The effects of a combination of hyaluronic and amniotic membrane on the formation of peritendinous adhesions after flexor tendon surgery in chickens

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We have investigated the effects of the intra-operative application of a combination of hyaluronic acid and amniotic membrane on adhesions in the flexor tendons of a chicken model. We used 144 tendons which were partially divided and then repaired by a modified Kessler technique. There were four test groups: group 1, simple tendon repair, group 2, repair site wrapped with amniotic membrane, group 3, hyaluronic acid injected around the repair site, and group 4, repair site wrapped with amniotic membrane and hyaluronic acid injected within it.

At three and six weeks, the extent of the adhesions and the healing of the tendon were evaluated macroscopically and histologically. The range of movement of the toe and tensile strength of the repaired tendons were measured at 20 weeks. The least adhesions were observed in group 4 but no significant difference was found in the healing of the tendons. Overall, the intra-operative application of a combination of hyaluronic acid and amniotic membrane appears to be effective in preventing adhesions of the flexor tendon.

In spite of improvements in surgical techniques and post-operative mobilisation programmes, the result of surgery on flexor tendons is still highly unpredictable because of the formation of adhesions. Many different approaches have been tried to prevent the formation of peritendinous adhesions. Refinements in suture techniques, reconstruction of the tendon sheath and early controlled mobilisation have led to a decrease in the formation of adhesions.[1-4] However, these methods have not solved the problem entirely.

Various pharmacological agents have been used to modify the formation of adhesions. Prostaglandin inhibitors, such as indomethacin and ibuprofen, have been found to have a small beneficial effect.[5-7] Steroids, antihistamines and beta-aminoproprionitrile have shown experimental promise but cannot be used clinically because of toxicity or impairment of wound healing.[8] Aprotinin and 5-fluorouracil have been used with variable results.[9-11] Recently, there has been much interest in hyaluronic acid (HA) which is found in quantity in the extracellular matrix of soft connective tissues and in synovial fluid. Previous experimental studies have shown that the application of HA between an injured tendon and its sheath promotes healing of the tendon and decreases the formation of adhesions.[12-15]

Several different types of material, both biological and synthetic, have been used as a barrier around the site of tendon repair.[3,16-18] These isolation techniques have generally been unsuccessful. Some were found to cause impairment of the healing process and some stimulated a severe inflammatory response.[19]

In this experimental study the site of tendon repair was wrapped with human amniotic membrane (HAM) in order to prevent fibrous ingrowth from the surrounding tissues. HA was injected into the HAM envelope since, in previous experimental studies, it has been shown that encirclement of the tendon with some substance failed because of the scar formation at the ends of these materials.[20]

Our purpose was to investigate the effects of HA and HAM, singly and in combination, on the formation of peritendinous adhesions and the healing of the flexor tendons in an adult chicken model.

Materials and Methods

We used 72 adult white Leghorn chickens weighing from 2 kg to 3 kg. All the procedures were performed in the Experimental Animals Breeding and Research Center of the Medical Faculty of Uludağ University. The care of the animals was carried out with the prior approval of the Animal Experimental Ethics Committee.

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Table I. Macroscopic grading system for adhesions according to Tang et al[20]

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

Table II. Histopathological evaluation of adhesions according to Tang et al[20]

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

Preparation of human amniotic membrane. Fresh amniotic membranes were obtained from Caesarian sections in seronegative mothers. The amniotic epithelial cell layer was gently peeled from the underlying chorion under sterile conditions. Blood was washed from the amniotic membrane using sterile saline solution. It was then placed in a 1% neomycin sulphate solution and kept at 4°C. All amniotic membranes were used within four hours of harvesting.

