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Effect of Mitomycin C in the prevention of tendon adhesion after surgery and the effect of biomechanical stretching on tendon histology

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ABSTRACT

Objective: In this study, optimal dose to reduce tendon adhesion, by using the dose-dependent fibroblast proliferation inhibition effect of Mit-C, and the level, which the tendon histologies are affected, using biomechanical stretching, is investigated.

Methods: 56 chicken flexor tendons were used in this study. A total of 9 groups were formed. Mit-C were applied between the tendon and the sheath; 0.9% NaCl for surgical control groups (groupII, groupIII), 0.1mg/ml Mit-C (groupIV, groupVII), 0.2mg/ml Mit-C (groupV, groupVIII) 0.5 mg/ml Mit-C (groupVI, groupIX). Macroscopic, microscopic, synovial sheath thickness and active fibroblast count were compared between the groups that underwent biomechanical stretching (groups III,V,VII,IX) and groups without biomechanical stretching (groups I,II,IV,VI,VIII).

Results: After the macroscopic and microscopic examination, it was observed that the groups with the most adhesion were surgical control groups. The best results from the experimental groups were seen in group VIII, but the results of the groups were similar. When active fibroblast count was examined, it was seen that group VIII had the least active fibroblast count.

Conclusion: According to the results of the evaluation, Mit-C, by inhibiting fibroblast proliferation and decreasing synovial sheath thickness, decreased adhesion formation. At the same time, it was concluded that the optimal dose for adhesion prevention was 0.2mg/ml, biomechanical stretching affected tendon histology and the drug was suitable for clinical studies.

Key words: *Chicken, Mitomycin C, tendon, adhesion*

Introduction

Hand injury is a frequently encountered orthopedic problem. Approximately 1/5 of traumatic patients admitted to the ER are due to hand injuries [1]. 4% of hand injuries result in adhesion, despite treatment [2]. Flexor tendon healing occurs with both intrinsic and extrinsic mechanicsms. In extrinsic mechanism, it has been reported that there has been adhesion as a result of the fibrosis caused by irregular fibroblasts that are positioned between flexor tendon and the sheath [1,3-5]. To sum up, treatment of the sliding function following tendon injury is an important problem for those interested in hand surgery.

Various studies have been conducted to prevent

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tendon adhesion. Several drugs and substances have been used, such as; synovial allograft [6], slow release hyaluranic acid [7], chitosan collagen hydrogel [8], hyaluronan-derived hydrogel [9], vitamin e analogues [10], nonsteroidal anti-inflammatory drug [11] flouruouracil [12], suturing materials [13]. In addition, the effect of rehabilitation programs are extensively researched [14]. In spite of the progress in treatment, there is still no effective treatment. Common objectives of the studies are, to prevent tendon adhesion and provide full finger movement, to have a positive effect, or at worst not having a negative effect on tendon healing.

Mitomycin C is a DNA alkylating antitumor antibiotic that inhibits fibroplast proliferation in vivo with anti-fibrinolytic activity [15] and it has been reported to be effective in preventing intraabdominal adhesions in rats [16]. In addition, 0.2 mg / ml is used to prevent postoperative adhesions in strabismus surgery and it has been reported to reduce adhesion [17]. Several studies on tendons show that Mit-C reduces adhesions associated with extrinsic healing mechanisms [18,19]. In these studies, the dose which had the adhesion inhibition effect was not stated and a biomechanical comparison was not presented. In this study, we evaluated the Mit-C in the chicken model by using a dose study and biomechanical comparison to prevent tendon adhesion.

Material and Method

The study was carried out by using both legs of Leghorn chickens with 1500 gr average weight in Karadeniz Technical University Faculty of Medicine Surgical Research and Application Laboratory.

Surgical procedure was performed on middle toes of both feet. From a total of 54 tendons, 9 groups were formed. Right legs were included in the histological and the left legs in the histological + biomechanical study except the non-surgical control group (Table 1).

Surgical Technique

After the preperations made , a Carl Zeis Opmi 99 × 4 surgical microscope was used for magnification. A midlateral incision (zone II) was performed on the volar face of the middle finger to pass the skin and the subcutaneous to reach the sheath. Flexor digitorum profundus tendon was revealed with a 2 cm incision in the sheath. The distal and proximal parts of the incision site were determined with two needles. A transverse incision was made to the tendon, leaving the 20% to the central as intact. It was sutured with 5.0 trophylene, using modified Kessler technique. Then, the planned dose of drug was administered between the sutured tendon and the sheath for 5 minutes using a strip. The sheath was closed with 6.0 trophylene, the skin with 3.0 silk.

