

Prevention of adhesions in surgery of the flexor tendons of the hand: what is the evidence?

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Introduction: Despite advances in knowledge and refinements of technique, the management of flexor tendon injuries within the digital sheath continues to present a formidable challenge. This in turn has led to a massive expansion in search of modified surgical therapies and various adjuvant therapies, which could prevent adhesion formation without compromising digital function.

Sources of data: A search of PubMed, Medline, CINAHL and Embase databases was performed using the keywords 'tendon adhesion prevention', 'tendon healing', 'adhesion prevention in tendons' and 'adjuvants for adhesion prevention'. Studies detailing the use of surgical, pharmacological and non-pharmacological agents for adhesion prevention in digital flexor tendons were identified, and their bibliographies were thoroughly reviewed to identify further related articles. This search identified 41 studies, which investigated the use of various pharmacological agents in adhesion prevention in digital tendons.

Areas of agreement: There is a need to develop and utilize an optimal method for the prevention of adhesions in the flexor tendons of the hand, due to post-surgical complications.

Areas of controversy: Even though there have been significant advances in the prevention of adhesions in flexor tendons, it remains to be proved which, if any, of the current methods are the most beneficial.

Growing points: The only thing that appears clinically justified in adhesion prevention is the need for early post-operative mobilization of digits after tendon injury or repair but the best method of mobilization remains controversial.

Areas timely for developing research: Suggested changes in surgical techniques and various proposed pharmacological and non-pharmacological modalities need to withstand the test of adequately powered human trials, before their justification for potential benefit in clinical practice is accepted.

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Introduction

Peritendinous adhesions after repair of an injury to the digital flexor tendons are a major problem in hand surgery. The adhesions are part of the healing process and almost inevitably produce functional disability following the biological response of the tendon to injury.¹ To achieve better gliding function of the digital tendons by reducing peritendinous adhesions without adversely affecting the healing process, several options, including physical, surgical and pharmacological, have been explored. This has led to the introduction of several new surgical techniques and various pharmacological and non-pharmacological modalities. However, the scientific evidence behind these methods should be thoroughly scrutinized before they are widely incorporated into routine clinical practice. This article reviews these options, and evaluates the scientific evidence behind them.

Methods

A search of PubMed, Medline, CINAHL and Embase databases was performed using the keywords ‘tendon adhesion prevention’, ‘tendon healing’, ‘adhesion prevention in tendons’ and ‘adjuvants for adhesion prevention’. Studies detailing the use of surgical, pharmacological and non-pharmacological agents for adhesion prevention in digital flexor tendons were identified, and their bibliographies were thoroughly reviewed to identify further related articles. This search identified 41 studies (demonstrated in Fig. 1), which investigated the use of various pharmacological agents in adhesion prevention in digital tendons.

Tendon adhesion=487, tendon healing=2722, adhesion prevention in tendons=71, adjuvants for adhesion prevention=124



Combining search of keywords, using inclusion criteria and manual search of the selected articles resulted in 55 articles.



Exclusion of articles in language other than English=14

Resultant articles considered for study=41.

Fig. 1 Flow diagram of literature search strategy.

Exclusion criteria

We excluded studies in language other than English, studies not dealing with digital tendons, studies not reporting on adhesion prevention along with case reports and letters to editor.

Tendon healing and adhesion formation

Collagen constitutes the main part of the tendon, with water, proteoglycans and cells forming the matrix. There is a change in the composition of proteoglycan produced by cells in the pressure-bearing areas compared with tendon-transmitting areas. Chondroitin sulphate is predominant in the pressure contact areas, whereas dermatan sulphate is dominant in the tension-transmitting segments, i.e. the areas of the tendon being stretched and becoming taut. It therefore seems likely that the differences in the type and proportion of proteoglycans in the tension and pressure-bearing segments of the tendon are related to the functional needs of the tissue, and thus may influence the formation of adhesions following tendon injury and repair.²

Intrinsic and extrinsic healing

Tendon healing proceeds by a combination of intrinsic and extrinsic processes that occur simultaneously. Intrinsic healing occurs within the tendon as a result of the activity of tenocytes and appropriate nutrition to them. Extrinsic healing occurs through the chemotaxis of the specialized fibroblasts into the defect from the ends of the tendon sheath.^{3,4} Synovial fluid diffusion also contributes to intrinsic healing by providing an additional nutritional source.^{4–10}

