

REVIEW ARTICLE

HYALURONIC ACID IN ORTHOPEDICS

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Hyaluronic acid (HA) as a compound was discovered in 1934 by Karl Meyer and John Palmer as one of the glycosaminoglycans (GAG) in the vitreous body of the bovine eye. HA occurs naturally in many organs, tissues and body fluids, and especially is presented in large quantities in articular cartilage and synovial fluid. It is a non-protein, non-sulfate glycosaminoglycan which has an important role in the physiological biomechanics of synovial fluid, there is responsible for lubrication and drug-elasticity. In the musculoskeletal system, hyaluronic acid is produced by synoviocytes, fibroblasts and chondrocytes. The concentration of hyaluronic acid decreases not only with age, but also in connection with the progression of certain diseases, for example osteoarthritis (OA). For this reason, it has been used for almost 50 years to try to alleviate and treat symptoms of OA in humans and animals. Numerous studies confirmed the beneficial effect of hyaluronic acid supplementation in OA. Patients which has intraarticular viscosupplementation of HA experience less pain and have a reduced need to take nonsteroidal anti-inflammatory drugs. Intra articular HA administration shows a low risk of local and systemic side effects while maintaining proper administration under aseptic conditions. Nevertheless, local inflammatory reactions occur, but it are most often self-limiting or do not require invasive treatment. The issue of recommending hyaluronic acid in osteoarthritis is still ambiguous and controversial.

KEY WORDS: osteoarthritis, hialauronic acid, orthopedics, history, recomendation

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INTRODUCTION

Hyaluronic acid (HA) was isolated in 1934 by Karl Meyer and John Palmer from the vitreous body of the bovine eye. HA is a glycosaminoglycan (GAG) from the group of structurally complex linear, anionic, hetero-polysaccharides. The name "hyaluronan" appeared in 1986 to adapt the names of polysaccharides. Further studies identified its occurrence in other organs - in the joints, skin, human umbilical cord, nervous system, epithelial, connective tissue and in the rooster comb. In addition, some bacterial strains, such as *Streptococcus zooepidemicus*, *Escherichia coli*, *Bacillus subtilis*, are able to produce hyaluronic acid [1-3]. Other compounds belonging to this group include: keratan sulfate I and II, heparan sulfate, chondroitin sulfate, and dermatan sulfate [4].

Hyaluronic acid is the only mucopolysaccharide that is not synthesized in the Golgi apparatus, it occurs primarily in the extracellular matrix (ECM) and is composed of a repeating disaccharide unit with a molecular weight of about 400 Da. Disaccharide units can form longer chains of up to 25,000 disaccharide units with an approximate molecular weight (MW) of 107 Da [4].

The first HA therapeutic injections were given to horses in an attempt to treat post-traumatic joint changes, which proved to be effective and has been widely used in veterinary medicine since then [5,6]. In humans, HA has been used since 1970 for the treatment of osteoarthritis (OA),

and its use has recently expanded significantly, including outside orthopedic diseases [7-9].

SYNTHESIS OF HA

There are three hyaluronic acid synthases that are responsible for its formation (Has1, Has2 and Has3). The synthesis takes place on the inside of the cell membrane and keeps individual polymer parts outside the cell [10]. It differs from the synthesis of other polymers because it correlates with the length of HA molecules and their viscosity. The difference between synthase products is the variable chain length of HA produced. Depending on the length of the chain, we can distinguish between small, medium and large polymers. The first two forms have pro-angiogenic and anti-apoptotic properties that stimulate heat shock protein (HSP) synthesis and are potent immunostimulants. On the other hand, large polymers act mainly in immunosuppressive and anti-angiogenic functions [11].

HA DEGRADATION

Enzymatic and chemical processes are important in HA catabolism. We distinguish the following hyaluronidases: HYAL1 - is an enzyme associated with lysosomes that breaks down HA into tetrasaccharides, HYAL2 - breaks down high molecular weight HA into 20 kDa, HYAL-3

and HYAL-4 products occur in numerous tissues, but their participation in the process the distribution of hyaluronan is insufficiently explained [10]. HYAL-4 is known to be an isoenzyme with lower specificity, in addition to hyaluronan degradation, it also has affinity for other GAGs. The group of hyaluronidases also includes PH-20 - sperm isozyme produced in the testes, also known as spreading factor and sperm adhesion molecule 1 (SPAM-1). Participates in the degradation of hyaluronan surrounding the egg - enabling penetration of the sperm, which can lead to fertilization. However, it is not clear at what point HA fragmentation changes from the extracellular process or on the cell surface into an endosomal or lysosomal process [4].