Postoperative incised fingers were immobilized by patch fixation to be in flexion for 3 days. Three days later they were released for active mobilization. Antibiotherapy was performed by applying cefazolin sodium 100mg/kg for three days. All animals were sacrificed three weeks later with high dose anesthesia. Middle fingers were disarticulated from MP joint and macroscopic, histological and biomechanical evaluations were performed.

Table 1. Experimental study groups.

Experimental and control groups
Group 1: Control group without surgery. Histological study was performed using both legs of 4 chickens.
Group 2: Surgical control group. Histological study was performed using 0.9% SF. Right leg was used.
Group 3: Surgical control group. Biomechanical + histological study was performed using 0.9% SF. The left legs of Group 2 were used.
Group 4: Surgical experimental group (0.1 mg / ml mit-C applied and histologically evaluated group). Right legs were used.
Group 5: Surgical experimental group (0.2 mg / ml mit-C applied and histologically evaluated group). Right legs were used.
Group 6: Surgical experimental group (0.5 mg / ml mit-C applied and histologically evaluated group). Right legs were used.
Group 7: Surgical experimental group (0.1 mg/ml Mit-C applied and biomechanically + histologically evaluated group). Left legs of group 4 were used.
Group 8: Surgical experimental group (0.2 mg/ml Mit-C applied and biomechanically + histologically evaluated group). Left legs of group 5 were used.
Group 9: Surgical experimental group (0.5 mg/ml Mit-C applied and biomechanically + histologically evaluated group). Left legs of group 6 were used.

Macroscopic Evaluation

For macroscopic evaluation, firstly the nature of adhesion was examined in the disarticulated fingers of the MP joint. The fingers were then dissected from the skin and subcutaneous tissue. At this stage, the length of the adhesion was measured with a ruler. The criteria for macroscopic examination of adhesion were made according to the system described by Jin Bo et al. [20]. According to this classification, scores were given according to the length, property and grading of the adhesion. Then, the scores were added and statistical comparisons were made (Table 2).

Histological examination: Performed in 2 ways, according to the system described by Jin Bo et al.

1. Microscopic: Adhesion density, length, tendon mobility, tendon mobility was evaluated by looking at the degree of adhesion affect. Each chicken was evaluated separately. The results were collected and presented as cases and groups in the table as a result of total and mean macroscopic examination.

After the surgery, active fibroblast count and synovial sheath thickness in the tendons were microscopically measured. The results were presented by comparison table (Table 3).

2. Synovial sheath thickness: Each measured thickness was recorded by measuring in mm at hundred magnification on a light microscope. Groups and recorded thicknesses were indicated by table. Total and mean synovial sheath thickness of each group were determined.

3. Active fibroblast count: Fibroblasts and fibrocytes were counted at hundred magnification under light microscope. Their ratio to each other was evaluated as the number of active fibroblasts. Then, the number of active fibroblasts was determined by table according to cases and groups. Total and average active fibroblast number for each group was stated and these numbers were compared according to the groups.

4. Biomechanical examination: Tendons to be used for biomechanical examination, were attached 1 cm away from both ends with glue and in a manner that would not cause rotation, of the biomechanical stretching machine, which is Karadeniz Technical University, Faculty of Mechanical Engineering, Department of

Table 2. Criteria for Macroscopic Evaluation of Adhesion, by Jin Bo et al. (20).

Points	Appearance of adhesion
Length	
0	No adhesion
1	Longitudinal adhesion, local, up to 10 mm
2	Adhesion between 10-15 mm
3	Dense adhesion, bigger than 15 mm
Property	
0	No adhesion
1	Loose, elastic, highly mobile.
2	Moderately dense, mobile.
3	Dense, hard and immobile
Evaluation of adhesion	
0	No adhesion
2	Mild adhesion
3, 4	Moderate adhesion
5, 6	Severe adhesion

Table 3. Histopatological examination evaluation criteria according to Jin Bo et al. (20).