Risk factors for adhesion formation

Matthews *et al.*³ noted that the tendon injury itself was not the sole stimulus for the development of adhesions. When flexor tendons were severed, the ends retracted and became rounded, lying freely within the sheath with no adhesions. Similarly, immobilization itself did not lead to an adhesive response from the digital sheath. However, excision of the synovial sheath followed by immobilization most frequently resulted in adhesive response. Also, greater degrees of trauma to the synovial sheath and gaps of 3 mm or more have been related to increased adhesion formation.^{3,11}

The degree and extent of tendon adhesions

Siegler *et al.*¹² classified the degree and extent of adhesions into four grades: Grade 0, complete absence of adhesions; Grade I, thin avascular, filmy and easily separable; Grade II, thick, avascular and limited to the site of anastomosis; Grade III, thick, vascular and extensive. This classification has been used for evaluation of severity of adhesion formation in various human and animal models.

Available options

With increasing information available concerning the nature of the scar tissue responsible for the peritendinous adhesions, along with changes in surgical and post-operative rehabilitation techniques, several modalities, such as modulation of inflammatory response and growth factors that promote scarring by various pharmacological agents, introduction of mechanical barriers between the tendons and the proliferating tissue, use of ultrasound and electromagnetic therapy and, recently, gene therapy, are being explored.

Modifications in surgical technique

Enhanced appreciation of tendon structure, nutrition and biomechanical properties and investigation of factors involved in tendon healing and adhesion formation have resulted in various modifications of surgical technique in handling tendon injuries.

Multistrand repair

The initial strength of tendon repair is roughly proportional to the number of suture strands that cross the repair site. The most commonly used technique involves a two-strand repair.¹³ Increasingly, four-, six- and even eight-strand repairs are now used,¹³ allowing more aggressive early rehabilitation without a greater rupture rate. Generally, the greater the number of suture strands that cross the repair site, the more technically demanding the technique, the greater the amount of surgical handling of the tendon and the greater the amount of suture material on the outside of the tendon.^{14,15}

There is a limited information about the effect of increasing strand numbers on the healing or adhesion response in a repair. High friction suture techniques may cause more adhesion formation than the lower friction suture techniques following passive post-operative therapy.¹⁶ Strick *et al.*,¹⁷ however, did not find a difference. Most studies (Table 1) on gliding resistance after various suturing techniques are

Table 1 Surgical options.

Reference	Year	Subjects	Study design	Results
Multistrand repair Zhao ¹¹⁶	2001	Canine model	Sixty FDP tendons repaired with either a modified Kessler or Becker suture technique and supplemented with a simple running suture	High friction suture techniques may cause more adhesion formation than the lower friction suture techniques under passive post-operative therapy
Dinopoulos ¹¹⁷	2000	Canine model	Twenty-two flexor tendons were repaired using the 4- and an 8-strand suture technique, and tested to failure after 10 days of <i>in vivo</i> healing	8-strand repair is significantly more resistant to initial gapping during <i>ex vivo</i> tensile testing than the 4-strand repair
Gill ¹⁹	1999	Fresh-frozen human hands	Forty flexor tendons were harvested from fresh-frozen human hands and divided into 4 groups of 10 tendons each. Each group of tendons was repaired with a specific technique: group 1, the modified Kirchmayr (modified Kessler) technique; group 2, the single-loop 2-strand technique described by Tsuge; group 3, Tsai's double-loop 4-strand modification of Tsuge's technique; and group 4, Tsai's double-loop 6-strand modification of Tsuge's technique	The 6-strand double-loop suture technique improves the repair's strength and its resistance to gapping without increasing tendon handling or bulk
Thurman ²⁰	1998	Cadaver models	The 2- and 4-strand core sutures were placed using a suture interlock technique with radial and ulnar grasping purchase of the tendon on each side of the transverse part of the repair	The tensile strength of the 6-strand repair (mean, 78.7 N) was significantly greater than either the 4-strand (means, 43.0 N) or 2-strand (mean, 33.9 N) repair
Strick ¹⁷	2004	Chicken model	The FDP tendon of the right middle toe of 80 broiler chickens was cut and then repaired with either a single (2-strand) or double (4-strand) modified Kessler core suture, followed by a running epitendinous suture	Adhesion formation and gliding resistance of tendons after 2- or 4-strand modified Kessler core suture were not significantly different
Tendon sheath: to repair or not to repair? Peterson ³²	1986	Chicken model	Tendon gliding of flexor sheath excision versus incision/closure following primary flexor tendon repair was examined biomechanically and histologically in 41 chickens	There was no significant difference in either the tendon excursion required to fully flex the digit or in the work of flexion between the sheath excised and sheath closed groups

