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Article *in* Annals of plastic surgery · June 2017

DOI: 10.1097/SAP.0000000000001169

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Prevention of Peritendinous Adhesion Formation After the Flexor Tendon Surgery in Rabbits

A Comparative Study Between Use of Local Interferon-α, Interferon-β, and 5-Fluorouracil

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Background: Peritendinous adhesion is the most common complication after tendon surgery, particularly in zone II of the hand. Prevention of inflammation around the tendon, which develops after trauma and surgery, can decrease the tendon adhesion formation. This study compares the effect of some anti-inflammatory cytokines with 5-fluorouracil (5-FU) on the tensile strength and in prevention of peritendinous adhesion formation.

Methods: Sixteen rabbits were allocated equally into 4 groups. Tendons of the index and ring fingers in zone II of the right hind paw were cut in all animals and then repaired. Interferon (IFN)-α in group 1, 5-FU in group 2, normal saline in group 3, and IFN-β in group 4 were locally applied to the repaired sites. Three weeks later, tensometric and histopathologic evaluations were performed.

Results: The force required for removing the tendon from the sheath was not different between the groups ($P = 0.130$), but the time required for removal was significantly shorter in 5-FU group ($P = 0.049$). The strength of repair was not different between the groups in terms of force and time needed for rupture ($P = 0.11$ and 0.67, respectively). In histopathologic examination, normal architecture of the tendon and peritendon environment was less disturbed in the IFN groups, especially in IFN-β specimens.

Conclusions: Local application of 5-FU significantly reduced peritendinous adhesion. Local IFN-α and IFN-β had no significant effect on the prevention of peritendinous adhesion formation. The strength of the repair was not affected by these cytokines and 5-FU.

Key Words: interferon-α, interferon-β, 5-fluorouracil, peritendinous adhesion, tendon surgery, tendon injury

(*Ann Plast Surg* 2017;00: 00–00)

Received January 7, 2017, and accepted for publication, after revision May 4, 2017.

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Conflicts of interest and sources of funding: None of the authors has a financial interest or conflicts of interest and ethical adherence in any of the products, devices, or drugs mentioned in this article. This study was funded and supported by Iran University of Medical Sciences (Grant No 15151).

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ISSN: 0148-7043/17/0000–0000
DOI: 10.1097/SAP.0000000000001169

The most common complications after tendon surgeries are peritendinous adhesion formation and rupture.[1–6]

Adhesion is more common in zone II of the flexor tendons of the hand and leads to functional disturbances, which call for prolonged rehabilitation and reoperation and cause psychosocioeconomic problems.[1,2,7,8]

Two mechanisms are thought to mediate tendon repair: the intrinsic repair that is based on the inherent healing functions of the tendon cells (tenocytes) and the extrinsic repair process, which includes any repair action that originates from outside of the tendon. Any intervention that blocks extrinsic repair and/or enhances intrinsic repair can prevent adhesion formation and increase the strength of the repair.[1,3,9–12]

There are numerous studies that have investigated the prevention of peritendinous adhesions. Modification of surgical techniques, such as meticulous manipulation of the tendon, repair of the tendon sheath, number of sutures, use of mechanical barriers, systemic or local application of medications and chemicals, postoperative mobilization protocols, and postoperative application of the ultrasound and electromagnetic waves, are examples of such maneuvers to improve the tendon surgery results and prevent adhesion formation.[1,3,8,9,13–28]

If peritendinous inflammation can be prevented during the repair period, then adhesion formation decreases and tendon gliding is facilitated.[1,9,11,25]

Inflammation is the result of cell proliferation or change in the cellular behavior. Cytokines are hormone-like proteins that modulate cell behavior and include interleukins (ILs), lymphokines, monokines, interferons (IFNs), tumor necrosis factors, and chemokines.[29]

Cytokines are divided into broad categories: pro-inflammatory and anti-inflammatory. Interleukin-1, IL-12, IL-18, IFN-γ, and tumor necrosis factor are pro-inflammatory cytokines. Interleukin-4, IL-10, IL-13, IFN-α, and IFN-β are anti-inflammatory cytokines. Cytokines in the latter category prevent cell proliferation and reduce inflammatory response. Exact cytokine actions are not predictable, and they may have paradoxical behaviors in various doses.[29–32]

For the first time in the literature, this study was designed to evaluate the effects of IFN-α and IFN-β, as anti-inflammatory cytokines, on peritendinous adhesion formation and tensile strength after the flexor tendon surgery. The obtained results were compared with those of 5-fluorouracil (5-FU) and control.

