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Letter to the Editor

Justification of the Topical Use of Pharmacological Agents on Reduce of Tendon Adhesion after Surgical Repair

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Tendon injuries are the second most common hand injuries in orthopedic patients. Tendon adhesions are one of the most concerning complications after surgical repair of the flexor tendon injury, particularly in zone II, which extends from the A1 pulley to the distal insertion of the Flexor Digitorum Superficialis (FDS) tendon in the finger [1,2].

Despite advances in surgical techniques and improvements in postoperative rehabilitation programs, adhesions between the tendon and the surrounding tissues continue to be an important problem after primary flexor tendon repair [2].

Several studies have shown that some pharmaceutical agents which are used topically at the site of tendon repair decrease adhesion formation after flexor tendon surgery. From these pharmaceutical agents the most frequently applied topical substances are Hyaluronic Acid (HA) and its derivatives, 5-Fluorouracil (5-FU), lubricin and topical application of growth factors.

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 amino sugar. Therefore, they proposed the name "hyaluronic acid" and this marked the birth announcement of one of Nature`s most versatile and fascinating macromolecules [3,4]. Hyaluronate (HA) is found in synovial fluid around tendon sheaths. Its use in experimental studies showed the decrease of the adhesion formation after tendon repair [5]. To evaluate the effects of HA, different experimental models have been used: animal species (dog, chicken, rabbit, rat, and horse), tendons (intra or extra synovial; auto or allograft), and procedures of induced tendon damage (surgical, collagenase, or steroid lesion) [6]. In previous experimental studies, it was shown that HA reduced peritendinous adhesions and promoted tendon healing [7-9]. Ozgenel [10] 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.

Antimetabolite drugs work by inhibiting essential biosynthetic processes, or being incorporated into macromolecules, such as DNA and RNA, and inhibiting their normal function. The fluoropyrimidine 5-fluorouracil (5-FU) does both [11]. Besides its use in chemotherapy it is proved that 5-FU reduce proliferative and inflammatory response, recent studies have shown that 5-FU also reduce cellular cytokine response and the activity of the known pro-scaring agent, transforming growth factor beta (TGF-b) 1 [12]. 5-FU has also found application in ophthalmic surgery in an attempt to control scarring after glaucoma surgery.

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 the prevention of scar after glaucoma filtration surgery, 5-FU has been proposed as a possible anti adhesive pharmacological agent after flexor tendon surgery [13-17].

Several studies have been performed to evaluate the efficacy of 5-FU on adhesions, gliding resistance, and tendon healing.

The effect of 5-FU in reduction of adhesion formation after flexor tendon surgery is evidenced in a study conducted by Guo, et al. [18] who assessed the effect of 5-FU applied topically in a concentration of 25 mg/ml on tendon adhesion and the healing process after flexor tendon repair in Lenghorn chickens. The macroscopic and histological observation showed that the peritendinous adhesions were looser when compared with the control group.

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) genes [19].

Recent studies also showed that lubricin is visualized on the surface of fibro cartilaginous 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 [20]. 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. [21] demonstrated that treatment with the lubricin-containing gel after flexor tendon injuries on canine model is effective in decreasing postoperative flexor tendon adhesions.

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 [22].

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). These growth factors have important, varied roles within the healing tendon.

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

High levels of TGFß-1, for example, 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. [23] has conducted *in vivo* studies on TGFß-1and -2 within the healing rabbit zone II 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 II 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 (defined as the combined angular measurement of flexion at the proximal and distal interphalangeal joints) that those that did not [24].

Traumatic injuries of the tendon are very common. 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. However, most studies have been carried out in animals with very few human trials.

Applications of topical pharmacological agents to reduce of tendon adhesions need to withstand the test of adequately powered human trials before their justification for potential benefits in clinical practice.

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