Points	Appearance of adhesion
Length	
0	No adhesion.
1	A small number of scattered flaments.
2	A great number of flaments.
3	Innumerable flaments.
Property	
0	No adhesion.
1	Narrow, elongated, thin, filamentous
2	Irregular, mixed, shortened, filamentous.
3	Dense, not-filamentous
Adhesion rating	
0	No adhesion
2	Mild adhesion
3, 4	Moderate adhesion
5, 6	Severe adhesion

Figure 1. View of the chicken feet.

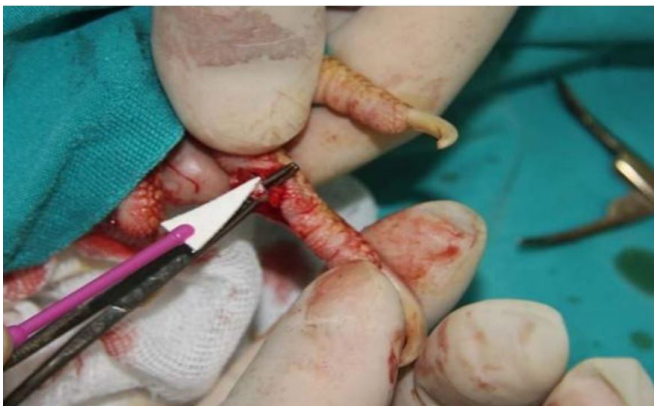

Figure 4. Application of the drug to sutured tendon and sheath.

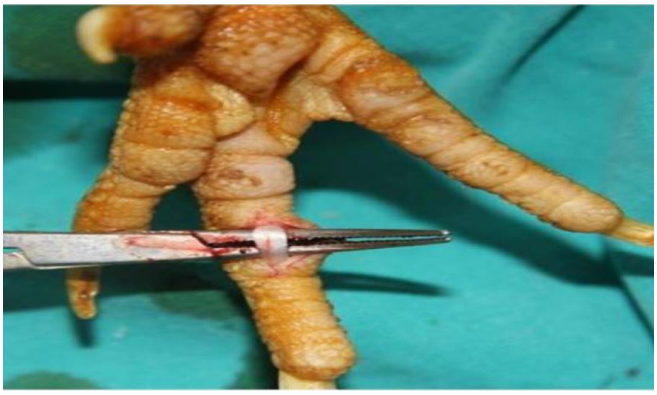

Figure 2. Uncovering of flexor digitorum profundus tendon in chicken foot.

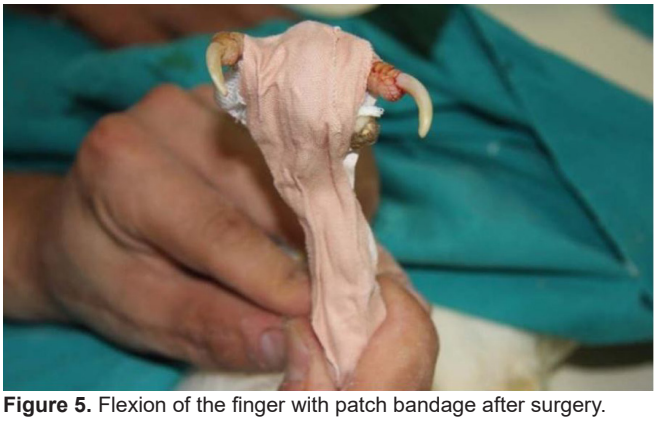

Figure 5. Flexion of the finger with patch bandage after surgery.

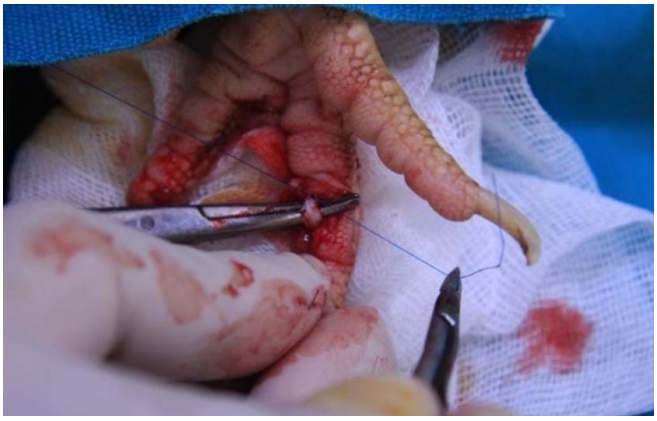

Figure 3. View of the tendon cut from the edges with modified kessler method after suturin.