MATERIALS AND METHODS

Sixteen white New Zealand rabbits were chosen for this study. The national protocol on using and caring for animals in experimental studies was observed. The study was confirmed by ethics committee of the university. The animals were transferred to the laboratory 3 days before the operation and were allocated equally into 4 groups (1–4).

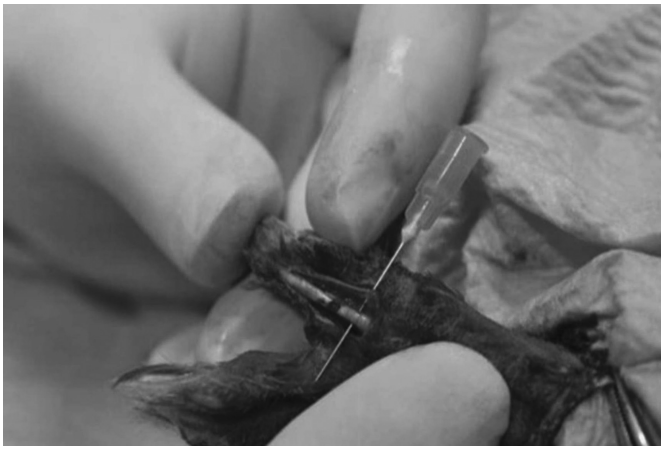

FIGURE 1. Exploration and sharp cut of the flexor digitorum profundus.

The rabbits were anesthetized by intramuscular injection of 50 mg/kg ketamine (Alphasan, Netherlands) and 5 mg/kg xylazine (Alfasan, Netherlands).

For each rabbit, the right hind paw was shaved and scrubbed and the animal was then transferred to a sterile field. All the procedures were performed by a single surgeon under 4.5 times loupe magnification. Operation was performed over index and ring fingers in each right hind paw to increase samples and also prevent spreading of testing materials on adjacent fingers. Through a longitudinal incision over the middle phalanx, the skin was cut and the flexor sheath was opened. Then, the flexor digitorum profundus tendon was explored and sharply transected. The flexor digitorum superficialis tendon was removed. Repair was done using modified Kessler technique with 5/0 nylon for core suturing supplemented with 6/0 nylon peripheral sutures (Figs. 1 and 2). The animals in each group were treated as follows: group 1, IFN-α; group 2, 5-FU; group 3, normal saline; group 4, IFN-β.

The 5-FU solution (50 mg/mL, EBEWE Pharma, Austria), IFN-α solution (10^6 IU/mL, PDFeron-B, Pooyesh Darou, Iran), and IFN-β solution (10^6 IU/mL, Betaferon, Bayer, Germany) were prepared according to their respective manufacturer's direction. Small cotton pieces were used for application. Care was taken to prevent cross contamination. Each finger was treated for a period of 5 minutes. The tendon sheath was not repaired. A proximal tenotomy was done for unloading the tension off the repair site. Then, the skin was closed by interrupted 4/0 nylon sutures, and a splint was applied for 72 hours.

FIGURE 2. Repaired tendon.

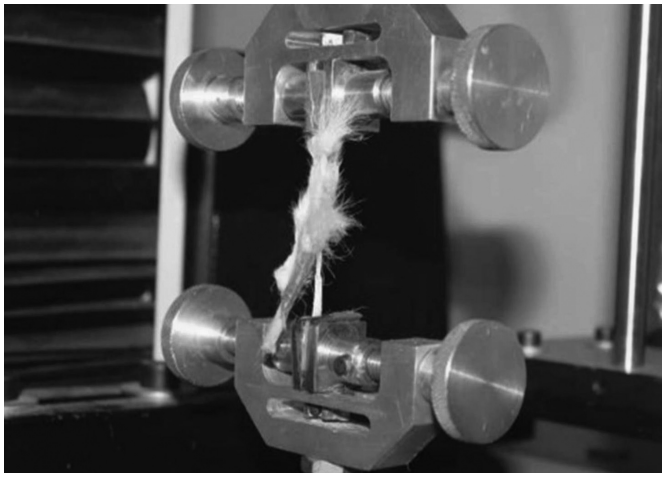

FIGURE 3. Tensometric evaluation.

