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Review Article

Effects of Topical Application of Pharmacological Agents after Flexor Tendon Injury and Methods Used For Evaluation of Tendon Healing Process

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Abstract

Tendons are anatomical structure that connects muscle to bone to allow the force to be transmitted from the muscle to the bone, allowing movement of fingers. The main objective of this study is to present the recent data from animal experimental studies where pharmacological topical agents are used after tendon repair in prevention of adhesion formation. Some of the most commonly used topical agents are: Hyaluronic Acid (HA) and its derivatives, 5-Fluorouracil (5-FU), lubricin, alginate solution and topical application of growth factors. These studies have shown that the above mentioned substances reduce adhesion formation through different mechanisms. The successes of the tendon healing after tendon repair in experimental studies using topical agents, can be evaluated using a variety of methods such as: biomechanical evaluation, macroscopic and microscopic evaluation, cell isolation and analysis of growth factors. However, most authors agree that despite good tendon repair and topical application of these substances, creation of adhesion formation continues to be a great problem for hand surgeons.

Introduction

Tendons are anatomical structure that connects muscle to bone to allow the force to be transmitted from the muscle to the bone, allowing movement of fingers [1]. Tendons are composed of approximately 70% molecules made up of peptide chains in a triple helix configuration (tropocollagen). Tendon fascicles consist of mature fibroblasts (tenocytes) and type I collagen fibers. Individual bundles of collagen are covered by the endotenon; externally, the septa of the endotenon join together to form fibrous a outer layer, the epitenon that covers the surface of the tendon. The flexor tendon fascicles in the hand are covered by a thin visceral and parietal adventitia, the paratenon, which is associated with a fluid environment similar to synovial fluid [2]. Flexor tendon injuries are quite frequent as the tendons lie close to the skin and so are usually the result of either lacerations from knives or glass, from crush injuries and they can rupture from where they are joined at the bone during contact sports such as football, rugby and wrestling [1]. Restoration of the normal hand function following flexor tendon injuries requires reestablishment not only of the continuity of the tendon fibers, but also of the gliding mechanism between the tendon and its surrounding structures. Like many other tissues, tendons heal by deposition of scar tissue at the site of injury. While the initial formation of scar tissue between the tendon ends provide physical continuity at the site of the disruption, proliferation of the scar tissue between the tendon and surrounding tissues is undesirable because these attachments impede tendon gliding and might be the cause of restricted tendon movement that is of great clinical importance [3-5].

Adhesions between tendon and the surrounding tissues continue to be an important problem after primary flexor tendon repair, especially in zone II, which extends from A1 pulley to the distal insertion of the Flexor Digitorum Superficialis Tendon (FDS) in the finger. Zone II is known as "no man`s land" by Bunnell based on the belief that primary repairs should not be done in this zone because of the frequency of complications including adhesion formation [4,6].

Attempts at reducing postoperative adhesion formation have included low-friction surgical repair techniques, early postoperative rehabilitation, physical barriers to adhesion formation, tendon surface lubrication and the use of pharmacological antiadhesive reagents. The adhesiogenic nature of tendon healing or repair, improvements in surgical technique alone with the postoperative rehabilitation will help, but not prevent adhesion formation [7].

The most frequently applied topical substances to decrease adhesion formation after flexor tendon surgery are Hyaluronic Acid (HA) and its derivatives, 5-Fluorouracil (5-FU), lubricin, alginate solution and topical application of growth factors.

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Effects of pharmacologic agents on adhesion formation after flexor tendon repair

