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Evaluation of Anti-Nociceptive, Anti-Inflammatory, and Anti-Fibrotic effects of noscapine against a rat model of Achilles tendinopathy

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Highlights

- Noscapine dose dependently reduced thermal hyperalgesia, mechanical and cold allodynia, deterioration of motor coordination, tendon adhesion score in an animal model of tendinopathy.
- Noscapine dose dependently attenuated microscopic indices, namely histological adhesion, vascular prominence and angiogenesis in an animal model of tendinopathy.
- Noscapine dose dependently ameliorated hyper-proliferation and apoptosis histopathological indices Ki67 AND p53, respectively, in an animal model of tendinopathy.
- Noscapine dose dependently ameliorated fibrotic and inflammatory biomarkers (IL-6, TNF-α, TGF-β, VEGF) in an animal model of tendinopathy.
- Taken together, our findings suggested that noscapine could be a promising medicine for treating tendinopathies.

Abstract

During tendinopathy, prolonged inflammation results in fibrosis and the adherence of tendons to the adjacent tissues, causing discomfort and movement disorders. As a natural compound, noscapine has several anti-inflammatory and anti-fibrotic properties. Therefore, we aimed to investigate the effects of noscapine against a rat model of tendinopathy. We created a surgical rat model of Achilles tendon damage to emulate tendinopathy. Briefly, an incision was made on the Achilles tendon, and it was then sutured using an absorbable surgical thread. Immediately, the injured area was topically treated with the vehicle, noscapine (0.2, 0.6, and 1.8 mg/kg), or dexamethasone (0.1 mg/kg) as a positive

control. During the 19-day follow-up period, animals were assessed for weight, behavior, pain, and motor coordination testing. On day 20th, the rats were sacrificed, and the tendon tissue was isolated for macroscopic scoring, microscopic (H&E, Masson's trichrome, Ki67, p53) analyses, and cytokine secretion levels. The levels of macroscopic parameters, including thermal hyperalgesia, mechanical and cold allodynia, deterioration of motor coordination, tendon adhesion score, and microscopic indices, namely histological adhesion, vascular prominence and angiogenesis, and Ki67 and p53 levels, as well as fibrotic and inflammatory biomarkers (IL-6, TNF-α, TGF-β, VEGF) were significantly increased in the vehicle group compared to the sham group ($P<0.05–0.001$ for all cases). In contrast, the administration of noscapine (0.2, 0.6, and 1.8 mg/kg) attenuated the pain, fibrosis, and inflammatory indices in a dose-dependent manner compared to the vehicle group ($P<0.05–0.001$). Histological research indicated that noscapine 0.6 and 1.8 mg/kg had the most remarkable healing effects. Interestingly, two higher doses of noscapine had impacts similar to those of the positive control group in both clinical and paraclinical assessments. Taken together, our findings suggested that noscapine could be a promising medicine for treating tendinopathies.

Introduction

The strongest human tendon is the Achilles tendon, which attaches the triceps surae muscle to the calcaneus bone [1], [2]. Due to its necessity for weight tolerance and body movement, it is vulnerable to damage [1], [2], [3]. Achilles tendinopathy is one of the common musculoskeletal abnormalities as a result [4], [5]. Operative and nonoperative treatment options are available, with the nonoperative options carrying a 30% chance of tendon rupture [6]. Less tendon rupture occurs with surgical treatments [7]. However, tendon adhesion, a fibrotic tissue formation between the injured tendon and surrounding tissues, represents the highest risk associated with surgery-based treatment for Achilles tendinopathy [8]. Myofibroblast proliferation increased in injured tendon tissues, which boosted collagen III secretion, assisting in the formation of fibrotic ECM and maintaining the scar [9]. Degenerative and chronic tendinopathies are caused by the development of fibrotic ECM [10], [11], [12]. Therefore, a treatment that may encourage complete regeneration without the creation of fibrotic ECM and prevent tendon adhesion is needed [13].

The tendon healing process is a combination of intrinsic and extrinsic processes. Since tendon tissue has a low cellularity and vascular nature, its healing is weak [14], [15]. However, it appears that the production of adhesions is more affected by extrinsic healing factors [13]. Limited knowledge of the pathogenesis of tendinopathy and its healing prevented the progression of tendon therapy

Hence, surgical therapies need a recovery period [14], [16], [17]. These factors make alternative therapies necessary to modify the healing of the wounded tendon following surgical tendon therapy. Therefore, to lead to flawless tendon tissue regeneration without movement abnormalities, therapeutic techniques for tendinopathy with positive impacts on intrinsic processes, which include good tenocyte activities and extrinsic healing processes that include enough supplies of inflammatory mediators and growth factors, are needed [18], [19].

The first stage of tendon healing is the formation of a hematoma (inflammatory phase), followed by the infiltration of inflammatory cells and the release of cytokines and growth factors (proliferative phase), which result in the development of extracellular matrix, blood vessels, and well-organized tendon tissue (remodeling phase) [20], [21]**.** The length of each phase varies according to the kind of tendon damage, comorbidities, organism, and course of treatment [22], [23]. Hernandez et al. reported increased expression of the IL-6 and TGFβ1 genes in Achilles tendinopathy [24]. The VEGF-A and IL-6 expression levels are higher in the ruptured Achilles tendon than in the normal tendon [25]. Therefore, anti-inflammatory, anti-fibrotic, and anti-oxidant medications are promoted as a treatment for tendon adhesion [25], [26]. Systematic approaches, however, have drawbacks, including 1) limited drug bioavailability in the tendon tissue for cellular and molecular impact 2) short half-lives of drugs that are insufficient for the healing period of the damaged tendon and 3) inflammation as a primary event of tendinopathy, so its prolonged inhibition may interfere with tendon healing [27], [28], [29]. Many strategies, such as physiotherapy and drugs, are used to prevent tendon tissue adhesion [30], [31], [32], [33]. Although tendon adhesions can be controlled with nonsteroidal anti-inflammatory medicines (NSAIDs), using them has adverse effects [34].