Continued

Table 1 Continued

Reference	Year	Subjects	Study design	Results
Strauch ³¹	1985	Chicken model	Sheath closure after tendon grafting was accomplished by trapdoor of the original sheath, vein patch and vein conduit	Significantly greater functional return when the sheath was restored either with trap-door closure, vein conduit or vein patch compared with simple excision of the sheath
Saldana ³³	1987	Patients with lacerations of both flexor tendons	A modified Kessler suture was used to repair the profundus tendon. The tendon of superficialis tendon was repaired with a horizontal mattress suture. In 48 fingers, the flexor tendon sheath was left open and it was closed in the second group of 42 fingers	There was no statistical difference between the results of open sheath versus closed sheath in these two groups of patients
Gelberman ³⁴	1990	Canine model	Flexor sheath repair, sheath excision and autogenous sheath grafting were compared for biomechanical characteristics, and biochemical and ultrastructural alterations at the repair site at intervals over a 12-week period	Reconstruction of the tendon sheath, either by suture or autogenous graft, did not improve significantly the biomechanical, biochemical or morphologic characteristics of repaired tendons treated with early motion rehabilitation
Peterson ³⁵	1990	Chicken model	Three methods of sheath closure. I. Primary sheath repair; II. a fascia patch; III. a synthetic polytetrafluoroethylene surgical membrane patch, were compared with controls in which the flexor sheath was excised	At 3 and 6 weeks there was no significant difference in the work of flexion between either the sheath repair or fascia patch digits, and the sheath excised controls. In contrast, at 12 weeks all three methods of sheath reconstruction had similar tendon gliding biomechanics, and all were significantly better than the controls
Tang ³⁶	1994	Leghorn chickens	In the left foot, the tendon sheath was closed after tendon suture. In the right foot, the sheath was excised over the tendon suture	The sutured sheath disappeared after suturing and was associated with poor tendon healing. Sheath closure did not improve flexor tendon function in a delayed primary repair

Continued

Table 1 Continued

Reference	Year	Subjects	Study design	Results
Post-operative mobilization				
Adolfsson ³⁹	1996	Humans	Injured tendons were repaired within 24 h, and all patients were subjected to mobilization during the first 6 weeks using a passive flexion-active extension regime. After 6 weeks the patients were randomized into two groups; in group A full activity was allowed after 8 weeks while in group B unrestricted use of the injured hand was not allowed until 10 weeks after the tendon repair	No significant differences were observed between the groups regarding functional results, rupture rates, grip strength or subjective assessment, but absence from work was reduced by 2.1 weeks with the shorter mobilization programme
Gelberman ⁴⁰	1991	Humans	Fifty-one patients were randomly allocated to two controlled passive motion protocols. Group 1 patients received greater intervals of passive-motion rehabilitation using a continuous passive-motion device. Group 2 patients were treated with a traditional early passive-motion protocol for tendon rehabilitation	Duration of the daily controlled motion interval is a significant variable insofar as post-repair flexor tendon function is concerned Using Strickland and Glogovac's formula, the mean active motion for digits in Group 1 was 138 degrees \pm 6 degrees. Mean motion for tendons in Group 2 was 119 degrees \pm 8 degrees. The difference between Groups 1 and 2 was statistically significant. The effect of the number of tendons injured per digit within each group was not significant
Percival ⁴¹	1989	Humans	Fifty-one patients with isolated flexor pollicis longus tendon repairs were divided into two groups. I. was kept immobile; II. Underwent controlled dynamic mobilisation	The results of mobilisation were significantly better, with 62% achieving good or excellent results compared to 33% treated by fixed splintage
Pulley incision and pulley plasty				