Operative technique. The chickens were anaesthetised with an intramuscular injection of xylazin hydrochloride (5 mg/kg) and ketamine hydrochloride (10 mg/kg). The study was performed on the deep flexor tendons of the long toes of each foot giving a total of 144 tendons in the study. The operative site was draped in a sterile fashion and, under tourniquet control, a longitudinal incision was made on the plantar surface of the long toes of each foot. The flexor tendon sheath was excised between the first and second annular pulleys which were left intact. A 50% partial tenotomy was made and repaired by a modified Kessler technique using 5-0 monofilament polypropylene suture and a continuous adaptation suture of 7-0 monofilament polypropylene. All tendons underwent the identical surgical procedure. There were four groups of 36 tendons. In group 1, a simple tendon repair was performed, in group 2, the repair site was wrapped with HAM, in group 3, before closing the wound, 0.3 ml of HA was injected around the repair site, and in group 4, the repair site was wrapped with HAM and 0.3 ml of HA was injected inside the membrane. In groups 2 and 4, HAM grafts, approximately 1 x 2 cm in size, were wrapped around the repair site using multiple interrupted sutures of 7-0 polyglactin. The HAM was applied so that the mesenchymal surface was in contact with the site of tendon repair. The wound was closed with interrupted sutures of 4-0 braided polyglactin. All the chickens were immobilised for two weeks using plaster-of-Paris splints.

All the operations were performed by the same surgeon (GYO) using microsurgical techniques.

Table III. Histological grading system for tendon healing according to Tang et al[20]

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

Macroscopic evaluation. From each group 24 tendons (12 at three weeks and 12 at six weeks) were prepared for macroscopic evaluation after surgery. The macroscopic grading of the adhesions was done using the system of Tang et al[20] (Table I). The length of the adhesion and the length, density and movement capability of the repaired tendon were evaluated.

Histological evaluation. From each group 24 tendons (12 at three weeks, 12 at six weeks) were prepared for histological evaluation. The digit and tendon complexes underwent a standard procedure of fixation using 10% neutral formalin and decalcification solution for a period of 48 hours which allowed the excision of the specimens. The tendons were cut longitudinally and embedded in paraffin after routine processing. Serial 5 μm sections were prepared and stained with haematoxylin and eosin.

The grading scale of Tang et al[20] was used to evaluate the extent and severity of the formation of adhesions in the peritendinous region (Table II). In this grading system, the adhesions were evaluated both quantitatively and qualitatively. The healing status of the tendons 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 fibres[20] (Table III).

An experienced histopathologist as a blind observer performed the review without having any information about the tendons.