Metallurgy's Insron 3382 universal testing machine. The tendons were then stretched at a constant tension of 10 mm / min under 1kg / Nt load. At the same time, the load-elongation graph was monitored on the monitor by the program named Instron Bluehill 2.

5. Statistical evaluation: Macroscopic and microscopic scoring and active fibroblast count and synovial sheath thickness analyses were performed in two ways.

Groups 2 and 3, groups 4 and 7, groups 5 and 8, groups 6 and 9 were compared with the Mann Whitney U test.

Groups 2, 4, 5, 6, and 3, 7, 8, 9 were evaluated among themselves by Kruskal Wallis Variance Analysis test with post hoc analysis by corrected Bonferroni corrected Mann Whitney U test (Figures 1-5).

Results

Macroscopic Findings

A total of 54 tendons were evaluated according to the macroscopic criteria in Table I for 9 groups planned in our experimental study.

Group II (surgical control group) and group III (surgical control group with biomechanical evaluation) had the highest adhesion. While there was no statistically significant difference between the groups with the

Table 4. Macroscopical evaluation results.

Adhesion	No Adhesion Number(%)	Mild Number(%)	Moderate Number(%)	Severe Number(%)
Group I	6(%100)	-	-	-
Group II	-	-	1(%16)	5(%84)
Group III	-	-	3(%50)	3(%50)
Group IV	-	2(%32)	4(%68)	-
Group V	-	2(%32)	4(%68)	-
Group VI	-	3(%50)	3(%50)	-
Group VII	-	1(%16)	5(%84)	-
Group VIII	-	3(%50)	3(%50)	-
Group IX	-	3(%50)	3(%50)	-
Total	6 (%12)	14 (%25)	26(%48)	8(%15)

Table 5. Histological evaluation results.

Adhesion	No Adhesion Number(%)	Mild Number(%)	Moderate Number(%)	Severe Number(%)
Group I	6 (%100)	-	-	-
Group II	-	-	1 (%16)	5 (%84)
Group III	-	-	5 (%84)	1 (%16)
Group IV	-	-	6 (%100)	-
Group V	-	2 (%32)	4 (%68)	-
Group VI	-	3 (%50)	3 (%50)	-
Group VII	-	2 (%32)	4 (%68)	-
Group VIII	-	4 (%68)	2 (%32)	-
Group IX	-	3 (%50)	3 (%50)	-
Total	6 (%11)	14 (%26)	28 (%51)	6 (%11)

same dose of Mit-C ($p > 0.005$), there was a numerical difference. In the evaluation among the groups I, II, IV, V, VI, which were not biomechanically evaluated, there were no statistical difference. ($p > 0.008$). Biomechanically stretched groups were evaluated statistically among themselves and there was a statistical difference between group III and other groups ($p < 0.008$) (Table 4).

Microscopic Findings

Histopathological evaluation: A total of 54 tendons with 6 tendons in each group evaluated according to the criteria described in 2 by Jin Bo et al. The results are shown in Table-5.

Histologically, adhesion was the highest in group II and group III. Group VIII was evaluated as the group with the least adhesion. Mann Whitney U test was applied to the same dose of drug and biomechanically stretched and non-stretched groups were compared and a significant difference was found between groups II and III, groups IV and VII ($p < 0.05$). There was no

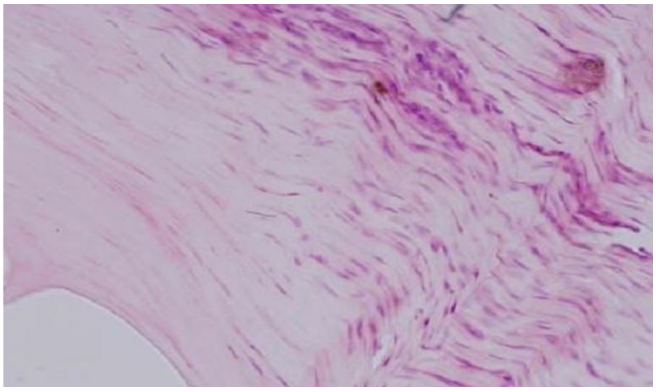

Figure 6. 40x magnificated view of the sample histological section of the biomechanically stretched control group.