Continued

Table 1 *Continued*

Reference	Year	Subjects	Study design	Results
Tang ⁴⁵	2007	Leghorn chickens	52 leghorn chickens were divided into four experimental groups and one control group. An <i>in vitro</i> study was conducted to investigate the biomechanical effects of pulley incision, Kapandji pulley plasty, excision of one slip of the FDS or closure of the incised pulley on function of the profundus tendons	Eight weeks after surgery, incision of the pulley improved excursion of the digitorum profundus tendon and decreased the work of digital flexion over pulley closure. Kapandji pulley plasty did not increase tendon excursion and decrease the work compared with a simpler pulley incision. Adhesions were more severe with pulley plasty closure than with pulley incision. Kapandji pulley plasty did not improve outcomes over simple pulley incision
Simultaneous repair Tang ⁴⁶	1994	Humans	A study was carried out in 33 patients (37 fingers) with lacerations of both FDS and FDP tendons in the area covered by the A2 pulley. Both lacerated tendons were repaired in 19 fingers, and repair of only FDP with regional excision of FDS was performed in 18 fingers	Follow-up of at an average of 12 months showed no significant difference in the end results. The fingers with suture of both tendons showed a higher rate of re-operation due to adhesions or rupture of repair. This study suggests that it is better to repair only FDP with regional excision of FDS when both tendons are injured in zone 2C

in vitro or animal studies. We were not able to identify any human trials.^{16–20}

Tendon sheath: to repair or not to repair?

Sheath closure following flexor tendon repair is frequently attempted.²¹ This practice is largely based on the concepts that flexor tendons within the region of synovial sheaths are mainly nourished through synovial diffusion,²² and that lacerated tendons can heal sufficiently through their intrinsic cellular activities without the necessity of adhesion formation.²³ Restoration of sheath integrity is believed to preserve nutrition of the tendons, provide them with a smooth gliding surface for tendons, and decrease peritendinous adhesions.^{21–30}

There are conflicting views on the advantages of sheath closure (Table 1). Restoration of sheath integrity in flexor tendons reduces adhesion formation.³¹ However, sheath closure has not proved consistently effective in improving tendon gliding function.^{32–35} For example, the sutured sheath may disappear after suturing, and is associated with poor tendon healing.³⁶ In a human trial,³² no statistical difference between the results of leaving the sheath open versus closing it in two groups of patients was noticed.

Post-operative mobilization

Post-operative mobilization decreases adhesion formation and improves function after flexor tendon repair.^{37,38} There are now several post-operative mobilization regimes like shortened passive flexion/active extension versus normal passive flexion/active extension;³⁹ continuous passive motion versus controlled intermittent passive motion;⁴⁰ dynamic splintage versus static splintage;⁴¹ active flexion versus rubber band traction;⁴² controlled passive flexion with active extension (modified Kleinert) versus controlled passive mobilization (modified Duran);⁴³ grasping suture and early controlled active mobilization versus modified Kessler technique with early controlled passive mobilization⁴⁴ to improve gliding function of tendons (Table 1).

There is, however, insufficient evidence from randomized, controlled trials to define the best mobilization strategy.

Pulley incision and pulley plasty

Outcomes of flexor tendon repairs in the area covered by major pulleys are often unpredictable. Tang *et al.*⁴⁵ showed that incision of the pulley-improved excursion of the flexor digitorum profundus (FDP) tendon and decreased the work of digital flexion over pulley closure. Kapandji pulley plasty did not increase tendon excursion and decrease the work compared with a simpler pulley incision. Adhesions were more severe with pulley plasty or closure than with pulley incision (Table 1).

Simultaneous repair

Tang⁴⁶ studied 33 patients (37 fingers) with lacerations of both flexor digitorum superficialis (FDS) and FDP tendons in the area covered by the A2 pulley. Both lacerated tendons were repaired in 19 fingers, and repair of only FDP with regional excision of FDS was performed in 18 fingers. Follow-up of average 12 months revealed that there was no significant difference in the end results. The study suggests that it is better to repair only FDP with regional excision of FDS when both tendons are injured in zone 2C (Table 1).

Pharmacological adjuvants

Several pharmacological adjuvants have evolved in the search to find the answer to rapid recovery and function in hand tendons after injury or surgery. These adjuvants fall into two main categories, namely drugs and barriers.

