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Intra-articular injection of xanthan gum: A potential therapy for osteoarthritis

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ABSTRACT

Osteoarthritis (OA) means inflammation of the joints, with the symptoms of joint pain, stiffness, and swelling of the joints. It is a degenerative disease that appears to be caused by both biomechanical and biochemical factors. Intra-articular (IA) injection treatment is one of the main treatment methods for OA because of its positive effect in reducing joint pain and increasing joint mobility. IA injection of xanthan gum (XG) could protect the joint cartilage, relieve the synovitis and reduce the OA progression in experiment OA. The injection of XG may have a long-lasting effect in the joint cavity, which could avoid frequent IA injections. However, for the development of this potential therapy, further studies such as the effective long-term pain relief properties, the detailed action mechanism and the pharmacokinetics of the XG injection will be conducted. This article briefly reviewed the preparation, safety evaluation, pharmacodynamics and possible action mechanism of XG injection, and come up with the ideas for further development of this potential therapy for OA.

Keywords: Osteoarthritis; Xanthan Gum; Pharmacodynamics; Action Mechanism

1. INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder and is a major cause of disability and impaired mobility worldwide [1]. It is characterized by cartilage degradation and synovial inflammation which is directly related to clinical symptoms such as joint swelling, synovitis and pain [2]. Since both aging [3] and obesity [4] are associated with increasing rates of OA, the prevalence of OA is likely to continue to rise. Development of new OA treatment method is important and necessary to reduce its public health impact.

Current pharmacotherapy aims at symptom relief and cartilage protection. It includes systemic analgesics, nonsteroid antiinflammatory drugs (NSAID) and intra-articular (IA) injections with glucocorticoids and viscosupplementation agents such as sodium hyaluronate (SH) [5, 6]. IA injection of SH is widely used in the treatment of OA, and clinical trails showed that SH therapy is effective and safe for the OA patients [7-9]. The main objective of IA injection of SH is to make up for the loss of viscoelastic properties of OA synovial fluid and to protect against degradation of cartilage [10-12]. However, SH will be quickly degraded through hydrolytic and enzymatic reactions *in vivo* due to its instability [13]. Therefore, a compound possessing similar function to SH, but with a longer efficacy is really needed to avoid frequent IA injections.

Xanthan gum (XG) is a high molecular weight anionic polysaccharide produced from microbial fermentation [14]. It is similar to SH in viscosity and rheology [15,16], however, it is likely to be more stable than SH and not be easily degraded *in vivo* [17]. Previous studies demonstrated that IA injection of XG could protect the joint cartilage, relieve the synovitis and reduce the OA progression in an experiment OA model [17]. XG injection probably has a long-lasting protective effect on articular cartilage to avoid numerous injections. In this article we briefly reviewed the preparation, safety evaluation, pharmacodynamics and possible action mechanism of XG injection, and come up with the ideas for further development of this potential therapy for OA.

2. BRIEF INTRODUTION OF XG

XG (**Figure 1**) is a microbial extracellular heteropolysaccharide produced by the bacterium *Xanthomonas campestris*. Its molecular weight distribution ranging from 2×10^6 to 2×10^7 Da [14]. The primary structure of XG is based on repeated pentasaccharide units. The backbone chain consists of two glucose units linearly by

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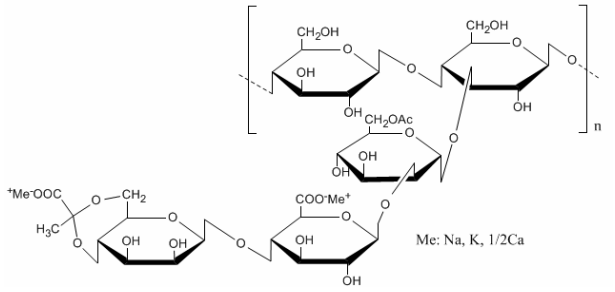

Figure 1. Xanthan gum.

β1→4 linkages, and the trisaccharide side chain is composed of two D-mannose units alternating D-glucuronic acid. The internal mannose unit is acetylated and on approximately half of the terminal D-mannose units residues a pyruvic acid moiety [18,19]. The secondary structure of XG is a fivefold helical structure formed by the trisaccharide side chain wrapping back the main chain through hydrogen bonds. The main chain is protected by the side chains from the outside environment. The tertiary structure of XG is a net work structure formed by helical complex [14].

The properties of XG are quite different and unusual for its special structure, such as a high viscosity even at low concentrations, a high degree of pseudoplastic, stability and compatibility with most metallic salts, excellent solubility and stability in acidic and alkaline solutions and resistance to degradation at elevated temperatures and various pH levels [20]. Besides, XG is nontoxic and biocompatible.