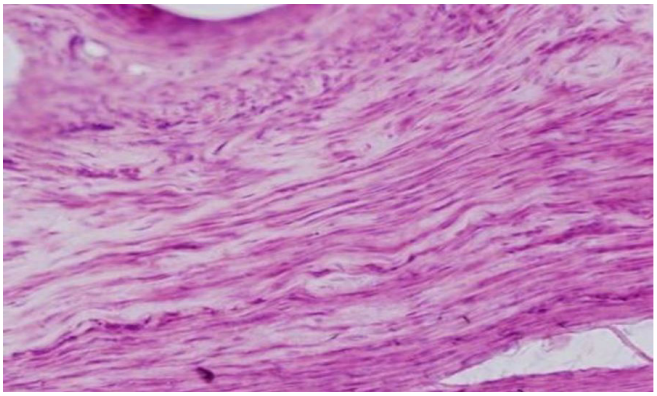

Figure 7. 40x magnificated view of the section taken from the group with 0.2 mg/mlt application and no biomechanical stretchin.

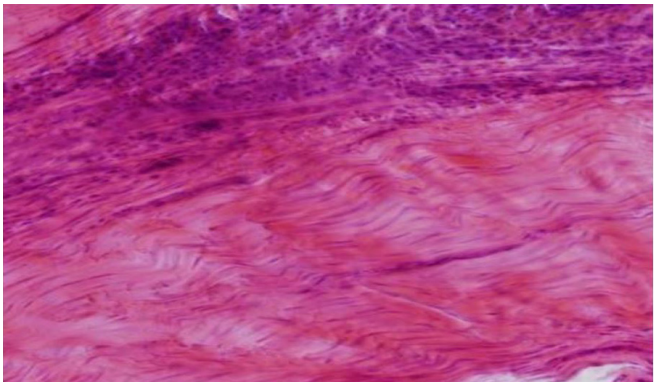

Figure 8. 40x magnificated view of the section taken from the group with 0.2 mg/mlt application and biomechanical stretching.

Table 6. Average values of active fibroblast numbers.

Group No	Mean	Std. Deviation
1	0.5300	0.05244
2	7.3167	1.10208
3	5.5300	0.87599
4	4.6243	0.43015
5	4.6386	0.52894
6	3.8233	0.64027
7	4.4057	0.64010
8	2.9000	0.30458
9	4.5033	0.55099
Total	4.3135	1.73652

Table 7. Statistical analysis of synovial sheath thickness.

Grup	Mean	Std. Deviation	Median	Minimum	Maximum
1	0.1	0.000	0.1	0	1
2	2.67	0.516	3.00	2	3
3	2.17	0.408	2.00	2	3
4	1.43	0.535	1.00	2	2
5	1.14	0.378	1.00	1	2
6	1.17	0.408	1.00	1	2
7	1.71	0.488	2.00	1	2
8	1.00	0.000	1.00	1	1
9	1.50	0.548	1.50	1	2
Total	1.44	0.780	1.00	0	3

statistically significant difference between the other groups but there was a numerical difference. Histological findings were in accordance with macroscopic finding (Table 5) (Figures 6-8).

Active fibroblast count: The number of active fibroblasts of 9 groups used in our study was compared with each other statistically (Table 6).

As can be seen from the table above, observing the number of highest active fibroblasts group II and then in group III was in accordance with the purpose of this study. The minimum number of active fiboblasts was seen in group VIII. The numbers of active fibroblasts between the other groups were numerically close to each other.

Mann Whitney U test was used to compare the biomechanically stretched and non-stretched groups. There was a significant difference between group II and III, group V and VIII ($p < 0.05$). There was no significant difference between groups IV and VII, groups VI and IX ($p > 0.05$).

Synovial sheath thickness: A total of 54 tendons were examined, with 6 tendons in each group for synovial sheath thickness.

For synovial sheath thickness, Kruskal Wallis variance analysis was performed, with $p < 0.05$ There was a significant difference between group I and the other groups.

Although there was not a significant difference between group II and group III, there was significant difference among other groups.

In the comparison among Mit-C applied groups, sheath thickness was lowest in group VIII and highest in group IX.

In the comparison between the biomechanically stretched and non-stretched groups which had the same dosage of the drug, there was no statistical difference between group V and VIII, group VI and IX, and group IV and VIII, but there was a numerical difference (Table 7).

Discussion

This study was designed to investigate the dose application effects of mit C on tendon adhesion. Many drugs were applied between tendon and sheath to prevent tendon adhesion and positive results were obtained. Mit C is used to prevent intrabdominal adhesion and to prevent adhesion in strabismus surgery. Several studies have been conducted to prevent tendon adhesion and have been reported to reduce adhesion. In this study, chicken tendon, which is very similar to human tendon structure, was used and the dose study was used to provide an idea about the appropriate dose.