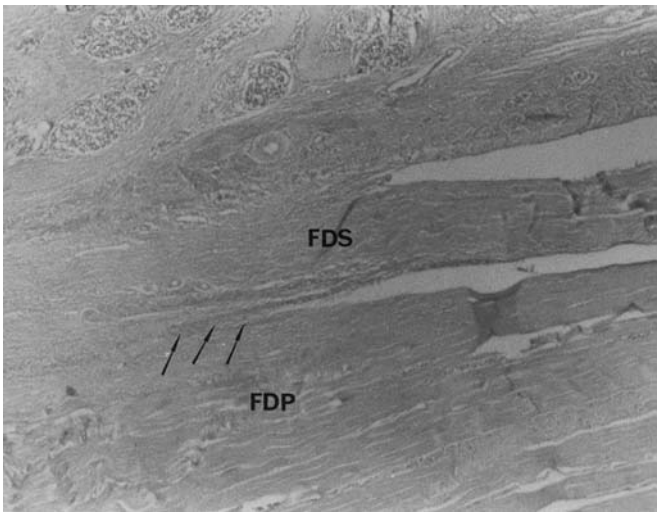

Fig. 1a

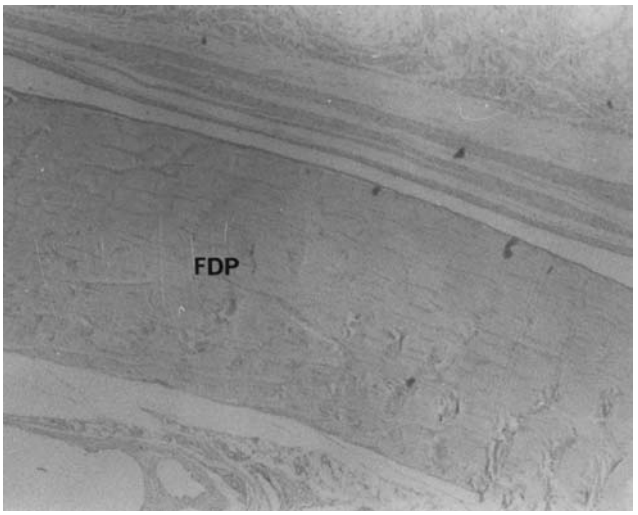

Fig. 1b

Photographs of longitudinal sections through the repaired tendons and soft tissues at six weeks after surgery. Fig. 1a – Obvious adhesions (arrows) were observed between the flexor digitorum profundus tendon (FDP) and flexor digitorum superficialis tendon (FDS) in those which received no treatment after simple repair of the tendon. Fig. 1b – Few adhesions were observed in the peritendinous region in the tendons which had received the combination of human amniotic membrane and hyaluronic acid (haematoxylin and eosin x 60).

Biomechanical evaluation. From each group 12 tendons were prepared for evaluation of peritendinous adhesions by measuring the active and passive flexion of the metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal (DIP) joints using a goniometer at 20 weeks. The deep flexor tendons of the toes were transected just distal to their junction with the main body of the deep flexor muscles. The metatarsal bones of the long toes of the chickens were mounted on a measurement platform by passing two pins through the metacarpal bone. The active range of movement of the MCP, PIP, and DIP joints was measured with a goniometer when the deep flexor tendon was pulled by the horizontal force of 50 g and the passive range of movement was measured when this weight was applied to the distal end of the toe. The active and passive range of movement of the MCP, PIP, and DIP joints indicated the level of formation of adhesions.

After the measurements of toe movement had been taken, the tensile strength of the repaired tendons was measured with a tensiometer (Shirley Development Ltd, Lancaster, UK). The deep flexor tendons were freed from the bones and skin leaving the site of repair intact and the ends were then grasped with the compressive clamps of the tensiometer. The latter pulled the tendon at a constant speed of 110 mm/s, gradually increasing the tensile load until the tendon ruptured. Measurements of the tensile load were recorded on an x-y recorder. The ultimate breaking strength of the tendons reflected the differences in the healing of the tendon between the groups.

Statistical analysis. The statistical significance in the results of grading the adhesions and the healing of the tendons was determined using the non-parametric analysis of variance (ANOVA) Kruskal-Wallis test followed by the Mann-Whitney test. Because the data were limited and the values of the variables were ordinary scales, the non-parametric test was used. The results of the tensile strength of the repaired tendons were evaluated by ANOVA. In all tests a p value of <0.05 was considered to be significant.

Results

Macroscopic findings. Wound infection was not seen in any of the groups. Quantitatively, at three and six weeks the adhesion lengths were longest in group 1, shorter in groups 2 and 3 and shortest in group 4. Qualitatively at three and six weeks in group 1, rigid, dense and immobile adhesions were observed around the repaired tendons. In groups 2 and 3 loose, elastic and mobile adhesions were observed. In group 1, almost no adhesions were seen.

As a result of the quantitative and qualitative valuations, the extent and severity of the formation of adhesions in the peritendinous region at three and six weeks were highest in group 1, significantly lower in groups 2 and 3, and lowest in group 4. The quantitative summary values of the macroscopic results of the peritendinous adhesions are presented in detail in Tables IV to VII. The p values are summarised in Tables V and VII.