OCCURRENCE

HA is involved in many processes in the body. It is widely used in medicine because of its specific binding properties for a large number of water molecules. HA improves tissue hydration and resistance to mechanical damage. Interest in this compound is due to the fact that it is fully absorbable and biocompatible, which means that it is also widely available. The human body weighing 70 kg contains about 15 g of HA, which is present in many structures and tissues, including in the joints, eyes and skin. In addition to removing free radicals or rheological properties, it also plays an important role in wound healing, ovulation, fertilization, signal transduction and cancer pathophysiology [4].

THE AIM

The purpose of the article is to approximate the use of hyaluronic acid in orthopedics.

For this purpose, selected literature was reviewed.

REVIEW AND DISCUSSION

Hyaluronic acid is often used in orthopedics due to its common occurrence in synovial fluid and articular cartilage. This compound is mainly administered to patients with osteoarthritis or rheumatoid arthritis. OA is a very common disease entity, especially in the elderly population, inevitably leading to disability and a significant reduction in the quality of life due to joint mobility restrictions and chronic pain [12].

Intra-articular changes that can be seen in OA include a decrease in GAG and an increase in collagen-degrading enzymes. As a result of inflammation, there is an increased production of reactive oxygen species that degrade collagen, laminins and hyaluronic acid [13]. An important aspect of the impact of HA on joint structures is the chondroprotective effect and stimulating the synthesis of proteoglycans. High molecular weight HA reduces chemotaxis and migration of inflammatory cells, leading to a reduction in inflammation, and additionally protects against free radicals [14]. Several clinical trials have shown a slowdown in OA during HA treatment [15-17]. In addition, HA has an analgesic effect in OA [14, 18].

In 2008, Balogh et al. published the results of a study aimed at assessing the absorption, distribution and elim-

ination of orally administered HA in rats and dogs [19]. High molecular weight technetium HA labeled HA was used for this purpose to measure HA uptake by connective tissue. Scintigraphy was performed after administration of one dose of HA-labeled, which revealed a higher concentration of compound, including in joints, salivary glands, ribs. It can be assumed that the distribution of HA in the human body looks similar [19].

In one clinical study, oral administration of HA (200 mg / day) for 12 months led to a reduction in knee OA symptoms in patients aged 70 and younger, combined with exercises to strengthen the quadriceps muscle of the thigh [20]. Similar results were obtained by Nelson et al. [21] also confirmed that oral HA supplementation leads to a reduction in the severity of OA symptoms. Their observations showed that oral administration of HA leads to the regulation of inflammation detected both in serum and in SF (synovial / synovial fluid) and influences the normalization of HA circulation in SF. This suggests that the effect on the normalization of HA turnover in SF slows the progression of OA, because in preclinical models, HA turnover is associated with the severity of the disease [21].

In a randomized study, Kalman's DS et al. noted a reduced intake of acetaminophen in the study group who received oral HA. However, all authors stress that further research is needed on the impact of HA [25].

De Lucia et al. in 2020, they reviewed the systematic work comparing the effects of HA and corticosteroids (GKS) in intra-articular injection [23]. A total of 370 HA administrations were evaluated for eight different joints (shoulder, knee, ankle, foot, elbow, wrist, fingers and toes). The assessment of treatment effectiveness was performed using various scales of function and pain disorders. In summary, each study resulted in an improvement in joint function and a reduction in pain compared to baseline [23]. Saito et al. concluded that, regardless of the joint, both HA and GKS showed similar efficacy in the treatment of rheumatoid arthritis (RA) i OA [24].