The animals were housed in separate cages with free access to food and water.

After 3 weeks, the animals were euthanized by using CO2 gas. The limbs were amputated at the ankle level. From each group, 3 and 5 fingers were used for histopathologic and tensometric examinations, respectively.

In tensometric examination, the insertion (distal part) of the flexor digitorum profundus was transected through a small incision in the distal phalanx of the finger. The tip of the finger was secured to the fixed jaw of a tensometric machine (SANTA, STM-20, Iran), and the proximal part of the tendon was fixed to the moving jaw (load, 20 kg or 200 N; speed, 5 mm/min); then, the tendon was pulled out of the sheat (Fig. 3).

The force and time required for removing the tendon from the sheath were recorded. These 2 variables were measures of the severity of peritendinous adhesion. We also recorded the force and time required for the rupture of the tendon repair site.

For histopathologic examination, the specimens fixed in 10% buffered formaldehyde solution were decalcified using formic acid-sodium citrate method, which was prepared as follows: solution A, 50 g sodium citrate was dissolved in 250 mL of distilled water; solution B, 125 mL of 90% formic acid was added to 125 mL of distilled water. To make a working solution, we mixed equal volumes of solution A and solution B before use. The decalcified specimens were processed in a tissue processor. Paraffin blocks were made and 5- to 6-nm-thick sections were cut by a microtome. The sections were then stained with Harris hematoxylin and eosin and examined using a binocular; the width and length of the tendon adhesion were measured at a magnification of 50 times with an eyepiece graticule. Moreover, subjective assessments of regeneration criteria at the adhesion site including fibroplasia, fine vascular formation, and collagen precipitation were carried out. In each specimen, multiple filed examinations were performed.

The data were analyzed by Kolmogorov-Smirnov test to confirm normal distribution and Levene test to assess the equality of variances in different samples using SPSS 21. Then, the data were analyzed using 1-way analysis of variance. Dunnett test was also used as a post hoc method to compare each individual group.

RESULTS

The results are summarized in Tables 1 to 4. The difference between the groups was not significant regarding the force needed for removal of the tendon from the sheath ($P = 0.130$), but the difference in time required for tendon removal between the groups was significant

TABLE 1. Force and Time for Removal of the Tendon From the Sheath

Group	Force (Mean and Standard Deviation), N¶	*P*	Time (Mean and Standard Deviation), s¶	*P*
INF-α	16.26 ± 4.61	0.130	10.04 ± 4.72	0.005
Control	14.19 ± 7.18		8.57 ± 1.70	
5-FU	9.85 ± 5.30		5.15 ± 2.02	
INF-β	14.37 ± 3.76		6.09 ± 1.13	

¶The unit measurement of force is Newton (N); the unit measurement of time is second (s).

($P = 0.005$) (Table 1). It showed that there was a significant difference between the control and 5-FU groups ($P = 0.049$) (Table 2).

There was no significant difference between the groups in terms of force ($P = 0.11$) and time ($P = 0.67$) needed for rupture of the tendon at the repair site (Table 3). In histopathologic evaluation, the characteristics of tendon and peritendinous environment showed a lesser degree of alteration in IFN groups, especially in IFN-β specimens (Table 4). The normal architecture of the tendon and peritendinous structure appeared normal in the IFN-β group. In the 5-FU group, there was severe adhesion and inflammation. This finding was inconsistent with tensometric findings.

DISCUSSION

To the best of our knowledge, the present study is the first survey in the literature designed to show the effect of local anti-inflammatory cytokines, such as IFN-α and IFN-β, on the tensile strength and in the prevention of peritendinous adhesion formation after the flexor tendon surgery and compare those results with the local use of 5-FU. The gained data from the present study showed that the local use of IFN-α and IFN-β did not reduce the peritendinous adhesion formation after the tendon surgery. In contrast, 5-FU significantly reduced the peritendinous adhesion formation. Moreover, all of the studied agents did not increase the tensile strength.