Histological findings. As a result of the quantitative and qualitative histological evaluation, in group 1, a large quantity of dense filamentous fibrous adhesions was observed involving the tendon, the tendon sheath and the underlying bone (Fig. 1a). In group 4, almost no adhesions were observed around the repaired tendons (Fig. 1b). There

Table IV. Descriptive statistics of macroscopic evaluation of tendon adhesions at three weeks

Groups	Mean ± SEM	Median	SD	Confidence interval (%)
1	5.00 ± 0.30	5.00	1.04	4.33 ± 5.66
2	3.25 ± 0.37	3.50	1.28	2.43 ± 4.06
3	3.25 ± 0.30	3.50	1.05	2.57 ± 3.92
4	1.75 ± 0.25	2.00	0.86	1.20 ± 2.30

Significance p <0.001

Kruskal-Wallis test v=3, χ^2=25.774

Table V. Statistical comparisons of the groups regarding the macroscopic evaluation of the tendon adhesions at three weeks

Groups	Mann-Whitney U test	p value
1 and 2	24.00	0.004
1 and 3	21.00	0.002
1 and 4	0.00	0.00
2 and 3	71.00	0.95
2 and 4	26.50	0.007
3 and 4	22.00	0.003

Table VI. Descriptive statistics of macroscopic evaluation of tendon adhesions at six weeks

Groups	Mean ± SEM	Median	SD	Confidence interval (%)
1	5.16 ± 0.24	5.00	0.83	4.63 ± 5.69
2	3.50 ± 0.19	3.00	0.67	3.07 ± 3.92
3	3.41 ± 0.25	3.50	0.90	2.84 ± 3.98
4	1.75 ± 0.25	2.00	0.86	1.20 ± 2.30

Significance p < 0.001

Kruskal-Wallis test v=3, χ^2=33.376

Table VII. Statistical comparisons of the groups regarding the macroscopic evaluation of the tendon adhesions at six weeks

Groups	Mann-Whitney U test	p value
1 and 2	11.00	0.00
1 and 3	12.50	0.00
1 and 4	0.00	0.00
2 and 3	70.50	0.92
2 and 4	7.00	0.00
3 and 4	14.00	0.001

Table VIII. Descriptive statistics of the histopathological evaluation of tendon adhesions at three weeks

Groups	Mean ± SEM	Median	SD	Confidence interval (%)
1	5.16 ± 0.29	6.00	1.02	4.51 to 5.82
2	3.50 ± 0.43	4.00	1.50	2.54 to 4.45
3	3.41 ± 0.55	3.50	1.92	2.19 to 4.64
4	1.75 ± 0.41	2.00	1.42	0.84 to 2.65

Significance p <0.001

Kruskal-Wallis test v=3, χ^2=20.658

Table IX. Statistical comparisons of the groups regarding the histopathological evaluation of the tendon adhesions at three weeks

Groups	Mann-Whitney U test	p value
1 and 2	29.50	0.01
1 and 3	29.50	0.10
1 and 4	2.50	0.00
2 and 3	69.50	0.88
2 and 4	32.50	0.02
3 and 4	31.50	0.02

Table X. Descriptive statistics of histopathological evaluation of tendon adhesions at six weeks

Groups	Mean ± sem	Median	SD	Confidence interval (%)
1	4.75 ± 0.30	4.50	1.05	4.07 to 5.42
2	2.66 ± 0.55	3.00	1.92	1.44 to 3.88
3	2.50 ± 0.39	3.00	1.38	1.62 to 3.37
4	0.83 ± 0.29	0.00	1.02	0.17 to 1.48

Significance p <0.001

Kruskal-Wallis test v=3, χ^2=25.848

Table XI. Statistical comparisons of the groups regarding the histopathological evaluation of the tendon adhesions at six weeks

Groups	Mann-Whitney U test	p value
1 and 2	25.00	0.01
1 and 3	12.50	0.00
1 and 4	0.00	0.00
2 and 3	66.00	0.72
2 and 4	30.50	0.01
3 and 4	24.50	0.00

were significantly fewer severe adhesions in group 4 than in the other groups. The p values are summarised in Tables IX and XI. In groups 2 and 3, a small or moderate amount of dense adhesions was observed around the repaired tendon. No significant difference was found between groups 2 and 3.

Furthermore, adhesions in groups 2 and 3 were statistically greater than those in group 4 and lower than in group 1. The descriptive statistics of the histological findings regarding the peritendinous adhesions and comparison of the groups are summarised in Tables VIII to XI.