In literature, two mechanisms have been defined for tendon repair; intrinsic and extrinsic. The highly

proliferative and inflammatoru reaction of the sinovial sheath, increased cytokine reactivity and degradation of the matrix in the sinovial fibroblasts, support the extrinsic mechanism. Extrinsic mechanism produces irregular kollagens in the injury area and dominance of the extrinsic mechanism result in adhesion and scar formation between the tendon and sheath [2]. Actually, fibroblasts are responsible for most of the adhesions between the tendon and the flexor sheath, and increasing research is going on to find the substance or method, which will serve as a barrier between the tendon and the sheath, but which also will not negatively effect the tendon lubricity and the healing process.

Mit-C can be such an agent. Mit-C is a DNA alkylating antitumor antibiotic that inhibits fibroblast proliferation in vivo with anti-fibrinolytic activity obtained from Streptococcus coespitasus [13]. Mit-C has been reported to be effective in preventing intraabdominal adhesions in rats [14]. In addition, 0.2 mg/ml is used to prevent postoperative adhesions in strabismus surgery and it has been reported to reduce adhesion [15]. Several studies have shown that Mit-C reduces adhesions associated with extrinsic healing mechanisms [16,17]. In these studies, it was observed that the dose of adhesion inhibiting effect was not specified and they did not provide biomechanical comparison. In this study, we evaluated Mit-C's tendon adhesion prevention in a chicken model by using a dose study and biomechanical comparison.

In our study, Leghorn chickens were used, due to their use in the previous tendon studies, similarity of tendon structure to humans and being cheap and easy to obtain [21,22].

The results of the study showed similar characteristics except group I, group II and group III. The least adhesion was seen in group I, and the highest adhesion was seen in group II and III. Severe adhesions were not seen in group IV - group IX. When the macroscopic and histological results were compared, no significant difference was found between the groups using 05mg/ml Mit-C and 0.2 mg/ml Mit-C groups. A significant difference was found between 0.1mg/ml Mit-C and 0.2mg/ml Mit-C groups. These results, while giving an idea about the ideal dose, also suggest that the use of a high concentration of drugs does not inhibit fibroblast proliferation (Figures 9,10).

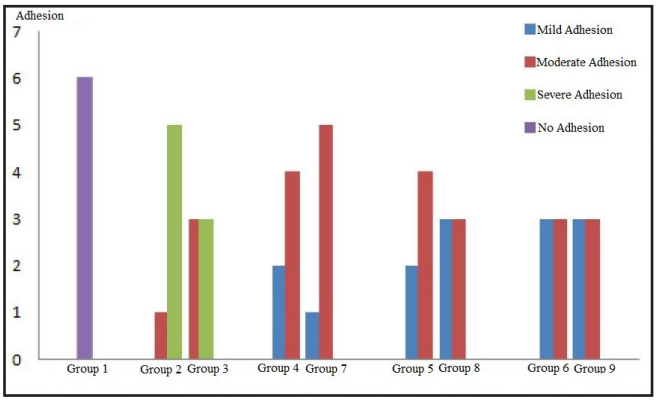

Figure 9. Macroscopical evaluation results.

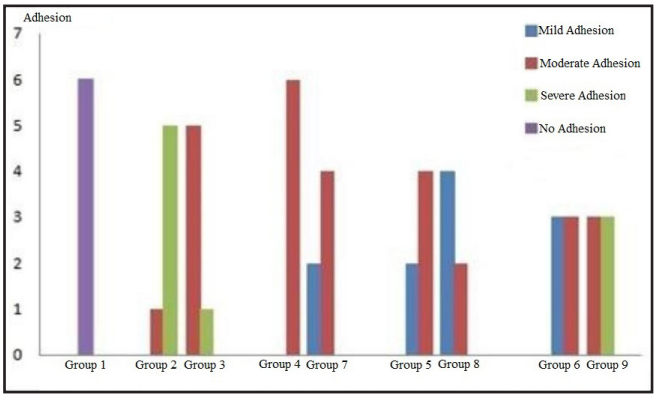

Figure 10. Histological evaluation results.