There are many HA preparations on the pharmaceutical market with different molecular weights - low (500–730 kDa), intermediate (800–2000 kDa) and high (~ 6000 kDa) for IA (articular) injection [25]. The therapeutic efficacy of these products may vary depending on the origin of HA, production method, treatment protocol, viscoelasticity, molecular weight (MW) and many other properties. The half-life of HA-containing products in the joint is significantly shorter than the duration of the therapeutic effect [26]. There is no evidence in the available publications that a particular type of HA is superior to others. However, some clinical studies show that preparations with a higher MW were more effective than those with a lower MW in relieving pain associated with OA [27, 28]. Intra-articular application of HA increases the quality of synovial fluid by increasing its viscoelastic properties. The half-life of exogenous acid is very short and ranges from 2-7 days [29]. However, some researchers have shown the presence of HA in cartilage and synovium even 28 days after administration [30]. Contrary to the above results, the long-term

benefits of viscosupplementation, such as pain reduction and improvement of joint mobility, last from half to even a year, and may be associated with increased production of endogenous HA [31, 32].

The articular HA preparations are characterized by good tolerance and satisfactory therapeutic effects (pain reduction), which is confirmed by randomized studies [14, 33]. A very important aspect of HA is the lack of systemic effects, which reduces the risk of drug interactions, which is particularly important in patients with OA who usually have multiple comorbidities [34]. Patients under 65 with a low OA severity are a group of patients who will definitely feel the beneficial effect of HA viscosupplementation [35]. HA can be recommended for both preventive and therapeutic use of IA as an anti-inflammatory agent, reducing the severity of symptoms and modifying the course of the disease [15-17].

RECOMMENDATIONS FOR USING HA IN OA

Currently, the positions of specialist groups are divided as to the use of hyaluronic acid in the treatment of OA. According to some societies, HA is not recommended as a reliable method of treating degenerative joint changes. AAOS (American Academy of Orthopedic Surgeons) in recommendations does not recommend the use of hyaluronic acids in the treatment of knee degenerative changes [36]. ACR (American College of Rheumatology) also does not recommend the use of hyaluronic acid in the treatment of knee and hip degenerative disease [37]. However, the international organization Cochrane states that there is evidence of positive effects of hyaluronic acid in degenerative changes in the knee joints [38]. OARSI (Osteoarthritis Research Society International) recommends the use of hyaluronic acid for intra-articular injection in the knee, hip and polyarticular OA [39]. EUROVISCO (European Viscosupplementation Consensus Group) also recommends the use of hyaluronic acid in osteoarthritis. However, recommendations on HA viscosupplementation were divided taking into account the strength of the recommendations on a 1-9 scale:

- It is recommended to collect synovial fluid prior to injection for bacteriological examination when administering HA to any joint (recommendation 9).
- It is recommended to follow the dosing schedule - the number of HA injections and the interval between injections - as demonstrated in controlled randomized studies regardless of the joint to be treated (strength of recommendation 8).
- It is recommended to administer HA to the knee by the lateral patellofemoral route (strength of recommendation 9).
- It is recommended to administer HA under fluoroscopy or ultrasound control to the hip (recommendation strength 9), ankle (recommendation strength 8), shoulder (recommendation strength 8), metacarpal I (recommendation strength 8), and to the temporomandibular joint (strength of recommendation 8)
- Injections with the help of ultrasound or fluoroscopy are recommended (strength of recommendation 9) [40].

CONCLUSION

The impact of the hyaluronic acid used for delivery still raises controversy in the orthopedic circle, but many years of research prove the beneficial effects of this type of injection into joints in the treatment of degenerative changes. The studies cited above show the benefits of administering HA to OA patients, especially regarding the reduction of pain experienced by patients. Some results also suggest improving a small degree of joint mobility, but this may be due to a reduction in the pain component felt. HA monotherapy does not lead to the regeneration of joint surfaces, however, it contributes to the reduction of inflammation in OA and better nutrition of the remaining articular cartilage. Indirectly, the beneficial effect of HA in OA also consists in reducing the amount of nonsteroidal anti-inflammatory drugs taken by patients. Intra-articular injection of HA shows a low risk of systemic and local adverse effects when administered under aseptic conditions and with proper administration. Nevertheless, local inflammatory or allergic reactions occur, which, however, usually do not require invasive methods of treatment. The issue of recommending HA administration in osteoarthritis is still ambiguous, and the decision to use this type of therapy as supportive therapy for OA should be made in consultation with the patient.

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Conflict of interest

Magdalena Ratajczak is an employee of Euroimmun Poland a Perkinelmer Company.

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