The mean and SEM values of the histological findings regarding the process of tendon healing were 2.50 ± 0.23 in group 1, 2.08 ± 0.22 in group 2, 2.00 ± 0.24 in group 3, and 1.83 ± 0.24 in group 4 at three weeks and 2.58 ± 0.28 in group 1, 2.33 ± 0.33 in group 2, 1.83 ± 0.20 in group 3, and 1.75 ± 0.21 in group 4 at six weeks. The chi-squared values were 3.78 at three weeks and 5.72 at six weeks. No signif-

Table XII. Descriptive statistics of values for tensile load at 20 weeks

Groups	Mean ± SEM	Median	sd	Confidence interval (%)
1	66.15 ± 1.64	67.35	5.68	62.54 to 69.77
2	64.56 ± 2.10	65.12	7.29	59.93 to 69.20
3	66.19 ± 2.00	67.84	6.95	61.77 to 70.61
4	66.72 ± 1.70	67.37	5.90	62.97 to 70.47

Significance p=0.863

ANOVA v_1=3, v_2=44, F=0.247

Table XIII. Median values with confidence intervals of the active range of toe movement at 20 weeks (Kruskal-Wallis test)

	Median (degrees)			Confidence interval (%)		
Groups	MCP	PIP	DIP	MCP	PIP	DIP
1	60.00	50.00	37.50	54.03 to 63.46	42.09 to 53.73	31.21 to 43.78
2	72.50	60.00	50.00	69.03 to 78.46	53.81 to 67.85	43.97 to 51.85
3	75.00	60.00	52.50	69.65 to 77.84	54.36 to 67.30	45.80 to 58.35
4	85.00	70.00	62.50	80.37 to 87.95	67.49 to 76.66	59.03 to 68.46

Table XIV. Statistical comparisons of the groups regarding the active range of toe motion at 20 weeks

	Mann-Whitney U test			p value		
Groups	MCP	PIP	DIP	MCP	PIP	DIP
1 and 2	10	26.5	29.5	0.00	0.01	0.01
1 and 3	11	26.5	21.0	0.00	0.01	0.00
1 and 4	1.0	1.0	1.5	0.00	0.00	0.00
2 and 3	69.5	72.0	50.5	0.88	1.00	0.20
2 and 4	20.5	28.5	8.0	0.00	0.01	0.00
3 and 4	15.0	29.0	25.5	0.00	0.12	0.00

Table XV. Median values with confidence intervals of the passive range of toe movement at 20 weeks (Kruskal-Wallis test)

	Median			Confidence interval (%)		
Groups	MCP	PIP	DIP	MCP	PIP	DIP
1	50.00	50.00	30.00	48.02 to 61.14	70.63 to 80.19	26.34 to 36.15
2	77.50	62.50	52.50	70.63 to 80.19	58.65 to 68.84	49.21 to 56.61
3	67.50	57.50	45.00	62.42 to 73.41	51.35 to 64.47	41.17 to 50.49
4	85.00	75.00	60.00	83.18 to 88.48	69.31 to 79.01	59.19 to 67.47

Table XVI. Statistical comparisons of the groups regarding the passive range of toe movement at 20 weeks

	Mann-Whitney U test			p value		
Groups	MCP	PIP	DIP	MCP	PIP	DIP
1 and 2	7.50	9.00	2.00	0.00	0.00	0.00
1 and 3	24.0	31.5	12.5	0.00	0.00	0.01
1 and 4	0.00	0.00	0.00	0.00	0.00	0.00
2 and 3	38.0	44.0	32.5	0.04	0.10	0.02
2 and 4	17.0	24.5	16.5	0.00	0.00	0.00
3 and 4	4.5	15.0	5.5	0.00	0.00	0.00

icant difference was observed between the groups in the healing status of the tendons at three and six weeks. The p values were 0.286 and 0.126, respectively.

Biomechanical findings. The mean tensile load values are summarised in Table XII. There was no significant difference in the mean tensile load required to rupture the repaired tendon between the groups at 20 weeks (p = 0.863).