XG has been approved for its use in the production of foods by the United States Food and Drug Adminstration (FDA) without any specific quantity limitations in 1969 [20]. Now, XG has been widely used in variety of foods for its special and important properties. XG is also well known to be employed as a thickener in many other industries such as papermaking, textile and cosmetics industries [14]. XG is biocompatible allowing its use in various medical and pharmaceutical applications such as topical ocular application [21,22], implantation [23], controlled-release carriers [24,25] or component in hydrogels [26]. XG is demonstrated to be biodegradable [27] and bioadhesive, which increases retention at the site of application [28,29]. Moreover, it also has the antineoplastic effects [30] and can promote wound-healing [31].

3. APPLICATIONS OF XG ON OA TREATMENT

3.1. Preparation of XG Injection

A high quality is necessary for XG injection including high viscosity, high purity and endotoxin-free. However, the purification of XG is difficult. XG fermented broth contains many undissolved matter such as bacterial cell residues, proteins and other biopolymers [32]. Furthermore, the purification processes need to not only obtain a high quality product but also suit for large-scale production. The high viscosity of XG fermented broth make the purification more difficult. To obtain high quality of XG for IA injection, the purification process containing the preparation and resolution of raw XG samples, 1% (w/v) diatomite absorption, cake filtration, enzymolysis, 1% (w/v) active carbon absorption, cake filtration, fine filtration with 0.45 μm microporous membrane, precipitation using isopropanol and stoving was established [17]. This purification process is easy to meet large-scale production, and the XG preparation obtained is high viscous.

3.2. Safety Evaluation of XG Injection

The safety of IA injection of XG was evaluated by Han, *et al.* [33]. When intra-articularly injected with 0.5% - 2% XG (0.1 mL/kg) in rabbit knee joint once a week for 5 weeks, there was no significant changes of the width of the knee joint, hematological and biochemical parameters observed, and no obvious histopathological changes in liver, kidney and knee joint detected [33]. *In vitro* experiments, the XG (10 - 2000 μg/mL) did not significantly modify chondrocytes viability and the production of matrix metalloproteinases (MMP), tissue inhibitor of metalloproteinase-1 (TIMP-1) in chondrocytes. XG displayed no cytotoxicity to rabbit chondrocytes [34]. However, the long-term toxicity of XG IA injection has not been evaluated.

3.3. Therapy Effect of XG Injection on OA

IA injection of XG may inhibit the continuous lesions on the cartilage and delay the progression of OA [17]. In an experimental model of OA induced by papain, IA injection of XG once every 2 weeks for 5 weeks decreased the severity of swelling of the knee joint, reduced the damage of cartilage surfaces, inhibited the chondrocytes changes, structural changes and loss of Safrain O staining intensity of femoral condyle and tibial plateau and also inhibited cells hyperplasia and infiltration of mononuclear cells in the synovium [17]. Futhermore, IA injection of XG once every 2 weeks for 5 weeks and IA injection of SH once a week for 5 weeks had similar effectiveness. IA injection of XG is likely to be injected fewer times than SH to get the same treatment results. XG could also preserve the proteoglycans (PG), which is the extracellular matrix mainly composed of. PGs maintain the water of articular cartilage and provide important biomechanical functions, such as load bearing, load distribution and shock absorption. When XG was added to interleukin-1 beta (IL-1β)-treated chondrocytes, there were significant restorations in chondrocytes prolifera-

tion, inhibition in the protein expression of MMP-1, -3, and -13, increase in TIMP-1 production in a dose-dependent manner in doses ranging from 100 to 1000 μg/mL [34].

4. POSSIBLE ACTION MACHANISM OF XG INJECTION

4.1. Restore the Viscoelasticity of Synovium Fluid

OA is a degenerative disease that appears to be caused by both biomechanical and biochemical factors [35]. Extensive investigations of femorotibial alignment have demonstrated that the mechanical forces play an important role in knee OA progression. Compared with normal synovial fluid, the synovial fluid in OA patients is markedly less viscoelastic due to lower concentration and reduced molecular weight of the SH, so its ability to lubricate and absorb shock is decreased [10]. Attention to the important role of mechanical factors in OA etiopathogenesis and therapies directed at unloading or reduceing the forces in the OA joints is required.