Effects of topically administered hyaluronic acid after flexor tendon repair

In 1934, Karl Meyer and his colleague John Palmer isolated a previously unknown chemical substance from the vitreous body of cow's eyes. They showed that this substance contained an uronic acid and an aminosugar. Therefore, they proposed the name "hyaluronic acid". HA is a negatively charged high-molecular-weight polysaccharide, which forms strikingly viscous solutions. Chemically is one group of connective tissue polysaccharides containing hexosamine, collectively called glycosaminoglycans [10]. When not bound to other molecules, it binds to water giving it a stiff, viscous quality similar to "Jell-o" [8,9]. The main biological function of HA is still unknown but several roles have been assigned to it. HA possesses a number of protective physiochemical functions that may provide some additional chondroprotective effects in vivo and may explain its longer term effects on articular cartilage. In experimental osteoarthritis, HA has protective effects on cartilage and exogenous HA is known to be incorporated into cartilage [8,10-13]. HA has also been successfully used in ophthalmology, cardiovascular system and dermatology. HA is a major component of the extracellular matrix, and it plays an important role in the early wound healing process [8,14]. Exogenous HA enhances chondrocyte HA and proteoglycan synthesis reduces the reproduction and activity of proinflammatory mediators and matrix metalloproteinases and alters the behavior of immune cells. These functions are manifested in the scavenging of reactive oxygen-derived free radical, the inhibition of immune complex adherence to polymorphonuclear cells. The inhibition of leukocyte and macrophage migration and aggregation and the regulation of fibroblast proliferation [15]. HA is an endogenous stimulator of Interleukin-1 (IL-1) production and IL-1 affects fibroblast proliferation and collagenase production [16]. HA is highly hydrophilic, it is a polymer that is well suited to applications requiring minimal cellular adhesion. Postoperative adhesions, which form between adjacent tissue layers following surgery, impede wound healing and often require additional surgical procedures to be repaired successfully. Barriers made from cross-linked HA have been effectively used to prevent such adhesions [17,18]. HA is a constituent of synovial fluid and has been shown to be present in a tendon sheath fluid [18]. In previous experimental studies, it was shown that HA reduced peritendinous adhesions and promoted tendon healing [19-21]. Ozgenel et al. [22] describe in own study effectiveness of a single application of HA in the control of peritendinous adhesions after flexor tendon surgery in humans. Their clinical study shows that repetitive injections of HA around the tenorrhaphy site after flexor tendon surgery reduce the formation of restrictive adhesions. However, large series are needed in order to support the results of this clinical study.

Effects of topically administered 5-Fluorouracil after flexor tendon repair

Antimetabolite drugs work by inhibiting essential biosynthetic processes, or being incorporated into macromolecules, such as DNA and RNA. 5-fluorouracil (5-FU) does both. Fluoropyrimidines were developed in the 1950s following the observation that rat hepatomas used the pyrimidine uracil-one of the four bases found in RNA, more rapidly than normal tissues, indicating that uracil metabolism was a potential target for antimetabolite chemotherapy [23].

5-FU is widely used in the treatment of a range of cancers, including colorectal and breast cancers, and cancers of the aerodigestive tract. Although 5-FU in combination with other chemotherapeutic agents improves response rates and survival in breast and head and neck cancers [24].

5-FU has also found application in ophthalmic surgery in attempt to control scarring after glaucoma surgery [25]. Refinements in the clinical technique have emerged from experiments based on the principle that a 5- minute irrigation with the 5-FU caused a long-term, titratable, and focal inhibition of scarring. Therefore, based on these results achieved by ophthalmic surgeons in prevention of scar after glaucoma filtration surgery, 5-FU has been proposed as a possible antiadhesive pharmacological agent after flexor tendon surgery [26-30].

Several studies have been performed to evaluate the efficacy of 5-FU on adhesion after flexor tendon surgery.

Sheng, et al. [31] assessed the effect of 5-FU applied topically on tendon adhesion biomechanical observation showed significant reduction in tendon adhesion.

Effects of topically administered lubricin after flexor tendon repair

The most important function of articular cartilage is to provide a low-friction surface that allows the bones of diarthrodial joints to slide smoothly against each other. Such remarkable frictional properties of the tissue are achieved, at least in part, by lubricin, a mucinous glycoprotein synthesized and secreted into synovial fluid both by chondrocytes in the superficial zone of the articular cartilage and by synoviocytes, and which is encoded by the Proteoglycan 4 (PRG4) gene [32]. During normal joint articulation, expression of lubricin plays a crucial role in both preventing cell attachment to the articular surface as well as maintaining lubrication properties at the cartilage-synovial fluid interfaces. Loss of lubricin influences the functional properties of synovial joints and could have a role in the pathogenesis of cartilage degeneration [33]. Furthermore; a recent study by Flannery, et al. [34] demonstrated that intra-articular lubricin injection following an Anterior Cruciate Ligament (ACL) injury was beneficial in retarding the degeneration of cartilage and the development of post-traumatic Osteoarthritis (OA).

