Effect of Heparin on Post-Operative Adhesion in Flexor Tendon Surgery of the Hand

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Abstract Flexor tendon laceration is a common hand injury. Timely and correct diagnosis of this defect is an important factor for restoring hand function. Post-operative adhesion is a frequent problem after tendon repair and its prevention is difficult in some types of tendon lacerations. There have been some controversial studies on the positive effect of some materials and substances on prevention of these adhesions. This study aims to evaluate effects of the Heparin in postoperative tendon adhesions. In this clinical trial, 100 patients with laceration of flexor tendons in zone II of the hand were enrolled. The patients were randomly divided into two groups. In the first group, 0.5 cc Heparin (5000 IU/cc) was injected into each tendon ends before tendon repair. In the control group, repair was carried out without any heparin injection. After 3 months the total active range of motion (TAROM), mean extension gap (MEG) and mean flexion gap (MFG) were measured and compared between these two groups. The TAROM and MEGs were not significantly different between two groups; but MFGs were significantly better in Heparin treated group

($P < 0.02$). However rupture rate was significantly higher in heparin treated group ($P = 0.003$). Heparin may improve the tendons function and reduce the postoperative adhesions in zone II of the hand; however there is a significant risk of tendon rupture.

Keywords Flexor tendon · Heparin · Tendon adhesion · Tendon rupture

Introduction

Flexor tendon laceration is a common injury after hand trauma which is more commonly seen in males at their second and third decades of life¹. Its prevalence rate is about 1 in 7000 in industrial countries [1, 2].

Reconstruction of superficial and deep flexor tendons in the second zone (Zone II) of the hand is of great importance. The most prominent point that distinguishes the Zone II from other zones is that the superficial and deep tendons pass through a synovial canal made by annular and cruciate pulleys from distal palm to middle phalanx. Preservation of these pulleys is mandatory during surgical reconstruction of tendons. The adhesion of tendons in zone II is sometimes severe and this zone is called the “no man’s land” or forbidden region and repairing tendons in this zone has always been accompanied with difficulties and complications [3–5].

Three important principles in tendons repair are as follows: High power/high-forced repair; Active physiotherapy protocol and Making changes in tendon restoration mechanism by using different medications. There are reports of using different methods and medications including systemic drugs such as steroids, antihistamines and NSAIDs to decrease postoperative adhesion formations. However it seems that local medications are effective in prevention of inflammation and

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adhesion simultaneously [6–8]. Heparin is a non-cytotoxic, inexpensive and easily available drug which has an anti-inflammatory effect in addition to its anticoagulant characteristic. It affects different stages of tissue repair. Fibroblast growth factors (aFGF, bFGF) have a tendency for attachment to the heparin. FGF has a critical role in wound healing; therefore the tendency of this molecule to the heparin can affect different stages of tissue repair [9]. Based on published articles on impact of heparin in preventing post operative adhesions, we decided to evaluate the effect of the heparin on decreasing possible post-operative adhesion in hand's flexor tendon repair.

Materials & Methods

This Randomized Clinical Trial was conducted on patients who referred to the emergency department of Hazrat Fatemeh Hospital with Zone II hand flexor tendon laceration from November 2007 to March 2009. Every patient with inclusion criteria were evaluated (Table 1). Iran University ethics committee approved the study, and written informed consent was obtained from all participants.

In order to calculate the sample size, we used a program called SamplePower by IBM. (<http://www-01.ibm.com/software/analytics/spss/>). The power of the study was considered 80 % with $\alpha=0.05$. Total sample size was 120 patients. All eligible patients underwent a surgical operation after maximum 72 h following the occurrence of the lesion by one surgeon (AAKR). All operations were conducted with wrist block with or without IV (Intra Venous) sedation and with an arm tourniquet. One dose of prophylactic antibiotic (1 g Cefazolin) was administered for all patients and it was continued to three doses post-operatively. Thereafter, Cephalexin (500 mg, q6h) was orally administered for 1 week.