Drugs

Non-steroidal anti-inflammatory medications

Mechanism of action and role in adhesion prevention

Non-steroidal anti-inflammatory drugs (NSAIDS) competitively inhibit cyclo-oxygenase, an enzyme essential for the metabolism of arachidonic acid (AA) to prostaglandins. The end products and intermediate metabolites of AA metabolism are involved in the inflammatory process, ultimately leading to adhesion formation.⁴⁷

The net effect of treatment with NSAIDS is to decrease the metabolites and by-products of AA metabolism and, consequently, their effects on the local tissues. By reducing these pro-inflammatory agents, endogenous local damage may be decreased after trauma. The consequence could be a decrease in peritendinous fibroplasias.⁴⁷

Supporting evidence

Several studies have shown that NSAIDS appears to inhibit the formation of significant post-operative adhesion in a dose-dependent fashion when compared with control subjects (Table 2).^{47,48} Also, ibuprofen treatment did not appear to inhibit normal wound healing, nor did it cause abnormal bleeding or oozing at the operative site.⁴⁸

Hyaluronic acid

Mechanism of action and role in adhesion prevention

Hyaluronic acid (HA) is a polysaccharide found in synovial fluid. Although the exact mechanism of action in adhesion prevention is unknown, HA has been suggested to play a possible role during the early stages of healing of a variety of connective tissues, including injured tendon.^{49,50}

Supporting evidence

Hyaluronic acid has been extensively studied as an adjunct to adhesion prevention in digits. Some investigations suggest that HA promotes tendon healing and decreases adhesion formation (Table 2), but some studies did not show beneficial effects.⁵¹

Table 2 Pharmacological modalities and other therapeutic options.

Reference	Year	Subjects	Study design	Results
Drugs				
Mode of HA use				
Tanaka ¹⁰³	2007	Canine model	Surface treatment of tendons with carbodiimide-derivatized HA (cd-HA)	The adhesion score of cd-HA gelatin-treated tendons was significantly less than that in the saline-treated tendons at all times. However, there was no significant difference in strength at the distal tendon-bone interface, cellularity or tendon graft stiffness when comparing saline-treated and cd-HA treated tendon grafts <i>in vivo</i>
Zhao ¹⁰⁴	2006	Canine model	Surface treatment of flexor tendon autografts with cd-HA	Treating the surface of an extra synovial tendon autograft with a cd-HA-gelatin polymer decreases digital work of flexion and tendon gliding resistance in flexor tendon graft model <i>in vivo</i>
Akasaka ¹⁰⁵	2005	Canine model	HA injected around the tendon	HA diminishes the excursion resistance after flexor tendon repair
Hagberg ⁵¹	1992	Humans	HA injected around the tendon	Sodium hyaluronate had no statistically significant effect as evaluated by total active motion
Mode of Ibuprofen use				
Kulick ⁴⁷	1984	Cynomolgus monkeys	Group I. Peritendinous injections of 0.1 ml of ibuprofen every 12 h for 10 days to the 8 FDP tendons	In weeks 1–3, fewer inflammatory and reactive cells were observed in the ibuprofen-treated digits compared with control and standard digits
			Group II. Oral ibuprofen, 75 mg/kg, every 12 h for 10 days and peritendinous injections of 0.1 ml of ibuprofen every 12 h for 10 days to the 8 FDP tendons	The animal treated with supplemental oral ibuprofen showed a major reduction in peak force in the digits affected as compared to systemic medication alone
Kulick ¹⁰⁶	1986	Cynomolgus monkeys	Orally dosing of one of the four following doses: 25, 35, 45 and 75 mg/kg/day of ibuprofen	Treatment with oral ibuprofen significantly reduced the force required for tendon gliding following flexor tendon injury in zone II

