid	19	67	42	Croft 1-2 (15.8%) Croft 3-4 (84.2%)
	Saline	19	70	63	Croft 1-2 (15.8%) Croft 3-4 (84.2%)
Spitzer et al., 2010	HA	156	59	52	KLG (42%)
	Corticosteroid	156	59	51	KLG (58%)

Table 2: Summary of significant differences among different interventions.

Study	Interventions Compared	Outcome Score	Significant Difference at Time Points (Treatment Yielding Improvement)	Follow up
Atchia et al.	HA *vs*. Saline	WOMAC	No Significance	56 days
		Pain (NRS)	No Significance	
	Corticosteroid *vs*. Saline	WOMAC	7, 28, 56 days (Corticosteroid)	
		Pain (NRS)	7, 28, 56 days (Corticosteroid)	
	HA *vs*. Corticosteroid	WOMAC	No Significance	
		Pain (NRS)	No Significance	
Qvistgaard et al.	HA *vs*. Saline	WOMAC	14 days (HA)	90 days
		Pain on Walking	14, 28 days (HA)	
	Corticosteroid *vs*. Saline	WOMAC	14 days (Corticosteroid)	
		Pain on Walking	14, 28 days (Corticosteroid)	
	HA *vs*. Corticosteroid	WOMAC	No Significance	
		Pain on Walking	No Significance	
Migliore et al.	HA *vs*. Local anesthetic	Lequesne Index	3, 6 months (HA)	6 months
		Pain (VAS)	3, 6 months (HA)	
Richette et al.	HA *vs*. Saline	WOMAC	No Significance	90 days
		Pain (VAS)	No Significance	
Spitzer et al.	HA *vs*. Corticosteroid	WOMAC	4 weeks (Corticosteroid), 26 weeks*(HA)	26 weeks
		Patient Global Assessment	4 weeks (Corticosteroid), 26 weeks*(HA)	

*Significance only seen in KLG 3 patients.

al. (2006), Atchia et al. (2011), Migliore et al (2009), and Richette et al. (2009) compared HA with a placebo injection. Atchia et al. (2011) and Richette et al. (2009) found no difference between the control group and HA treated groups, while Migliore et al. (2009) found a significant improvement in the HA group over the placebo group up to 6 months and Qvistgaard et al. (2006) found improvements at up to 28 days.

Discussion

There is an increasing amount of research on the efficacy of intra-articular HA injections to relieve the pain experienced in patients with hip OA. Several previous retrospective and prospective studies have shown that HA injections in patients with hip OA can significantly improve pain [14-23]. One previous study demonstrated that the use of HA injections in the hip can delay the need for total hip replacement surgery [24]. A challenge in evaluating the current literature is that these studies do not compare HA to a control injection. Therefore, our systematic review focused solely on the limited number of papers that have compared HA with a control injection in patients with hip OA.

The randomized controlled trials that we reviewed were difficult to compare and analyze due to the different outcome scores used in the studies. The type of control injection used varied between studies creating a challenge to appropriately analyze the data. When HA was compared to Corticosteroid injections no significant difference was found in two out of three studies. These three studies indicate that HA is comparable to Corticosteroid injections in improving patient symptoms and has a lengthened duration of pain relief compared to Corticosteroids, particularly in patients with higher grade OA. The short length of pain relief achieved from corticosteroid injections in other joints has been highlighted in many other reviews, with pain relief achieved for an average of 4 weeks [25-27]. Given the short-term effects of Corticosteroid, HA appears to provide longer lasting pain relief in patients with OA.

The randomized controlled trials analyzed in this systematic review are a promising start to researching other options for pain relief in hip OA. One weakness in all of the studies was the short follow-up duration with the longest follow up time of 6 months [28]. Migliore et al. (2009) and Spitzer et al. (2010) both found that HA injected patients continued to show significant improvements at 6 months compared to control injections. This length of pain improvement with HA injections are drastically longer than the 56 day pain improvement with corticosteroid [29]. Given that OA is a chronic disease, follow-up time should be extended to one year or longer in future studies to determine the specific pain relief duration achieved from HA injections. A second limitation across all studies was the sample size. Spitzer et al. (2010) had the greatest number of patients with 156 in each injection group, while other studies had patient populations ranged from 19-43. Larger sample sizes in future studies may yield more powerful comparisons. Due to the larger patient population in the Spitzer et al. (2010) study outcome scores were analyzed by the grade of the patient's hip OA. This was helpful in showing higher grade OA had the greatest duration of pain relief with HA injections. This type of analysis in future studies may help determine the hip OA patient population that would receive the greatest benefit from HA injections. A final differentiating factor between studies was the imaging modality of ultrasound or fluoroscopy used for intra-articular hip injections. Intra-articular injections are difficult to perform due to the deep nature of the joint leading to difficultly in properly palpating anatomic landmarks. Ultrasound improves visualization of the hip anatomy and disease pathology, is easily accessible, and reduces radiation exposure when compared to fluoroscopy. Ultrasound-guided hip injections have also been shown to be less painful, more convenient, and more desirable in the opinions of patients then fluoroscopy [30].

Conclusion

The randomized controlled trials analyzed in this study showed that HA is comparable to corticosteroid injections. However, when compared to saline or local anesthetic injections, 50% found HA to have no significant difference and 50% found improvements with HA. Overall, the volume of data is insufficient to determine if HA is superior to corticosteroid and placebo injections at providing pain relief. There is a need for a greater number of randomized controlled trials comparing HA to a controlled injection in order to determine if HA provides pain relief in patients with hip OA.

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