The high viscoelasticity of XG injection is crucial for the augmenting and elevating the viscoelastic properties of synovial fluid. XG preparations could behave as a viscous liquid at low shear rates and as an elastic solid at high shear rates. So XG could act as an elastic shock absorber during low impact movements of the joint and as a viscous lubricant during high impact movement. IA injection of XG may increase the ability of synovial fluid to lubricate and protect articular tissues, and to absorb joint loads, inhibiting the further progression of OA.

4.2. Biochemical Actions

Significant progress on the role of inflammation in OA has been made in recent years. Studies show that the excessive production of cytokines, inflammatory mediators and growth factors by the inflamed synovium and activated chondrocytes play a pivotal role in the pathophysiology of OA [36-38]. Osteoarthritic chondrocytes and the synovium from OA patients produce a number of inflammatory mediators including IL-1β, tumor necrosis factor-alpha (TNF-α), prostaglandins and nitric oxide (NO) [36,37]. Interleukins (ILs) are a family of interrelated cytokines that regulate the acute inflammation process. IL-1β, a cytokine released by synovial cells and macrophages, plays a decisive role in amplifying inflammation in OA [39]. IL-1β can stimulate its own production and induce chondrocytes and synovial cells to produce other cytokines such as IL-8, IL-6, as well as stimulate proteases, NO and prostaglandin E_2 (PG E_2) production. IL-1β can alter chondrocytes anabolism by enhancing PG degradation and repressing the synthesis of PG. IL-1β up-regulates matrix degrading enzymes such as MMPs and down-regulates the TIMPs in chondrocytes [40]. Excess of MMPs plays an important role in cartilage breakdown, because of their ability to degrade the extracellular matrix proteins. The imbalance between MMPs and TIMPs is of great importance in the progression of OA [41].

XG has been demonstrated to have some biochemical actions on chondrocytes *in vitro*. Previous study showed that when XG was added to IL-1β-treated chondrocytes, there were significant restorations in chondrocytes proliferation, inhibition in the protein expression of MMP-1, -3, and -13, increase in TIMP-1 production. It was speculated that the protective effect of XG on cartilage might be associated with the prevention of destruction of IL-1β on chondrocytes and the regulation of MMP-1, -3, -13, TIMP-1 [33].

5. FUTURE PROSPECT

IA injection of XG is a potential therapy for OA. However, there are still many works to do for the development of this new treatment method. The future study will be designed to solve the following questions.

1) Whether XG could relieve OA pain

Pain is one of the most important symptoms of OA. The presence of local joint inflammation, altered cartilage and bone turnover in OA can lead to joint pain. The activation and release of local pro-inflammatory mediators in the joint such as prostaglandins and cytokines influence excitability of nociceptors of articular nerves [38]. However, angiogenesis in OA promotes ingrowth of new sensory nerves into peripheral joint tissue exposed to inflammation and damage, which contributes to persistent pain [42]. In experimental OA, articular nerves become hyperalgesic, spontaneously discharge, and are sensitive to non-noxious joint movements [38].

IA injection of XG with high viscosity is considered to be able to coat the receptor endings of the joint pain fibers, decrease their sensitization to inflammatory mediators, entrapment of endogenous pain substances or decreased activation to their receptor. IA injection of XG is very likely to relieve the OA pain. Our studies of XG on body torsion experiment in mice and the capillary permeability experiment showed that intraperitoneal injecttion of XG could reduce the times of torsion and inhibit capillary permeability (results not be published), supporting the hypothesis above. However, to prove the hypothesis that IA injection of XG may relieve OA pain, future study will be conducted.

2) Detailed action mechanism of XG

The OA pathogenesis is complex and the detailed mechanism of XG in chondrocytes and the inflammatory is not clear. Further study is needed to understand the detailed action mechanism of XG injection. For example, whether XG could affect the NO expressed in OA joint.

In OA chondrocytes, the inducible nitric oxide synthase (iNOS) enzyme is unregulated, resulting in over expression of NO and perpetuating the release of inflammatory cytokines and other catabolic processes. NO promotes chondrocyte inflammatory responses, mediates chondrocyte apoptosis, inhibits both PG and collagen synthesis, and activates MMPs. All of these activities contribute to the catabolic consequences of NO in cartilage. *In vivo* and *in vitro* experiments are necessary to know whether XG injection can be able to prevent the production of NO in OA [35].

3) Pharmacokinetic of XG injection

The efficacy of XG on OA seems to be highly related to its residence time in the joint cavity after injection. The actual joint distribution, residence time, mechanism of removal and degradation of the XG injection will be detailed studied.

4) Longer therapy effect of XG on OA

To evaluate the long-lasting effect of XG injection, the anterior cruciate ligament transection (ACLT) OA model or other experiment OA model will be adopted with the observation period extended.

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