Patients who met the criteria were randomly divided into two groups. The patients were randomized via centrally issued

sealed envelopes immediately prior to surgery. In the first group, tendon repair started following the injection of 0.5 cc Haprin (5000 IU/cc, Alborz-daroo, Iran) into tendon ends with 25 needle sizes. (0.25 cc in each end). Then tendon repair was conducted using Modified Kessler method. Core and Epitenon suture was done with nylon 4–0 and nylon 6–0, respectively. Digital nerve was repaired with nylon 8–0 under Loup magnification. In the second group the approach was the same but without Heparin injection.

In cases with simultaneous FDP and FDS lacerations, only FDP tendon was repaired. Postoperatively a dorsal hand splint was applied and rubber band was used for all patients. The patients were hospitalized and physiotherapy was initiated after 24 h with active extension and passive flexion, then the patients were discharged.

The patients were examined every week and underwent following physiotherapy protocol:

- First 3 weeks: active finger extension and passive flexion with rubber band
- Fourth and fifth weeks: active finger flexion without resistance and night splint
- Sixth and seventh weeks: active flexion with resistance.

In patients who completed the whole procedure, a physiotherapist, unaware of heparin injection, examined the operated finger 3 months after the operation. Total Active Range of Motion (TAROM), Extension Gap (EG) and Flexion Gap (FG) were measured using a standard Goniometer in each finger and thumb separately. Data were recorded for each patient in data sheet. Using the strickland's formula ($\text{Strickland} = \frac{(\text{active flexion PIP} + \text{DIP}) - (\text{extension deficit PIP} + \text{DIP})}{175^\circ} \times 100$) we measured the TAROM. Extension gaps and Flexion gaps were measured for each finger by a Goniometer based on the difference between active range of motion and normal range of motion at extension and flexion, respectively. Finally the mean for extension and flexion gaps were calculated and recorded.

Based on the type of laceration, patients were divided into three groups:

- Group 1: FPL (Flexor Pollicis Longus) laceration in thumbs (10 cases)
- Group 2: FDP (Flexor Digitorum Profundus) laceration in fingers (50 cases)
- Group 3: FDP and FDS (Flexor Digitorum Superficialis) lacerations in fingers (40 cases)

The data were analyzed using SPSS Version 16. Chi-square and independent sample t-tests were used for comparing and analyzing means and data. A p-value of less than 0.05 was considered statistically significant.

Table 1 Inclusion criteria for enrollment in the study

- Zone II flexor tendon injury
- 20–40 years including both sexes
- Penetrative, sharp lesion mechanism without any crushes injury to soft tissue, tendons and nerves
- Absence of any underlying diseases (including diabetes, cardiovascular disease, respiratory diseases, cancer, hematological diseases) and no history of using immunosuppressive and anticoagulation drugs
- No smoking or addiction
- Absence of any accompanying lesions such as fracture, dislocation, extensor or multi-level laceration (Only digital nerve lesion was acceptable as an accompanying lesion)
- Adequate blood circulation to the finger(s)
- No need for pulley reconstruction
- Having at least a high school diploma and residing in Tehran
- Patients should observe the physiotherapy protocol (described later in the text) for at least 8 weeks post-operatively.

This study has not imposed any extra costs to the patients and Heparin ampoules were offered to them free of charge. Prior performing the study, written and signed informed

consent were obtained from patients. Some patients did not refer for follow ups and this was the main limitation of the present research.

The Consort Flowchart

Results

Among totally 112 injured patients who met the inclusion criteria, 100 patients underwent the treatment procedure and all of them referred for follow-ups. There were 56 males (78 %) and 16 females (22 %) within the age range of 20–40 years (mean: 25.8 ± 5.45)

Causes of lesions regarding the order of frequency were as follows: knife (36 %), glass (26 %), metal sheets (16 %), razor (8 %), electric scissors (10 %), saucer (2 %) and can lid (2 %).

All patients, except two, were right-handed. Right and left hands were equally injured. Little finger was the most involved finger. Index, middle, ring and thumb fingers were followed the little finger respectively.

The mean time interval between onset of injury and operation was 45.4 h. In 64 % of the cases, there was no accompanying laceration. In 30 %, there was a unilateral digital nerve injury and in 6 %, there was bilateral digital nerve laceration.