Continued

Table 2 Continued

Reference	Year	Subjects	Study design	Results
Szabo ¹⁰⁷	1990	New Zealand white rabbits	Indomethacin solution (1 mg/kg/day) injected subcutaneously 2 h before operation and daily for 4 weeks	The animals treated with indomethacin had a greater tendon excursion and angular rotation of the joint than the control animals, implying suppression of adhesions
Mode of 5-FU use Moran ¹⁰⁸	2000	Leghorn chickens	5-FU solution applied topically	Histologic sections as graded by a blinded pathologist revealed decreased adhesion formation in all the 5-FU-treated animals. Overall, a single intra-operative application of 5-FU at concentrations of 25 mg/mL appears to be an effective mechanism for reducing post-operative flexor tendon adhesions
Akali ⁵³	1999	Rabbits	5-FU solution (50 mg/ml)-soaked sponge pledgets	There was a significant reduction in synovial sheath thickening, cell counts and proportional length of adhesions in the treated tendons
Mode of HAF use Ozgenel ⁵⁸	2001	New Zealand adult rabbits	Topical application	Application of HAF immediately after tenorrhaphy was effective in preventing peritendinous adhesion formation without impairment of tendon healing
Other pharmacological agent used Chang ⁵⁹	2000	New Zealand white rabbits	Neutralizing antibody to TGF- β 1	Intra-operative biochemical modulation of TGF-beta1 levels limits flexor tendon adhesion formation. Infiltration of neutralizing antibody to TGF-beta1 improves flexor tendon excursion
Namba ⁶³	2007	Japanese white rabbit	Surface coating of injured flexor digitorum communis tendon with alginate	When compared with the control group, the alginate-treated group demonstrated significantly greater toe flexion, with less scar tissue formation at the repair site. Histologically, complete tendon healing with longitudinal remodelling of collagen fibres was observed in the alginate-treated group, while a random pattern of fibres was observed in the control group

Continued

Table 2 Continued

Reference	Year	Subjects	Study design	Results
McCombe ⁶⁴	2006	Rat	In-continuity crush injury model in the rat hind foot flexor tendon to provoke adhesion formation. Animals in the treatment groups received collagen prolyl 4 hydroxylase inhibitor orally for 1, 2 or 6 weeks	The cutaneous wound healing rate was similar in all animals, but dermal collagen synthesis was reduced in the treated animals
Jones ⁶⁵	2002	Rabbits	Surface coating of deep flexor tendons with human-derived fibrin sealant	Highly significant difference in reduction of adhesions in the treated group
Nyska ⁶⁶	1996	Chickens	Surface coating of deep flexor tendons with Halofuginone	Almost complete absence of fibrous peritendinous adhesions in the histologic sections of the Halofuginone treated tendons. Halofuginone had no effect on the cellularity of the healing tissue
Speer ⁶⁷	1985	Lindsay chicken	Topically applied beta-aminopropionitrile base	Topical beta-aminopropionitrile was effective in the control of peritendinous adhesions, and achieves sufficient depth of penetration topically to affect the peritendinous location. No adverse effects of the topically applied agent were demonstrated
Porat ⁶⁹	1980	Chickens	Surface coating of long flexor tendons with an aqueous solution of enriched native collagen (ECS)	The exogenous collagen present at the site of injury binds the collagenase inhibitor released by tendon cells, thus providing enough active collagenase to control the formation of fibrous adhesions
Pharmacological modalities: barriers				
Hanff ⁷³	1998	Rabbits	Application of poly tetra fluoro-ethylene (e-PTFE) sheath after tendon repair in zone II	The e-PTFE group showed significantly lower maximum tensile load to flex the distal interphalangeal joint 50° during the first 6 weeks after surgery, indicating less formation of restrictive adhesions compared with the control group. Tensile strength of tendon repair was similar in e-PTFE and control groups
Peterson ³⁵	1990	Chickens	Application of sheath to traumatized flexor tendons	The synthetic patch (e-PTFE) was not associated with a significant inflammatory reaction at 3 weeks time period as compared to direct sheath repair or fascia patch grafted digits, and was clearly separated from the tendon

