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Animal evidence for hyaluronic acid efficacy in knee trauma injuries. Review of animal-model studies

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ABSTRACT

Introduction: Intra-articular injections of hyaluronic acid (HA) could have potential interest in therapy of acute knee trauma injuries, but few results are available in humans.
Objective: We reviewed the literature for animal studies of intra-articular HA injections after knee trauma injury to determine the interest of human clinical research into and/or use of such injections for knee trauma.
Methods: Systematic literature search on MEDLINE for studies involving animal models of osteoarthritis created by acute knee trauma injury, with HA injections beginning during the 2 weeks after injury.
Results: The search revealed 14 studies with a high methodological quality: 7 related to meniscus injury, 3 ACL injury, 1 combined ACL–meniscus injury and 3 cartilage injury. The animal models were rabbits in 10 studies. Four studies demonstrated positive effects and 3 moderate effects of intra-articular HA injection for meniscus injury; 1 positive effects and 2 no effect for ACL injury; 1 positive effects for combined ACL–meniscus injury; and 2 moderate effects and 1 no effect for cartilage injury.
Conclusions: With a high strength of recommendation, intra-articular HA injections in animal models with meniscus injury improved the healing process and/or had a protective role in articular cartilage, a slightly protective role in ACL injury animal models and low or no effect on healing in articular cartilage injury animal models.

1. Introduction

Hyaluronic acid (HA) is a principal constituent of normal synovial fluid and cartilage and contributes significantly to their rheological properties and joint homeostasis (Balazs, Watson, Duff, & Roseman, 1967; Gibbs, Merrill, Smith, & Balazs, 1968; Raman, Dutta, Day, Sharma, Shaw, & Johnson, 2008; Strauss, Hart, Miller, Altman, & Rosen, 2009). In the extracellular matrix of the cartilage, in concert with proteoglycans, hyaluronans (or HA) contribute to the compressibility, resilience, and resistance to mechanical forces applied on the articular joint (Axe & Shields, 2005; Goa & Benfield, 1994). Thus, HA could have a potential interest in clinical practice.

Indeed, in clinical practice, intra-articular injections of HA are used for treating knee osteoarthritis (OA) in humans. Moreover, "it is an effective treatment for OA of the knee with beneficial effects: on pain, function and patient global assessment" (Bellamy, Campbell, Robinson, Gee, Bourne, & Wells, 2006). Apart from improving viscoelasticity (Axe & Shields, 2005), such injections are suggested to have several biological activities such as anti-inflammatory activity, direct analgesia by inhibiting joint pain receptors, and improved synthesis and decreased degradation of the matrix of the articular cartilage (Axe & Shields, 2005; Balazs et al., 1967; Huang, Yang, & Chou, 2007; Kobayashi et al., 2000; Strauss et al., 2009); they reduce pain and improve functional outcome by supplementing the endogenous synovial fluid (Raman et al., 2008). Thus, intra-articular injections of HA are an important part of the knee OA non-surgical treatment in humans.

Given these mechanisms of action, intra-articular injections of HA could also be relevant and useful in treating acute knee trauma

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injuries (anterior cruciate ligament [ACL], meniscus and/or cartilage tear) (Axe & Shields, 2005; Strauss et al., 2009). Indeed, although HA injections have long been used for treating degenerative knee articular lesions with a symptomatic efficacy and safety in humans (Bellamy et al., 2006; Raman et al., 2008), to our knowledge, there is no recommendation for its use in treating acute knee trauma injuries despite its potential indication (Axe & Shields, 2005; Strauss et al., 2009). After an acute articular injury, there are chemical and biochemical changes which contribute to the development of pain and post-traumatic OA by altering lubricants concentration (Blewis, Nugent-Derfus, Schmidt, Schumacher, & Sah, 2007; Nelson et al., 2006). Decreasing doses of synovial fluid and proteoglycans, as well as HA constituents, resulted in increased friction between articulating cartilage surfaces in a cartilage-on-cartilage friction test (Schmidt, Gastelum, Nguyen, Schumacher, & Sah, 2007). HA injections could improve and help to heal these biochemical conditions. In addition HA which present healing proprieties, could help to heal the tissue injury itself. Thus, in acute knee trauma injury, intra-articular HA therapy may provide lubrication for range-of-motion exercise, anti-inflammatory pain relief, and recovery of muscle strength of knee flexion/extension and active capacity (Huang et al., 2007; Mathies, 2006; Strachan, Smith, & Gardner, 1990; Thein, Haviv, Kidron, & Bronak, 2010).