Generally, among 100 injured patients, Heparin was injected in tendon ends of 46 cases prior to the repair; in 54 cases, the injury was repaired without heparin injection. Table 2 represents type of injuries and their characteristics in injured patients.

In the first group, there was not any statistically difference between cases and controls regarding TAROM (108.3° vs. 102.5°) ($P=0.6$), MFG (0 cm vs. 0 cm) ($P=0.65$) and MEG (0 cm vs. 0.5 cm) ($P=0.4$) respectively.

In the second group, there was not any statistically difference between cases and controls regarding TAROM (226.5° vs. 212.1°) and MEG (0.75 cm vs. 1.4 cm) respectively; but there was a meaningful difference regarding MFG (1.4 cm vs. 2.06 cm) ($P=0.03$).

In the third group, there was not any statistically difference between cases and controls regarding TAROM (202.14° vs. 175.5°) and MEG (1.14 cm vs. 1.65 cm), respectively; but there was a meaningful difference regarding MFG (2.85 cm vs. 3.95 cm) ($P=0.02$).

Discussion

Laceration of flexor tendons in Zone II of the hand is a prevalent injury. Correct and proper repair of this injury will avoid certain morbidities in patients and also it is economically beneficial for both individuals and the society. Appropriate tendon repair can restore normal hand function, prevent frequent surgeries and facilitate the return of the casualty to the workplace. Adhesion is an important complication that may occur after tendon repair at this zone of the hand. Although adhesion can be prevented by a proper repair carried out at the hand of skilful surgeon, it is still a common complication in repairing hand flexor tendons at Zone II. Several strategies such as local and systemic drugs described previously have been suggested for preventing the adhesion formation. In some animal studies, using costly drugs have reduced adhesion to some extent.

Based on the results of these studies and the proved effect of Heparin in averting intra-abdominal adhesion, we decided to evaluate its impact on probable reduction of adhesion following reconstructive surgery of the flexor tendons at the Zone II of the hand. Since most injured patients are workers, using an inexpensive, available drug like Heparin can be of great benefit in reducing post-operative complications and returning them to their work more quickly.

In an animal study on rats, Tayyar studied the effect of Piroxicam and LMWH (Low Molecular Weight Heparin) on preventing adhesion in wounds. At the beginning, the uterus of rats was partially burned by an electrical cautery and they were classified into three groups. In the first group, 1 cc of Piroxicam (2 mg/cc) solution was injected into the peritoneum. In the second group, 1 cc of 50-units LMWH solution (1 dose) was injected. The third group was the control. Compared to the control group, adhesion was reduced considerably in the groups that had received Heparin and Proxicam injection [10].

In another animal study, Moran et al. evaluated the role of locally administered 5FU in repairing 3rd and 4th FDP tendon adhesion in chickens. After repairing the tendon, they administered the drug locally at various doses for 5 min. Thereafter they evaluated adhesion formation in all chickens receiving 5FU with doses higher than 25 mg/cc; it was observed that the possibility of post-operative adhesion reduced remarkably [11].

Demirkan studied role of human placenta amnion in preventing adhesion in repaired flexor tendons of chickens. It was observed that adhesion was clearly less in repaired tendons covered by a layer of amnion [12].

In Glasgow University, Darmani et al. injected L-NAME N (G) - nitro-1- arginine methyl ester into tendon repair site in rats in order to prevent adhesion. L-NAME is a Nitric oxide synthase inhibitor substance that prevents nitric oxide (NO) production. In this study, the flexor tendons of the middle toe of rats were crushed and the extent of adhesion was studied in two different groups. In case group, L-NAME injection was performed (5 mg/kg) and in another one (control group) that did not receive this drug, fibrosis was developed due to chronic inflammation [13].