Recent studies also showed that lubricin is visualized on the surface of fibrocartilaginous regions of the tendon, ACL, in the knee lateral collateral ligament, in the human Temporomandibular Joint (TMJ), disc and the bilaminar zone of the TMJ [35]. Therefore, besides its benefits in the treatment of rheumatoid arthritis and OA, lubricin has been shown to have an effect on reducing of tendon adhesion formation. Furthermore, a recent study by Zhao, et al. [36] demonstrated that treatment with the lubricin-containing gel after flexor tendon injuries on canine model is effective on decreasing postoperative flexor tendon adhesions.

Effects of topically administered alginate solution after flexor tendon repair

Alginate, a polysaccharide found in brown seaweed, has been used

extensively in the food, pharmaceutical and medical device industries. It is biocompatible and, in the form of crosslinked hydrogel, has a structure similar to that of Extracellular Matrix (ECM) [37]. Recently, alginate has been used in medicine as a wound dressing material and tissue engineering because of its easy gelation, good biocompatibility and low toxicity [38]. The best results have been obtained with alginate microcapsules in the field of allo- and xenogenic islet transplantation [39]. To create alginate with adequate handling properties in tendon surgery from Namba, et al. [40] was developed a technique involving very high concentrations of sodium alginate without using the crosslinking method. High molecular-weight alginate chains in this formulation adopt much coiled configurations in solution, such a configuration would allow permeation of molecules such as oxygen, glucose, insulin, and other nutrients of small molecular size that are necessary for cells and organs to survive. A possible mechanism by which alginate solution inhibits peritendinous adhesions is by providing a suitable environment for intrinsic tendon healing, both as a selective barrier and as a cell delivery medium. According to Namba, et al. [40] the instilled alginate solution works by interposing between the lacerated tendon and the injured sheath as a selective barrier, thereby avoiding early scar formation.

Effects of topically administered of growth factors after flexor tendon repair

Despite great advances in flexor tendon healing have been achieved through developing suture techniques and rehabilitation protocols, recent studies are focused more directly on bimolecular level of healing process [41,42]. Growth factors represent one of the largest of the molecular families involved in the healing process of tendon and a considerable number of studies have been undertaken in an effort to elucidate their many functions and behaviors during healing progression. Whilst a large amount of data on these molecules have been produced in recent years, much work still needs to be undertaken to fully understand their varied functions and multiple synergies [43].

The five of the best studied growth factors during tendon healing are: Insulin-Like Growth Factor-I (IGF-I), Transforming Growth Factor ß (TGF-ß), Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF), and Basic Fibroblast Growth Factor (bFGF).

IGF-I, PDGF and bFGF have vital functions during the early and intermediate stages of healing during which they aid in the migration and proliferation of fibroblast and stimulate the extracellular matrix synthesis. TGF-ß and VEGF also have some role in these processes and in addition play crucial role in the remodeling phase, regulating angiogenesis within the wound site [42].

Besides its use in the evaluation on process healing of tendon this molecule is employed also for therapeutic purposes.

The influence of growth factors on the ligament and tendons was demonstrated by a number of animal studies. Murray, et al. [44] has demonstrated improved healing in the primary intraoperative repair of porcine ACL, after biologic augmentation with growth factors.

High levels of TGFß-1 have been implicated in tendon adhesion formation, which can significantly decrease the range of motion of a tendon. In an effort to counter this Chang, et al. [44] has conducted in vivo studies on TGFß-1 and -2 within the healing rabbit zone 2 flexor tendon. Their work used to neutralize TGFß-1 and -2 antibodies in an attempt to decrease TGFß-1 and -2 activities and the associated loss of range motion. Twenty-two animals underwent a transaction of the zone 2 middle digit flexor digitorum profundus followed by a treatment of either phosphate-buffered saline.TGFß-1 antibody, or a combination of TGFß-1 and -2 antibodies. They observed that the animals that received antibodies to TGFß-1 had around twice the range of motion that those that did not

Some success has already been achieved utilizing growth factors as therapeutics using a variety of delivery techniques, including direct injection, surgical implants, collagen or gel vehicles and therapy. In most of these studies, the application of a single molecule has shown some enhancement of healing: however, in general this temporary boost of a single healing signal soon becomes diluted out and has only limited effect on the final outcome [45].

