Methods 47 (2009) 134–140

Contents lists available at ScienceDirect

Methods

journal homepage: www.elsevier.com/locate/ymeth

Review Article

Emerging intra-articular drug delivery systems for the temporomandibular joint

Paschalia M. Mountziaris [a], Phillip R. Kramer [b], Antonios G. Mikos [a,*]

[a] Department of Bioengineering, Rice University, P.O. Box 1892, MS 142, Houston, TX 77251-1892, USA
[b] Department of Biomedical Sciences, Texas A&M Health Science Center, Baylor College of Dentistry, 3302 Gaston Avenue, Dallas, TX 75246, USA

ARTICLE INFO

Article history:
Accepted 5 September 2008
Available online 1 October 2008

Keywords:
Temporomandibular joint
Temporomandibular disorder
Intra-articular
Drug delivery
Sustained release
Inflammation
Tissue engineering
Corticosteroid
Hyaluronic acid
Microparticle
Nanoparticle
Liposome
siRNA

ABSTRACT

Temporomandibular joint (TMJ) disorders are a heterogeneous group of diseases that cause progressive joint degeneration leading to chronic pain and reduced quality of life. Both effective pain reduction and restoration of TMJ function remain unmet challenges. Intra-articular injections of corticosteroids and hyaluronic acid are currently used to treat chronic pain, but these methods require multiple injections that increase the risk of iatrogenic joint damage and other complications. The small and emerging field of TMJ tissue engineering aims to reduce pain and disability through novel strategies that induce joint tissue regeneration. Development of methods for sustained, intra-articular release of growth factors and other pro-regenerative signals will be critical for the success of TMJ tissue engineering strategies. This review discusses methods of intra-articular drug delivery to the TMJ, as well as emerging injectable controlled release systems with potential to improve TMJ drug delivery, to encourage further research in the development of sustained release systems for both long-term pain management and to enhance tissue engineering strategies for TMJ regeneration.

1. Introduction

Temporomandibular joint (TMJ)[1] disorders are the main cause of chronic facial pain and a major cause of disability. Treatment of these disorders in the United States has an estimated cost of $4 billion per year [1]. Unlike other degenerative joint diseases, which are more common in the elderly, TMJ disorders affect up to one-third of adolescents and young adults. The chronic pain associated with progressive TMJ degeneration limits talking, chewing, and other basic daily activities [2,3]. Current treatments for TMJ disorders are limited. In severe cases, both effective pain reduction and restoration of TMJ function remain an unmet challenge [4].

One main type of TMJ disorder is an osteoarthritis-like degenerative joint disease characterized by progressive bone and cartilage destruction and subsequent inflammation, which exacerbates joint tissue catabolism [5]. Consequently, pharmacologic approaches to TMJ disorders have paralleled those for symptomatic treatment of osteoarthritis, including non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular injections of either steroids or hyaluronic acid into the superior joint space (see Fig. 1). However, use of these agents remains controversial in light of decades of mixed reports of intra-articular injections either accelerating TMJ destruction or triggering regeneration [6]. As in the case of osteoarthritis, no agents are available to reverse the underlying TMJ disease. Consequently, current pain reduction techniques are effective in the early stages of the disease, but fail to alleviate the severe, chronic pain caused by advanced joint degeneration [5,7].

There is a need for sustained release agents that effectively reduce pain and have minimal systemic side effects, enabling long-term administration without the disastrous ectopic effects seen with NSAIDs like rofecoxib (Vioxx®) [8]. This review discusses methods of intra-articular drug delivery to the TMJ, as well as emerging injectable controlled release systems with potential to improve TMJ drug delivery, to encourage further research in the development of sustained release systems for both long-term pain management and to enhance tissue engineering strategies for TMJ regeneration.

2. Current methods of intra-articular injection

A variety of injectable corticosteroid and hyaluronic acid formulations are used to reduce the persistent pain associated with TMJ destruction. Localized drug delivery via intra-articular injections

* Corresponding author. Fax: +1 713 348 4244.
E-mail address: mikos@rice.edu (A.G. Mikos).

[1] *Abbreviations used:* TMJ, temporomandibular joint; NSAIDs, non-steroidal anti-inflammatory drugs; FDA, food and drug administration; HA, hyaluronic acid; PCL, poly(caprolactone); PLGA, poly(lactic-*co*-glycolic acid); PLLA, poly(L-lactic acid); PPS, poly(propylene sulphide); RNA, ribonucleic acid; siRNA, small interfering ribonucleic acid; TNF, tumor necrosis factor; b-FGF, basic fibroblast growth factor.

1046-2023/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.ymeth.2008.09.001