Continued

Table 2 *Continued*

Reference	Year	Subjects	Study design	Results
Siddiqi ⁷⁴	1991	Chickens	Application of hydroxyapatite (Hap) sheath to excised flexor sheath	The mobility of the tendons was better in the HAp group. HAp sheath was not firmly adherent to either the granulation tissue or the surface of the tendon. Histology at 3 and 6 weeks in HAp groups revealed epitenon-like structure on the tendon surface including the tenorrhaphy, site and a wide space around the tendon after the HAp sheath was removed
Siddiqi ⁷⁵	1995	Chickens	Application of hydroxyapatite (Hap) and alumina sheath to injured profundus tendons in zone II	Decreased severity of post-operative adhesions in the HAp as well as in the alumina groups in comparison with the sheath repair and controls
Isik ¹⁰⁹	1999	Leghorn chickens	Application of HA sheath to repaired flexor profundus tendons at zone II in the second, third and fourth toes	There were few adhesions in the HA treated group microscopically at the third month as compared to control group
Karakurum ¹¹⁰	2003	Chickens	Seprafilm (a combination of carboxymethylcellulose membrane and hyaluronate)	Seprafilm was effective in preventing adhesions after tenolysis compared to control group
Kobayashi ⁷⁶	2001	Domestic fowl	Application of PVA-H sheath to injured deep flexor tendon of the third toe	Injured tendons shielded with PVA-H healed within about 3 weeks without adhesion to the surrounding tissues. Neither breakage of the PVA-H shield itself nor infection or degeneration in the surrounding tissue was observed
Sungur ¹¹¹	2006	Chickens	Application of bovine pericardia to injured flexor tendons in chicken toe	Significantly less adhesion formation in the bovine pericardia treated group
Ultrasound Maiti ⁷⁷	2006	Adult goats	pulsed ultrasound therapy was started 3 days after repair of tendinous injury at an intensity of 1 W/cm(2) for 10 min daily for 10 consecutive days	Air tenograms and ultrasonography examinations showed that there was a marked regression of peritendinous adhesion between the tendon and skin on day 30 post-tendon injury repaired. The tendon at the repair site attained near normal thickness and density. Adhesions were present in the repair site of superficial digital flexor tendon in all animals of the control group

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Table 2 Continued

Reference	Year	Subjects	Study design	Results
Turner ⁷⁸	1989	Cockerel	Application of ultrasound	Histopathologically, the granulation tissue was comparatively better organized at the healing site in the ultrasound-treated animals The application of ultrasound to sutured cockerel tendons produced no change in the mechanical strength of the tendon at 6 weeks, or its propensity to form adhesions, relative to untreated control sutured tendons

Human studies

To date, few studies have been carried out on human subjects. In a prospective double-blind, randomized, clinical study with open therapeutic control, sodium hyaluronate or physiological saline solution was injected into the tendon sheath after completion of tenorrhaphy or tendon grafting in 120 digits. Sodium hyaluronate had no statistically significant effect as evaluated on total active motion at follow-up.⁵¹ Another prospective, double-blind, randomized, controlled clinical trial⁵² to assess the use of ADCON-T/N (a glycosaminoglycan-rich substance similar to HA) after flexor tendon repair in zone II revealed no statistically significant effect on total active motion at 3, 6 and 12 months after ADCON-T/N therapy. Though there was no significant difference in the mean total active motion of the two groups, the ADCON group of patients took significantly less time ($P = 0.02$) to achieve the final TAM (10 weeks compared with 14 weeks in the control group). These studies do not demonstrate any significant benefit of HA in digital adhesion prevention in human trials.

5-Fluorouracil

Mechanism of action and role in adhesion prevention

Although the mechanism of the reduction in adhesion formation by 5-fluorouracil (5-FU) is not known, cell proliferation and the ability to contract a fibroblast-populated collagen lattice are inhibited within the synovial sheath.⁵³

Exposure of fibroblasts to 5-FU causes reduction of extracellular matrix molecules and growth factor production.⁵⁴ This suggests that 5-FU, by modulating cellular activity without preventing cell proliferation, could reduce adhesion formation without preventing wound healing.

Supporting evidence

The proliferative and inflammatory responses can be significantly reduced in tendons treated with 5-FU. There seems to be a reduction in the cellular cytokine response and in the activity of the known pro-scarring agent, transforming growth factor beta (TGF- β) 1.⁵⁵ Also, breaking strength of tendons treated with 5-FU was not different from control groups.⁵⁶ No human trials have been reported.

Human amniotic fluid***Mechanism of action and role in adhesion prevention***

Human amniotic fluid (HAF) is rich in substances such as hormones, cytokines, polypeptide growth factors that influence cell proliferation and differentiation of cells.

Although the exact mechanism of amniotic fluid in adhesion prevention has yet to be elucidated, amniotic fluid may have some type of inhibitory effect on fibroblast proliferation.⁵⁷

Supporting evidence

The least adhesion and the best healing were observed in tendons treated with HAF application when compared with control groups (Table 2).⁵⁸ No human trials have been reported.

Transforming growth factor beta inhibitors***Mechanism of action and role in adhesion prevention***

Transforming growth factor beta is a cytokine that plays multiple roles in wound healing but is also implicated in the pathogenesis of excessive scar formation.⁵⁹ TGF- β stimulates chemotaxis, promotes angiogenesis and regulates a wide spectrum of matrix proteins.