Methods Used for Evaluating the Healing Process after Tendon Repair in Experimental Research

There are several methods used for evaluating the healing process of tendons after repair: biomechanical testing, macroscopic evaluation, microscopic evaluation, cell isolation, and growth factor analysis.

Biomechanical evaluation of healing process after tendon repair

Biomechanical properties of tendons during their repair and regeneration have been studied extensively and their properties compared with normal tendon. These tests have shown that current procedures used for repair produce a tissue with biomechanical properties that are inferior to those of normal tendon [46].

Because the primary function of tendons is to transmit tensile forces, experimental studies of the biomechanical properties of these tissues are generally performed in uniaxial tension. Testing isolated tendon tissue is inherently difficult for several reasons (i.e., slipping of the specimen from the clamp, stress concentrations, shortness of substance of tendons).

Testing isolated tendon tissue is inherently difficult for several reasons (i.e., slipping of the specimen from the clamp, stress concentrations, shortness of substance of tendons). As a result, tensile tests have been performed with the tendon insertions to bone left anatomically intact (e.g., the entire bone-tendon-bone complex) [47]. From this test, the following parameters can be obtained representing the structural properties of the complex; include stiffness, ultimate load, ultimate elongation, and energy absorbed at failure [48].

From the same uniaxial tensile test, a stress-strain curve of the tendon substance can also be obtained. This is done by normalizing the tensile load by the cross-sectional area (i.e., stress) and by normalizing the change in elongation in a defined region of the tissue midsubstance by the initial length (i.e., strain). By engineering standards, this requires an aspect ratio (ratio to length width) of greater than 10 to 1 [46]. The parameters obtained from this test, represents the mechanical properties, or quality, of the tissue substance include the tangent module, ultimate tensile stress (or tensile strength), ultimate strain, and strain energy density of tendon substance [48].

Table 1: Macroscopic grading system for adhesions according to Tang et al. [44]

Points	Features of Adhesions
Length (quantity)	
0	No adhesions
1	<5 mm
2	5 to 10 mm
3	>10 mm
Density and tolerance for mobility (quality)	
0	No adhesions
1	Loose, elastic, mobile
2	Moderate mobility
3	Rigid, dense, immobile
Grading of adhesions	
0	Absent
1	1 to 2 Inferior
2	3 to 4 Medium
3	5 to 6 Severe

Table 2: Microscopic evaluation of adhesions according to Tang et al. [44]

Points	Features of adhesions
Quantity	
0	No apparent adhesions
1	A number of scattered filaments
2	A large number of filaments
3	Countless filaments
Quality	
0	No apparent adhesions
1	Regular, elongated, fine, filamentous
2	Irregular, mixed, shortened, filamentous
3	Dense, not filamentous
Grading of adhesions	
0	None
2	Slight
3 to 4	Moderate
5 to 6	Severe

Macroscopic evaluation of healing process after tendon repair

For macroscopic evaluation of adhesion formation the most commonly used method was grading system according to Tang et al. [49] (Table 1). According to this grading system, quantitative and qualitative analysis of tendon adhesions can be done. Quantitative analysis includes the length of tendon adhesions in relation with tendon sheath and surrounding structures. Qualitative analysis includes evaluation of density of adhesions, movement capability of the repaired tendon.

Table 3: Microscopic grading system for tendon healing according to Tang et al. [44]

Excellent	Continuity of the tendon was re-established, and the epitenon was smooth
Good	Regular intratendinous collagen bundles, but the epitenon was destroyed by adhesions
Fair	Irregular intratendinous collagen bundles, and partly interrupted by adhesions
Poor	Disconnection of the repair site by adhesion tissues

Microscopic evaluation

The grading scale according to Tang, et al. [49] also was used most commonly to evaluate the extent and severity of the formation of adhesions in the peritendinous region (Table 2). In this grading system, the adhesions were evaluated both quantitavely and qualitatively. The healing status of the tendons according to this grading scale was evaluated by the continuity of the repaired tendons, the condition of healing of the epitenon peritendinous adhesions and the arrangement of the intratendinous collagen fibers (Table 3).