Noscapine is a phthalide isoquinoline alkaloid with pharmaceutical properties such as anti-tussiveness [35], [36], [37], [38], [39]. A study displayed the efficiency of noscapine in decreasing cerebral injury in newborn rats suffering hypoxic ischemia. Additionally, a different trial showed that oral noscapine reduced mortality in people who had ischemic

stroke symptoms [40]. Studies show that noscapine is safe, well-tolerated, and has minimal toxicity [41]. Additionally, anti-fibrotic properties of noscapine were demonstrated in cultured human lung fibroblasts (HLFs) by suppressing TGF (transforming growth factor beta)-induced differentiation [42]. TGFF-β1 is a vital mediator in the pathogenesis of tendon adhesion [43], [44]. TGF-β1 mediates fibroblast-to-myofibroblast differentiation as well as myofibroblast proliferation through signaling pathways such as the canonical TGF-β/Smad2/3 and noncanonical mitogen-activated protein kinase (MAPK) pathways [45].

Because of these features, we anticipate that noscapine will be able to control inflammation during tendon regeneration and stop it from developing into fibrosis and adhesions. The goal of this study was to examine how the anti-adhesion properties of noscapine help to prevent the surgically repaired tendon from adhering to nearby tissues. We examined the effects of noscapine on the surgically repaired Achilles tendon by measuring the animals' levels of pain and their ability to move and coordinate their muscles. Additionally, using macroscopic and microscopic analyses, we assessed tendon adhesion, cell proliferation, collagen secretion, inflammation, fibrosis, and apoptosis in healing tendons.

Section snippets

Animal husbandry and Ethical statements

Thirty-six male Sprague–Dawley rats weighing between 200 and 250g were obtained from the Faculty of Medicine Animal Laboratory, Mashhad University of Medical Sciences, Mashhad, Iran. Animals were divided randomly into six groups (n=6/group) for all of the experiments. There were 12 light/dark cycles and unrestricted access to food and water for the animals. In addition, the rodents were acclimatized for one week before the study began. The Ferdowsi University of Mashhad's (Ethical approval…

Noscapine showed no abnormal effects on body weight

Based on the rats' daily weight data, the weight of the rats in each group fell within a comparable range at various points during the study period, and no abnormalities were seen in any group's body weight data, indicating disease states brought on by inflammation and damage (Fig. 1A).…

Noscapine reduced pain in surgically operated animals

Our results indicated that model-induced tendinopathy led to a significant increment in the levels of paw withdrawal threshold mechanical ($P<0.05$, Fig. 1B) and the number of lifts cold ($P<0.05$, Fig. 1C)…

Discussion

To our knowledge, the current study marked the first use of noscapine as a treatment for tendinopathy. In a rodent model, noscapine was used to prevent tendon adhesion. Our data revealed that noscapine has immunomodulatory, cell proliferation-modulating, and anti-fibrotic properties. All of the study's results demonstrated the therapeutic effects of noscapine on tendinopathy. In our previous study, we used 5, 15, and 45mg/kg dosage of noscapine. Several studies have been conducted to evaluate…

Conclusion

Noscapine was found to have anti-adhesion and anti-fibrotic effects by modulating inflammatory processes, cell proliferation, and apoptosis, as evidenced by our findings. All pain evaluations and motor coordination tests supported the efficacy of noscapine treatment as local wound management in surgical tendinopathy treatments. At the microscopic level, it was determined that noscapine is a non-disruptive agent for tendon repair. It could, therefore, be utilized as an ngineering.

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The…

CRediT authorship contribution statement

Zohreh Najafi: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis. **Zahra Moosavi:** Writing – review & editing, Visualization, Validation, Investigation. **Vafa Baradaran Rahimi:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Gholamreza Hashemitabar:** Writing – review & editing, Supervision, Methodology. **Vahid Reza Askari:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Project…

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Recommended articles

References (91)

M. O'Brien
The anatomy of the Achilles tendon
Foot Ankle Clin. (2005)

E.J. Strauss *et al.*
Operative treatment of acute Achilles tendon ruptures an institutional review of clinical outcomes
Injury. (2007)

I.F. Williams *et al.*
Cell morphology and collagen types in equine tendon scar
Res. Vet. Sci. (1980)

A.E.C. Nichols *et al.*
The cellular basis of fibrotic tendon healing challenges and opportunities
Transl. Res. (2019)

J.E. Carpenter *et al.*
Animal models of tendon and ligament injuries for tissue engineering applications
Biomaterials (2004)

M. Hope *et al.*
Tendon Healing
Foot Ankle Clin. (2007)

V. Tan *et al.*
Effects of nonsteroidal anti-inflammatory drugs on flexor tendon adhesion
J. Hand Surg. Am. (2010)

D.G. Shchukin *et al.*
Capsules with external navigation and triggered release
Curr. Opin. Pharmacol. (2014)

J.B. Tang
Clinical outcomes associated with flexor tendon repair
Hand Clin. (2005)

N. Ishiyama *et al.*
The prevention of peritendinous adhesions by a phospholipid polymer hydrogel formed in situ by spontaneous intermolecular interactions
Biomaterials (2010)

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