Table 2 Type of injury and their characteristics in injured patients

	Type of Injury	Repaired with Heparin Injection (cases)	TAROM	MFG	MEG	Repaired Without Heparin Injection (controls)	TAROM	MFG	MEG
Group 1	FPL	6	108.3°	0 cm	0 cm	4	102.5°	0 cm	0.5 cm
Group 2	FDP	20	226.5°	1.4 cm	0.75	30	212.1°	2.06 cm	1.14 cm
Group 3	FDP+FDS	20	202.14°	2.85 cm	1.14 cm	20	175.5°	3.95 cm	1.65 cm

FPL: Flexor Pollicis Longus; FDP: Flexor Digitorum Profundus; FDS: Flexor Digitorum Superficialis; TAROM: Total Active Range of Motion. MFG: Mean Flexion Gap; MEG: Mean Extension Gap

Ferguson et al. studied the role of Hydrogel sealant in preventing adhesion after flexor tendon repair in chickens. Surgical site was covered by hydrogel cement after repairing the deep flexor tendon of the 2nd and 4th toes; the possibility of adhesion was much lower than the control group [14].

In the United States, Tanaka et al. used a combination of Hyaluronic acid and gelatin on the repair site of tendon graft on legs of 12 dogs to observe adhesion reduction in comparison to the control group. They noticed that gross adhesion formation was less in the case group [15].

In an experimental animal model study by Esen et al., they evaluated the effect of LMWH on the healing of Achilles tendon in rats. These rats were randomized into 3 groups and underwent full-thickness surgical incision of Achilles tendon. Two groups received daily subcutaneous LMWH injections for 4 weeks and the third group remained untreated as control group. Tendon specimens were evaluated histologically and biomechanically. In comparison to control group, both LMWH-treated groups showed histologically improvement of tendons. They concluded that daily administration of single dose LMWH increases healing process [16].

Virchenko et al. evaluated the effects of Heparin on repair of Achilles tendon in 86 rats. They concluded that continuous injection of LMWH impairs tendon healing. Also this method will cause reduction in force at failure, stiffness and energy uptake. Also LMWH injection twice daily had no effect on tendon healing. They observed an increase in the activity of anti-factor Xa after treatment by LMWH, but its activity was normal between intermittent injections. It was presumed that returning of anti-factor Xa activity to the normal level in intermittent injection method, allows sufficient thrombin stimulation for repair [17].

In our study TAROM and Extension Gaps were better in the case group who received heparin injection in the process of their tendon repair but there was no significant statistical difference between case and control groups. However, the MFG in two groups (second and third groups) was significantly better in Heparin injected groups ($P=0.02$ and $P=0.03$).

Altogether there were not any statistically significant results in Heparin injected group, although improvement in data was observed. Complications like infection and bleeding were almost same in both groups and were controllable; but tendon rupture was only observed in the Heparin-injected group in those with simultaneous FDP and FDS laceration. On the other hand, 2 cases of tendon rupture were caused by heavy works and exercise. However, 4 rupture cases without history were not related to carrying heavy loads. These ruptures may develop due to a disorder in intrinsic healing mechanism of tendon induced by heparin just like the mechanism that prevents adhesion.

In all flexor tendon injuries at Zone II, the administration of the LMWH led to an increase in the range of finger joint movements and adhesion reduction but the results were not

significantly meaningful. However, the high rate of tendon rupture in heparin injected group may be due to compromising of tendon healing by heparin.

In a literature review study by Khanna et al. they found out that the only thing that will affect the adhesion prevention is the early post-operative mobilization of digits after tendon injury or repair; however there is a controversy in the best method of mobilization. Also the proposed pharmacologic and non-pharmacologic modalities need further evaluations and adequately powered human trials prior to implementation [18].

Conclusion

According to our results, local Heparin injection into tendons ends of flexor muscles at Zone II of the hand compromise tendon healing, therefore it is not recommended. Prior declaring any decision or suggestion about the role of Heparin in preventing tendon adhesion, other studies using local injection of heparin to external surface of the repair site or injection of Heparin into synovial canal after repair must be carried out.

Compliance with Ethical Standards

Funding This study was not funded by any institutes or organizations.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee of the Iran University of Medical Sciences and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest All Authors indicate that they do not have any conflict of interest in this study and they have not received research grants from any Company, Institute or organization.

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