Cell isolation

Human tendon cells with this method can be isolated. Tendons are cuted and placed into a 2% collagenase solution. The resulting tenocyte cell suspension is filtered, collagenase was removed and the tenocytes were cultured in Dulbecco`s modified Eagle`s medium with fetal bovine serum and penicillin/streptomycin. The tenocyte genotype are confirmed by quantitative real time polymerase chain reaction for the tenocyte markers tenascin-C, decorin, and collagen types I and III.

Growth Factor analysis

Growth Factors (GF), beside its use for therapeutic purposes also are used for evaluation of different stages of tendon healing.

Platelet-Rich Plasma (PRP) contains several growth factors, including PDGF, TGFß, fibroblastic growth factor, VEGF, IGF-I, and epidermal growth factor (EGF) [50].

There are currently several methods of concentrating GF. PRP involves extracting the portion of plasma that contains a higher concentration of platelets after centrifugation of autologous whole blood [51].

PRP preparations have certain steps in common. The first step is the withdrawal of the patients peripheral blood, followed by centrifugation to yield 3 layers – the red layer (containing erythrocytes), white layer (leukocytes and inflammatory cytokines), and the yellow layer (containing plasma, platelets and growth factors).

Currently, there are many commercial systems available for PRP preparation, for example: ACP-NS by Arthrex, GPS by Biomet and Magellan by Medtronic. These systems differ in terms of speed of centrifugation, number of centrifugations, the use of anticoagulant, the presence of leukocytes in the preparation, and the use of activators [52].

Conclusion

Surgical repair of the damaged tendon is often complicated by scar tissue formation around the damaged tendon. Numerous data from the literature suggest that in order to prevent scar formation,

topical pharmacological agents at the site of peripheral tendon repair can be applied. These pharmacological agents prevent scar formation at the site of tendon repair. The mechanisms of action by which these substances operate in prevention of adhesions are described in detail. There are several methods for evaluation of tendon repair following topical application of different pharmacological agents, such us biomechanical evaluation, macroscopic and microscopic evaluation, cell isolation, and analysis of growth factors. These methods are of great value in functional assessment of the damaged tendon. Although most of the studies have demonstrated that these topical pharmacological agents have a notable effect in the prevention of adhesion formation their application need to withstand the test of adequately powered human trials before their justification for potential benefit in clinical practice.