The incidence of tendon adhesion in the hand is approximately 4% to 10%.[1,19,28] Meticulous, nontraumatic surgical technique and postoperative mobilization are the main initiatives to prevent adhesion formation. There are numerous studies on the best techniques for tendon repair. Material, diameter, tension, and purchase of the core sutures, number of sutures, and technique of peripheral sutures are used the influential factors in formation or prevention of peritendinous adhesion. Although 4 or more stranded techniques have been recommended after development of active mobilization protocols, in one study, modified Kessler technique could decrease the adhesion formation by 134%.[1–3,33]

The importance of tendon sheath repair is the subject of extensive debates. There are well-designed studies on the effect of tendon sheath repair on prevention of tendon adhesion; also, there are other studies against it. However, no good clinical trial exists with regard to this topic.[1,9,13,15,22]

TABLE 2. Analysis of the Differences of Time Variable for Removal of Tendon from the Sheath

Comparing Group	Mean Differences	The Standard Error	*P*
INF-α versus control	1.46	1.37	0.58
5-FU versus control	−3.42	1.37	*0.049
INF-β versus control	−2.48	1.37	0.19

*Significantly different.

TABLE 3. Time and Force for Tendon Rupture

Group	Force (Mean and Standard Deviation), N¶	*P*	Time (Mean and Standard Deviation), s¶	*P*
INF-α	38.26 ± 9.53	0.11	4.61 ± 1.26	0.67
Control	42.86 ± 8.12		4.91 ± 1.26	
5-FU	43.84 ± 11.16		5.98 ± 3.11	
INF-β	32.36 ± 7.89		5.87 ± 4.72	

¶The unit measurement of force is Newton (N); the unit measurement of time is second (s).

Various mechanical barriers are widely used in experimental studies. Although they demonstrated good results in these studies, their clinical usage is not popular yet. Foreign body reaction, displacement, delayed tendon repair, tendon necrosis, and exacerbation of adhesion formation are complications of these barriers.[1,3,7,27]

Nonsteroidal anti-inflammatory drugs have been studied in animal and human experiments. These agents have weak anti-adhesion effects, but no well-designed clinical trial has addressed this effect so far.[1,27]

The onion extract (extractum cape) in rabbits, when used locally during repair, could decrease peritendinous adhesions.[25]

Although β-aminopropionitrile, which prevents collagen cross-linking, decreases adhesion by application to skin after tendon repair in experimental studies, it is not used for humans because of its toxicity.[34]

The lactoferrin peptide (PXL01) can prevent adhesion formation in the flexor tendons of rabbits; however, no clinical studies have been done to evaluate this effect.[7,8]

Transforming growth factor-β is a cytokine that has a role in healing process and increasing adhesion and scar formation. Local blockade of this factor by natural mannose-6-phosphate or synthetic antibody can prevent adhesion formation after tendon surgery in animal models.[1,9,35]

The most common local medications for reduction of tendon adhesion formation are hyaluronic acid and 5-FU. There are 2 explanations concerning the effect of 5-FU: decreasing gliding force and changing cellular proliferation and behavior; the latter mechanism has gained more credibility.[1,5,6,16,22,26]

In one study on the flexor tendon of dogs, local application of 5-FU could prevent adhesion formation without any adverse effects on tendon healing. However, prevention of adhesion formation was observed only on day 10; evaluation on day 21 and 42 showed no effect.[6]

In another study on chickens, the sustained-release gel of 5-FU could decrease adhesion formation at low concentration of 10 mg. Nonetheless, high doses of 20 and 30 mg produced severe inflammation and peritendinous adhesion.[26]

In this study, local application of 5-FU could prevent peritendinous adhesion formation. The force and time needed for removing the tendon from its sheath were proportional to the extent of adhesion to the neighboring tissue, and the time for tendon removal was significantly shorter in the 5-FU group ($P = 0.049$). However, in histopathologic examination of the specimens, severe inflammation and adhesion were noted, and this might restrict the application of this medication in clinical studies. We have no any explanation for these inconsistencies between mechanical and histopathology results.

Our results implied that 5-FU had no adverse effect on the strength of tendon healing.[10] Although we could not find any clinical trial evaluating these effects of 5-FU, we believe that there is enough evidence in experimental studies that could suggest phase 1 clinical evaluation of this antimetabolite medication for local application after tendon surgery.