Migration to the injured tendon, attachment and proliferation of the fibroblasts, protein synthesis, extracellular matrix formation are important processes for the tendon repair. While fibroblasts coming to the injury area play an important role in the tendon repair, they may also cause adhesion in the surrounding tissues [19]. When we compared the active fibroblast numbers in our experimental study, the statistically significant difference between group II - group III strengthened our opinion that Mit-C inhibited fibroblast proliferation ($p < 0.05$). The fact that Group VIII differed statistically and numerically from other Mit-C groups

suggested that the use of Mit-C 0.2mg/ml would be more effective in preventing adhesion. In a study with rabbits, Yamamato et al. reported that Mit-C inhibited subconjunctival fibroblast proliferation in seven days in a dose and time-dependent manner [23] (Figure 11).

After the flexor tendon repair, sinovial sheath must be closed for tendon sliding motion and tendon feeding, and it must be in the appropriate thickness. [20] As expected, synovial sheath thickness was highest in group II and group III. When Mit-C applied groups were compared, sheath thickness was lowest in group XIII and highest in group IX. Findings in the thickness of the synovial sheath strengthened our thesis that the use of 0.2mg/ml Mit C with active exercise can achieve successful results in reducing tendon adhesion (Figure 12).

When biomechanically stretched and non-stretched groups were compared, a statistically significant difference was found in some groups. The number of macroscopic, microscopic and active fibroblasts were significantly different from group VIII - group V ($p < 0.05$). The thickness of the synovial sheath was numerically different. There are macroscopic and microscopic differences between group IV - group VII and group VI - group IX.

In our study, it was seen that Mit C decreased chicken tendon adhesion at all doses. In a study on rats using Mit C, Kocaoğlu et al. reported that Mit C reduced peritendinous fibrous adhesions in rat foot tendons significantly [18]. The authors did not provide information about the appropriate dose in their studies. In addition, in their study, it was reported that biomechanical stretching reduced tendon adhesion and biomechanically stretched and of 0.2mg/ml Mit C applied group had reduced tendon adhesion both microscopically and macroscopically. This gave us an idea about the appropriate dosage. The effect on tendon adhesion is probably extrinsic and by reducing fibroblast proliferation.

In our study, it was demonstrated that a single dose

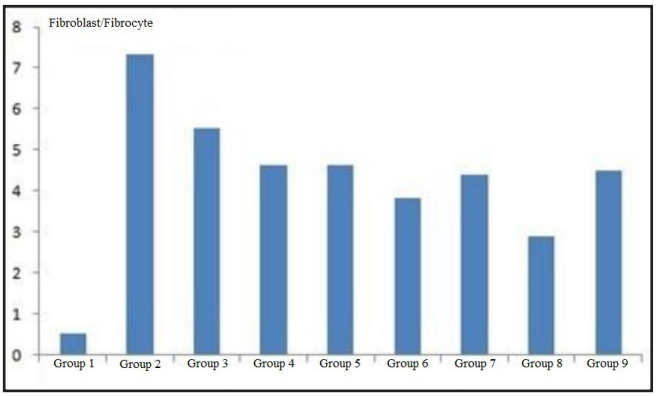

Figure 11. Average values of active fibroblast numbers.

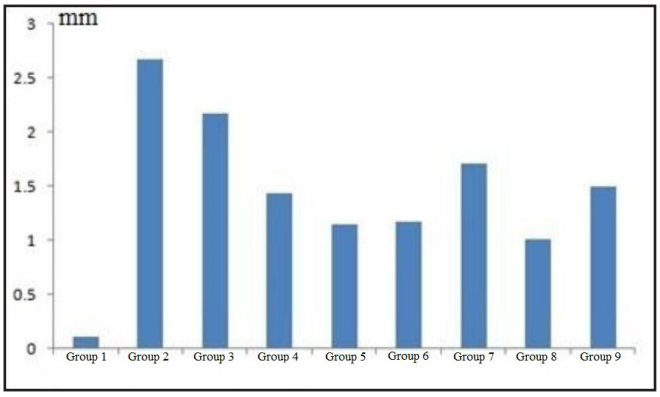

Figure 12. Statistical analysis of synovial sheath thickness.

of Mit C applied to the chicken flexor tendon sheath reduced peritendinous adhesions macroscopically and microscopically. Ideal dose was found to be in the biomechanically stretched group with 0.2mg/mlt Mit C application. Further studies are needed to find out the effects of the ideal dose on humans.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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