References

1. Griffin M, Hindocha S, Jordan D, Saleh M, Khan W. An overview of the management of flexor tendon injuries. Open Orthop J. 2012; 6: 28-35.
2. Strickland JW. Development of flexor tendon surgery: twenty-five years of progress. J Hand Surg Am. 2000; 25: 214-235.
3. Beredjiklian PK. Biologic aspects of flexor tendon laceration and repair. J Bone Joint Surg Am. 2003; 85-85A: 539-550.
4. Duci SB, Arifi HM, Ahmeti HR, Manxhuka-Kerliu S, Neziri B. Biomechanical and Macroscopic Evaluations of the Effects of 5-Fluorouracil on Partially Divided Flexor Tendon Injuries in Rabbits. Chin Med J (Engl). 2015; 128: 1655-1661.
5. Gelberman RH, Manske PR. Factor's influencing flexor tendon adhesions. Hand Clin. 1985; 1: 35-42.
6. Duci SB. Justification of the Topical Use of Pharmacological Agents on Reduce of Tendon Adhesion after Surgical Repair. SM J Orthop. 2015; 1: 1006.
7. Khanna A, Gougoulias N, Maffulli N. Modalities in prevention of flexor tendon adhesion in the hand: what have we achieved so far? Acta Orthop Belg. 2009; 75: 433-444.
8. Necas J, Bartosikova L, Brauner P, Kolar J. Hyaluronic acid (hyaluronan): a review. Vet Med. 2008; 52: 397-411.
9. Mrácek A, Varhaníková J, Lehocký M, Grundelová L, Pokopcová A. The influence of Hofmeister series ions on hyaluronan swelling and viscosity. Molecules. 2008; 13: 1025-1034.
10. Laurent TC, Fraser JR. Hyaluronan. FASEB J. 1992; 6: 2397-2404.
11. Mekaj AY, Morina AA, Bytyqi CI, Mekaj YH, Duci SB. Application of topical pharmacological agents at the site of peripheral nerve injury and methods used for evaluating the success of the regenerative process. J Orthop Surg Res. 2014; 9: 94.
12. Akmal M, Singh A, Anand A, Kesani A, Aslam N. The effects of hyaluronic acid on articular chondrocytes. J Bone Joint Surg Br. 2005; 87: 1143-1149.
13. Antonas KN, Fraser JR, Muirden KD. Distribution of biologically labelled radioactive hyaluronic acid injected into joints. Ann Rheum Dis. 1973; 32: 103-111.
14. Weigel PH, Fuller GM, LeBoeuf RD.A model for the role of hyaluronic acid and fibrin in the early events during the inflammatory response and wound healing. J Theor Biol. 1986; 119: 219-234.
15. Balazs EA, Denlinger JL. The role of hyaluronic acid in arthritis and its therapeutic use in Osteoarthrithis: Current Clinical and Fundamental Problems: Edited by Peyron JG. Basle: Geigy. 1984: 165-174.
16. Hiro D, Ito A, Matsuta K, Mori Y. Hyaluronic acid is an endogenous inducer of interleukin-1 production by human monocytes and rabbit macrophages. Biochem Biophys Res Commun. 1986; 140: 715-722.
17. Leach JB, Schmidt CE. Hyaluronan. Encyclopedia of Biomaterials and Biomedical Engineering. Marcel Dekker, New York. 2004; 779-788.
18. Hagberg L, Tengblad A, Gerdin B.Hyaluronic acid in flexor tendon sheath fluid after sheath reconstructions in rabbits. A comparison between tendon sheath transplantation and conventional two stage procedures. Scand J Plast Reconstr Surg Hand Surg. 1991; 25: 103-107.
19. Amiel D, Ishizue K, Billings E Jr, Wiig M, Vande Berg J. Hyaluronan in flexor tendon repair. J Hand Surg Am. 1989; 14: 837-843.
20. Hagberg L, Gerdin B. Sodium hyaluronate as an adjunct in adhesion prevention after flexor tendon surgery in rabbits. J Hand Surg Am. 1992; 17: 935-941.
21. Tuncay I, Ozbek H, Atik B, Ozen S, Akpinar F. Effects of hyaluronic acid on postoperative adhesion of tendo calcaneus surgery: an experimental study in rats. J Foot Ankle Surg. 2002; 41: 104-108.
22. Ozgenel GY, Etoz A. Effects of repetitive injections of hyaluronic acid on peritendinous adhesions after flexor tendon repair, a preliminary randomized, placebo controlled clinical trial. Ulus Travma Acil Cerrahi Derg; 2012; 18: 11-17.
23. Rutman RJ, Cantarow A, Paschkis KE. Studies in 2-acetylaminofluorene carcinogenesis. III. The utilization of uracil-2-C14 by preneoplastic rat liver and rat hepatoma. Cancer Res. 1954; 14: 119-123.
24. IMPACT. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Lancet. 1995; 345: 939-944.
25. Shaieb MD1, Singer DI.Tensile strengths of various suture techniques. J Hand Surg Br. 1997; 22: 764-767.
26. Lee H. Double loop locking suture: a technique of tendon repair for early active mobilization. Part I: Evolution of technique and experimental study. J Hand Surg Am. 1990; 15: 945-952.
27. Lim BH, Tsai TM. The six-strand technique for flexor tendon repair. Atlas Hand Clin. 1996; 1: 65-76.
28. Dovan TT, Ditsios KT, Boyer MI. Eight-strand core suture technique for repair of intrasynovial flexor tendon lacerations. Tech Hand Up Extrem Surg. 2003; 7: 70-74.
29. Savage R. In vitro studies of a new method of flexor tendon repair. J Hand Surg Br. 1985; 10: 135-141.
30. Viinikainen A, Göransson H, Huovinen K, Kellomäki M, Rokkanen P. A comparative analysis of the biomechanical behaviour of five flexor tendon core sutures. J Hand Surg Br. 2004; 29: 536-543.
31. Sheng J, Zeng B, Jiang P, Fan C. Effect of local basic fibroblast growth factor and 5-fluorouracil on accelerationg healing and preventing tendon adhesion after flexor tendon repair. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2011; 25: 711-7.
32. Su JL, Schumacher BL, Lindley KM, Soloveychik V, Burkhart W. Detection of superficial zone protein in human and animal body fluids by cross-species monoclonal antibodies specific to superficial zone protein. Hybridoma. 2001; 20: 149-157.
33. Young AA, McLennan S, Smith MM, Smith SM, Cake MA. Proteoglycan 4 downregulation in a sheep meniscectomy model of early osteoarthritis. Arthritis Res Ther. 2006; 8: R41.
34. Flannery CR, Zollner R, Corcoran C, Jones AR, Root A.Prevention of cartilage degeneration in a rat model of osteoarthritis by intraarticular treatment with recombinant lubricin. Arthritis Rheum. 2009; 60: 840-847.
35. Rees SG, Davies JR, Tudor D, Flannery CR, Hughes CE. Immunolocalisation and expression of proteoglycan 4 (cartilage superficial zone proteoglycan) in tendon. Matrix Biol. 2002; 21: 593-602.
36. Zhao C, Sun YL, Kirk RL, Thoreson AR, Jay GD. Effects of a lubricin-containing compound on the results of flexor tendon repair in a canine model in vivo. J Bone Joint Surg Am. 2010; 92: 1453-1461.
37. Lee KY, Mooney DJ. Hydrogels for tissue engineering. Chem Rev. 2001; 101: 1869-1879.