TABLE 4. Histopathology Characteristic of Specimens

Specimen No	Group	Granulation of Score	Adhesion of Length	Thickness of Tendon	Neovascularization	Fibroblasts	Collagen	Adhesion Sheath	Infection of Evidence	Final Score
1	Control	1	0	Normal	Mild	Normal	Normal	Mild	Negative	Good
2	Control	3	6.8 mm	2 times	Severe	Irregular	Focal	Severe	Negative	Bad
3	Control	2	6.4 mm	1.5 times	Moderate	Irregular	Normal	Moderate	Negative	Moderate
4	INF-α	1	0	Normal	Mild	Normal	Normal	Mild	Negative	Good
5	INF-α	1	4.3 mm	1.25 times	Mild	Normal	Normal	Moderate	Negative	Moderate
6	INF-α	1	7.9 mm	Normal	Mild	Normal	Normal	Mild	Negative	Good
7	5-FU	3	6.8 mm	2 times	Moderate	Irregular	Focal	Severe	Negative	Bad
8	5-FU	3	4.7 mm	1.25 times	Severe	Irregular	Normal	Moderate	Negative	Good
9	5-FU	3	5.9 mm	1.5 times	Severe	Irregular	Normal	Severe	Negative	Bad
10	INF-β	1	0	Normal	Mild	Normal	Normal	Mild	Negative	Good
11	INF-β	1	0	Normal	Mild	Normal	Normal	Mild	Negative	Good
12	INF-β	1	2.7 mm	2 times	Mild	Normal	Normal	Mild	Negative	Good

Treatment with hyaluronic acid is another popular method to reduce tendon adhesion formation. High concentrations and gel form of this naturally occurring compound are more efficacious in prevention of peritendinous adhesion.[12,14,21,28,36–38]

There is only 1 clinical trial with 22 patients that evaluated the effect of 3 local injections of hyaluronic acid for prevention of tendon adhesion. Total range of motion of the fingers was improved after this method of treatment.[18] It has been hypothesized that the effect of amniotic membrane, amniotic fluid, and synovial stem cell on tendon healing and adhesion is mediated through their effect on hyaluronic acid metabolism.[1,39]

It is intriguing that both 5-FU, an anti-metabolite, which prevents cell proliferation, and hyaluronic acid, which promotes the healing process, have favorable clinical effects on tendon adhesion formation, although their principle actions are totally different.[1,8,37,38]

In this study, anti-inflammatory cytokines were used to prevent inflammation around the tendon repair site and decrease peritendinous adhesion. Accordingly, it seems logical to modulate healing and inflammation at cellular and molecular levels.

Since promotion of internal healing and moderation of external healing processes are among the primary objectives of tendon surgery, we only treated the surface of the tendon repair site with abovementioned substances. No effect was observed in prevention of adhesion formation by IFN-α and IFN-β, although no adverse reaction was noted. One explanation for this particular observation might lie in the characteristics of cytokines; their behavior is not predictable, and they may have different effects at different doses. Thus, it is recommended that effects of these cytokines be evaluated at different concentrations. Another reason could be that the water-soluble cytokine becomes rapidly diluted after application. It may then appear logical that continuous application of this class of modulators during the first 2 weeks after tendon repair could possibly prevent adhesion formation. In histopathologic examination of the specimens, normal structure of the tendon and peritendon area was more conspicuous in the IFN-treated groups, especially in IFN-β specimens. Although corresponding findings were not observed in tensometric evaluation, this microscopic finding might be a source of some enthusiasm for researchers with interest in modulating cellular behavior for prevention of adhesion formation.

ACKNOWLEDGMENT

Authors would like to thank the following colleagues for their contribution to this study: Dr Gholamreza Moosavi, Dr Arash Najafbeigi, and Dr Zeinab Nematzadeh in rabbit's surgeries; Mr Reza Samani in preparing pathology samples; Mr Hossein Payandan in statistical analysis; Mr Manoochehr Fazli in taking care of animals; Ms Fatemeh Salimi cooperating in tensometric tests; and Ms Maryam Mohammadinia in preparing the article.

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