The active and passive range of movement at 20 weeks was smallest in group 1, significanty larger in groups 2 and 3 and the largest in group 4. In group 1, the digits could not be flexed fully because of the severe adhesions which encircled the tendons. There was no significant difference between groups 2 and 3, suggesting that the extent of the adhesions was similar. In these groups flexion was significantly better than that in group 1. One in group 4 was significantly better than in the other groups, indicating considerably less formation of adhesions. The p values are summarised in detail in Tables XIV and XVI. The quantitative summary of the values for active and passive range of movement and comparisons of the groups are summarised in Tables XIII to XVI.

Discussion

Our study has evaluated the application of HA and HAM, singly and in combination, in the prevention of peritendinous adhesions. We showed that the combination is highly effective in reducing the formation of surgically-induced adhesions in the deep flexor tendons of chickens.

Amnion has been used to cover surgical wounds, burns and ulcers in various parts of the body.[21,22] Vascular granulation tissue appears within a few days and the development of capillaries was attributed to an angiogenic factor in the amnion. HAM has been used with good results for the reconstruction of conjunctival defects, in surgery on the ear and in vaginal epithelialisation.[23-25] It has been used to prevent tissue adhesion in surgery on the abdomen or pelvis.[26,27] It has also been shown that HAM induces a down-regulation of transforming growth factor beta (TGF-β) signalling which plays multiple roles in wound healing including the recruitment of fibroblasts and macrophages and the stimulation of collagen production.[28] Chang et al[29] have shown that neutralising antibody to TGF-β is a promising agent for the reduction of the formation of peritendinous adhesions after surgery on the flexor tendons.

There are many reasons for our preference for using HAM. Harvesting HAM is a simple procedure and does not require special experience or equipment and it is readily available, easily stored and inexpensive. It is known that human amniotic epithelial cells do not express surface HLA-A, B, C and DR antigens or β_2-microglobulin.[30] In our study, no generalised inflammatory reaction was observed in tissues. HAM has antimicrobial potential that may be attributed to lysozymes, which are bactericidal.[31]

HA is a well-known constituent of synovial fluid and has been shown to be present in tendon-sheath fluid.[32] In previous experimental studies, it was shown that HA reduced peritendinous adhesions and promoted tendon healing,[13-15] but this effect has been variable. The molecular weight and the concentration of the preparation are critical to its potential beneficial effects. Low concentrations and low molecular weight seem to have a stimulating effect on the function of granulocytes. By contrast, high concentrations and high-molecular-weight HA inhibit the movements and phagocytosis by granulocytes. It has been found that the critical molecular weight seems to be 10^5 to 10^6 daltons for inhibition of the function of granulocytes.[13] Recent studies have reported that HA with a concentration of 19 mg/ml and a molecular weight of 6×10^6 significantly limits the formation of adhesions.[14] The molecular weight and the concentration of HA preparation used in our study were about 10^6 daltons and 15 mg/ml. Therefore this HA preparation would be expected to reduce scar formation by inhibiting the activity of mononuclear phagocytes and lymphocytes.

Our results have shown that a single application of HA in combination with HAM was effective in the control of peritendinous adhesions. Furthermore, the mean value of the adhesions in tendons treated only with HA was significantly higher than in those treated by the combination of HA and HAM. The reason for the reduced adhesions observed in group 4 may be the wrapping of the repaired site by HAM which may prevent the rapid dispersion of the HA. However, the single-dose application of HA around the sites of tendon repair could be a criticism of our study since restoration of the circulation to the area would rapidly remove it. We did not apply the solution repeatedly because the high risk of infection would not be considered to be a feasible clinical alternative. However, multiple injections of HA are the logical next step in this investigation.

Our study suggests that the intra-operative application of HA and HAM in combination prevents the formation of post-operative peritendinous adhesions without impairment of healing of tendons in chickens. This combination may be of benefit in clinical practice in order to reduce adhesions after repair of flexor tendons.

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