38. Skjak-Braek G. Alginates: Biosyntheses and structure-function relationships relevant to biomedical and biotechnological applications. Biochem Soc Trans. 1992; 20: 27-33.

39. Mullen Y, Maruyama M, Smith CV. Current progress and perspectives in immunoisolated islet transplantation. J Hepatobiliary Pancreat Surg. 2000; 7: 347-357.

40. Namba J, Shimada K, Saito M, Murase T, Yamada H. Modulation of peritendinous adhesion formation by alginate solution in a rabbit flexor tendon model. J Biomed Mater Res B Appl Biomater. 2007; 80: 273-279.

41. James R, Kesturu G, Balian G, Chhabra AB. Tendon: biology, biomechanics, repair, growth factors, and evolving treatment options. J Hand Surg Am. 2008; 33: 102-112.

42. Molloy T, Wang Y, Murrell G. The roles of growth factors in tendon and ligament healing. Sports Med. 2003; 33: 381-394.

43. Hefti FL, Kress A, Fasel J, Morscher EW. Healing of the transected anterior cruciate ligament in the rabbit. J Bone Joint Surg Am. 1991; 73: 373-383.

44. Murray MM, Spindler KP, Ballard P, Welch TP, Zurakowski D. Enhanced histologic repair in a central wound in the anterior cruciate ligament with a collagen-platelet-rich plasma scaffold. J Orthop Res. 2007; 25: 1007-1017.

45. Müller SA, Todorov A, Heisterbach PE, Martin I, Majewski M. Tendon healing: an overview of physiology, biology, and pathology of tendon healing and systematic review of state of the art in tendon bioengineering. Knee Surg Sports Traumatol Arthrosc. 2015; 23: 2097-2105.

46. Riemersa DJ, Schamhardt HC. The cryo-jaw, a clamp designed for in vitro rheology studies of horse digital flexor tendons. J Biomech. 1982; 15: 619-620.

47. Jung HJ, Fisher MB, Woo SL. Role of biomechanics in the understanding of normal, injured, and healing ligaments and tendons. Sports Med Arthrosc Rehabil Ther Technol. 2009; 1: 9.

48. Woo SL, Abramowitch SD, Kilger R, Liang R. Biomechanics of knee ligaments: injury, healing, and repair. J Biomech. 2006; 39: 1-20.

49. Tang JB, Shi D, Zhang QG. Biomechanical and histologic evaluation of tendon sheath management. J Hand Surg Am. 1996; 21: 900-908.

50. Lyras DN, Kazakos K, Verettas D, Botaitis S, Agrogiannis G. The effect of platelet-rich plasma gel in the early phase of patellar tendon healing. Arch Orthop Trauma Surg. 2009; 129: 1577-1582.

51. Creaney L, Hamilton B. Growth factor delivery methods in the management of sports injuries: the state of play. Br J Sports Med. 2008; 42: 314-320.

52. Lopez-Vidriero E, Goulding KA, Simon DA, Sanchez M, Johnson DH. The use of platelet-rich plasma in arthroscopy and sports medicine: optimizing the healing environment. Arthroscopy. 2010; 26: 269-278.