Despite the wide potential indications for intra-articular knee injections of HA in knee trauma, including acute knee trauma injury and surgical repair of ACL and/or meniscus (Strauss et al., 2009), few studies have investigated its use (indication, efficacy, safety, tolerability, risks, complications) in humans (Chau et al., 2012; Huang et al., 2007; Mathies, 2006), and the rationale for the use is still unclear. Indeed, to our knowledge, only three randomized controlled trials (RCTs) reported information on HA injections after knee injury or knee surgery in humans (Chau et al., 2012; Huang et al., 2007; Mathies, 2006). That is insufficient to support its use and to provide practical recommendations for physicians. Therefore, as a first step for better understanding/determining HA injections effect in acute knee injury, animal-model studies may be relevant. Indeed, animal models of OA represent a mixed model in which OA (degenerative injury) is induced experimentally by acute articular trauma such as ACL or meniscus transection (Ishima, Wada, Sonoda, Harada, Katsumi, & Moriya, 2000; Sah et al., 1997; Sonoda et al., 2000). These animal models could be of interest for research into musculoskeletal pathologies and especially knee trauma injury (Strauss et al., 2009).

In keeping with this context, the purpose of the present study was to review current published reports of animal studies for levels of evidence regarding the use of intra-articular knee injection of HA after acute knee trauma injury to determine the interest of clinical research into and/or use of such injections for knee trauma in humans. Our hypothesis was that intra-articular knee injections of HA provide good results in acute traumatic articular-injury models, which may help to support its use in humans in such as conditions.

2. Materials and methods

2.1. Literature search

Two authors (PE, EC) performed a systematic search of MEDLINE via PubMed for articles of intra-articular knee injection of HA published from 1966 to 2012 using the key words "*hyaluronic acid/hyaluronan/viscosupplementation*" with "*knee*" and "*injury/anterior cruciate ligament/meniscus/cartilage/arthroscopy*". We searched for reports published in only English or French, containing an abstract, and dealing with animals. Studies were included if animal models of OA were acute traumatic articular-injury models (partial or total meniscectomy, ACL transection, cartilage defects) and if HA injection began immediately or during the two weeks after the injury. We excluded studies that focused on other knee abnormalities, overuse articular injury (strenuous exercise), treatment for osteoarthritis, immobilization, cartilage repair, microfracture technique, engineered cartilage, or allograft, or in which HA injections were combined with other intra-articular injections.

Two authors (PE, EC) independently selected the reports initially on the basis of the title and abstract, then assessed whether the study met the inclusion criteria. Then, the full article was retrieved. References of selected articles were screened for appropriate studies. Because of the paucity of comparative studies dealing with intra-articular knee injection of HA, we initially sought all types of studies. Data extraction and analysis were independently performed by two authors (PE, EC). Disagreements were resolved by consensus.

2.2. Data extraction

Data were extracted on number and types of animals, injury, procedures, HA injection procedures, time and criteria of animal analysis, results and conclusions. The types of criteria used to determine HA effects were as follows, with differences according to studies:

Morphological: macroscopic articular cartilage aspects, area of injury, and/or healing process determined by microscopy imaging (Ishima et al., 2000; Kobayashi et al., 2000);
Histological and cytological: area of injury, healing process, cell death, and/or cell proliferation explored in analyzing abnormalities in structure, cell population, Safranin-O staining (for glycosaminoglycan [GAG] distribution), and tidemark integrity (Kobayashi et al., 2000);
Biochemical: hydration (quantitative measurement of water content), total GAG concentration (chondroitin sulfate, keratan sulfate, HA, etc.), S-sulfate incorporation (GAG synthesis), H-thymidine incorporation (DNA synthesis), reducible collagen cross-linking, and/or dihydroxylysinonorleucine measurement (Ishima et al., 2000; Kobayashi et al., 2000).

The methodological quality of the selected studies was evaluated based on the parameters outlined above.

3. Results

3.1. Study selection

The flow diagram for selection of studies is presented in Fig. 1. With the combination of key words, the literature search revealed 210 articles. One hundred and eighty-six of the articles were excluded after reading their titles because they did not meet the inclusion criteria. On the 24 articles, we excluded 11 articles from the abstract because the HA injections were performed two weeks after the injury. We finally chose 13 articles on the basis of the title and abstract and one from analysis of references in the selected articles. Thus, 14 articles met the study criteria: seven articles described studies of HA injection for meniscus injury (Table 1) (Hope, Ghosh, Taylor, Sun, & Read, 1993; Ishima et al., 2000; Kobayashi et al., 2000; Mihara, Higo, Uchiyama, Tanabe, & Saito, 2007; Sonoda et al., 2000; Sonoda, Harwood, Wada, Moriya, & Amiel, 1997; Suzuki, Takeuchi, Sagehashi, Yamaguchi, Itoh, & Iwata, 1998), three ACL injury (Table 2) (Ozkan, Ozkan, Ramadan, & Guven, 2009; Smith, Myers, Brandt, & Mickler, 1998; Smith, Myers, Brandt, Mickler, & Albrecht, 2005), one combined AC–meniscus injury (Table 2) (Kim, Han, Lee, & Yang, 1991), and three