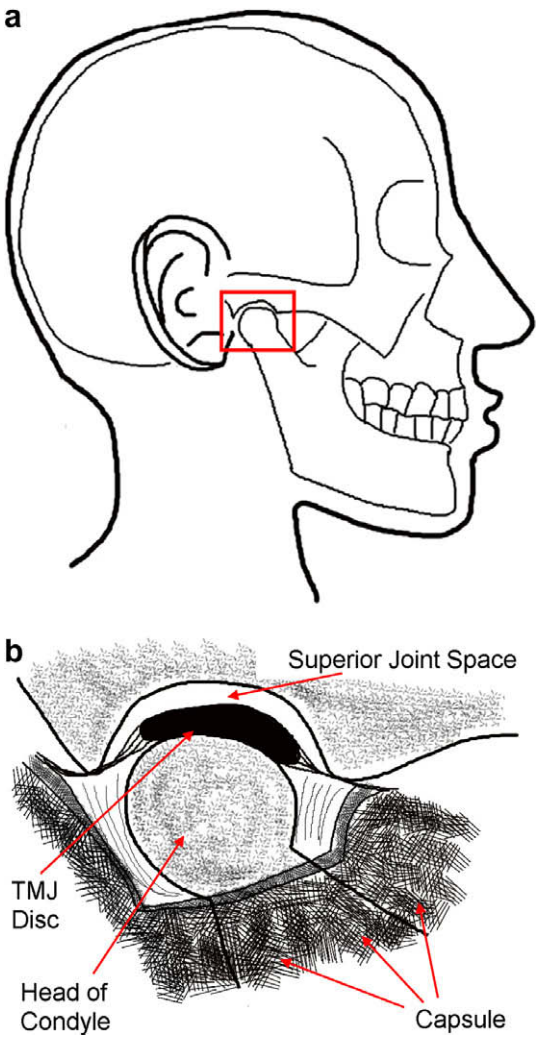

Fig. 1. Schematic depicting the temporomandibular joint (TMJ), indicated by the red box in (a). The second image (b) shows relevant components of joint anatomy, including the TMJ disc, the head of the mandibular condyle, and a portion of the connective tissue capsule that envelops the joint. The superior joint space is also specifically indicated, and it is into this space that intra-articular TMJ injections are made.

minimizes ectopic effects while alleviating joint pain and other symptoms. Although the Food and Drug Administration (FDA) has only approved intra-articular hyaluronic acid formulations for osteoarthritis of the knee, these formulations are still used to treat pain in a number of other joints, including the TMJ [5,9].

Studies of the efficacy of intra-articular TMJ injections have shown mixed results, with improvement in some patients and disease progression in others [6]. Alarming reports of post-injection complications, including cartilage destruction, bone necrosis, and progression of joint disease, have discouraged their use for TMJ pain [10,11]. These reports often describe isolated patients given repeated intra-articular injections [11–13]. High doses of corticosteroids are known to increase the risk of aseptic bone necrosis. In one case report, a previously asymptomatic patient with TMJ inflammation developed disc dislocation, chondrolysis, heterotopic bone formation, and necrosis of the articular tubercle following repeated, high doses of intra-articular corticosteroid (triamcinolone). Surgery was necessary to correct the resulting joint degeneration and limited range of motion [12]. In contrast, hyaluronic acid itself does not cause bone necrosis. This complication has nevertheless been reported following hyaluronic acid injections to the TMJ, and is attributed to bone trauma occurring during the intra-articular injection procedure [11,14]. This section reviews the efficacy of corticosteroid and hyaluronic acid injections for TMJ disorders, and highlights the unmet needs in existing intra-articular drug delivery strategies.

2.1. Corticosteroids

Reports of intra-articular corticosteroid injections to the TMJ date back to over 50 years ago [15]. Numerous corticosteroid formulations are available for intra-articular injection, ranging from solutions of more soluble agents to suspensions of triamcinolone hexacetonide and other relatively insoluble steroids. Although the efficacy of various corticosteroids is presumed to differ, studies of this topic have been limited [7,16,17]. A variety of methods are currently used for intra-articular corticosteroid injection to the TMJ, each with the goal of minimizing the potential for tissue damage.

Intra-articular corticosteroid formulations are often diluted with a local anesthetic prior to injection into the TMJ [18–20]. This method is thought to decrease the risk of soft tissue atrophy and other complications, although evidence supporting this claim is largely anecdotal [16,17]. In a controlled study of adults with TMJ arthritis, a single intra-articular injection of corticosteroid (methylprednisolone) diluted with lidocaine significantly reduced joint pain and other symptoms for 4–6 weeks [20]. The pharmacologic effect of intra-articular methylprednisolone lasts 3–4 weeks, so these findings were consistent with the expected timeline of corticosteroid effect. No adverse events were reported [20].

The most common treatment strategy is either a single injection [19–23] or a series of two injections spaced 14 days apart [24–28], although the best method has yet to be determined. Some clinicians have suggested that a single corticosteroid injection is beneficial for patients with severe TMJ pain, while further injections do not provide added pain relief, and may increase the risk of joint degeneration and other complications [12,21]. In a recent study of patients with TMJ arthritis, there was a significant improvement in TMJ mobility and symptoms, particularly pain and difficulty eating, following the first corticosteroid (triamcinolone) injection. No significant improvement was seen in patients given further injections, suggesting that a single injection is of greatest utility. One patient even developed subcutaneous atrophy after receiving a total of five injections to a single TMJ and required surgery [29]. This isolated case underscores the need for new methods of intra-articular drug delivery, particularly sustained release formulations, which would eliminate the need for numerous injections, each of which induces further damage to already degenerating TMJ tissue.

Several decades ago, Toller [21] suggested that intra-articular corticosteroid injections were only useful in adult patients with TMJ disorders; a single intra-articular injection resulted in resolution of TMJ pain and other symptoms in 62% of adult patients, compared to only 17% of pediatric patients [21]. However, the efficacy may vary depending on the specific cause of TMJ degeneration. In recent studies of juvenile idiopathic arthritis, intra-articular corticosteroid (triamcinolone) injections improved or even completely eliminated TMJ pain in 77–88% of children for several months [22,23,29]. Despite the young age of the patients, adverse events (e.g. facial swelling, asymptomatic intra-articular calcifications, and subcutaneous atrophy) were rare in these studies. This likely reflects the cautious injection methods used, which included general anesthesia and costly radiographic needle guidance [22,23,29].

As with any clinical technique, the accuracy of placement of intra-articular injections depends upon the experience of the medical practitioner. An estimated one-third to one-half of all steroid and hyaluronic acid injections are inaccurately placed, although