Transforming growth factor beta accelerates the wound-healing process in several animal models. However, this effect may proceed uncontrollably and result in pathologic fibrosis, with excessive disordered collagen deposition resulting in tendon adhesions.⁶⁰ Hence, inhibitors of TGF- β have been used to reduce adhesion formation.

Supporting evidence

Transforming growth factor beta inhibition using a neutralizing antibody was effective in blocking TGF- β -induced collagen I production in cultured flexor tendons.⁶¹

Also, intra-operative infiltration of neutralizing antibody to TGF- β 1 improves flexor tendon excursion.

As TGF- β 1 is thought to contribute to the pathogenesis of excessive scar formation, intra-operative biochemical modulation of TGF- β 1 levels limits flexor tendon adhesion formation (Table 2).⁵⁹ Mannose-6-phosphate is effective in reducing TGF- β up-regulated

collagen production in an *in vitro* model, which improves the range of motion after flexor tendon repair.⁶² No human trials have been reported.

Combination therapy

Addition of other substances to HA augments the action of HA in decreasing adhesions. Several combinations have been tried, such as amniotic membrane, dipalmitoyl phosphatidylcholine, carboxymethyl-cellulose and NSAIDS (Table 2). No human trials have been reported.

Others

Several other chemical adjuvants have also been investigated for their potential role in adhesion prevention. These are alginate solution, collagen synthesis inhibitor (CPHI-I), enriched collagen solution, plant alkaloid halofuginone, human-derived fibrin sealant and topical beta-aminopropionitrile. No human trials have been reported.^{63–65}

Barriers

The cellular activity of intra-synovial flexor tendons may be specially adapted to intra-synovial environments. Therefore, reconstruction of damaged flexor tendon sheaths with a biocompatible, diffusible membrane may not interfere with the nutrition and healing of repaired flexor tendons. Furthermore, acting as a barrier between surrounding tissues and the repaired tendon, an interposed membrane may be able to further reduce the formation of adhesions.⁶⁸ This concept has led to the development of several chemical barriers, which promise to reduce adhesion prevention in digital tendons.

Expanded polytetrafluoroethylene

Expanded polytetrafluoroethylene (e-PTFE) is a microporous synthetic material. It is biochemically stable, soft, with a smooth surface and a high tensile strength.^{68,69} e-PTFE has also been used for reconstruction of tendon sheath and pulleys with promising results,⁷⁰ and to decrease the formation of restrictive adhesions. Fascia lata patch grafts and autogenous free sheaths have also been used. Microscopic examination has shown that the area of healing was better organized with less restrictive-appearing adhesions when the sheath defect was grafted.⁷¹ Tang *et al.*⁷² demonstrated that the diameter of the repaired sheath exerts a significant influence on flexor tendon function. Enlargement of the flexor sheath may provide an additional way to improve the function of repaired tendons. No human trials have been reported.

Other materials

Several other materials such as hydroxyapatite, HA membrane, polyvinyl alcohol hydrogel (PVA-H) and bovine pericardia have also been tested for their efficacy on adhesion prevention.^{73–75} No human trials have been reported.⁷⁶

Other modalities

Other modalities such as ultrasound therapy and pulsed electromagnetic field have also been tried, but only in animals, with controversial results.^{77,78}

Ultrasound therapy

Mechanism of action and role in adhesion prevention

Ultrasound consists of inaudible high-frequency mechanical vibrations. The sound waves are transmitted by propagation through molecular collision and vibration, with a progressive loss of the intensity of the energy during passage through the tissue (attenuation), due to absorption and dispersion or scattering of the wave.⁷⁹

Ultrasound may interact with one or more components of inflammation, and produce earlier resolution of inflammation.⁸⁰ Also, accelerated fibrinolysis,^{81,82} stimulation of macrophage-derived fibroblast mitogenic factors,⁸³ heightened fibroblast recruitment,⁸⁰ accelerated angiogenesis,⁸⁴ increased matrix synthesis,⁸⁵ more dense collagen fibrils⁸⁶ and increased tissue tensile strength^{87–89} have all been demonstrated *in vitro*. Such findings form the basis for the use of ultrasound to promote and accelerate tendon healing, repair and adhesion prevention.

The non-thermal effects of ultrasound, including cavitation and acoustic microstreaming, may be more important in the management of soft tissue lesions and adhesion prevention than thermal effects.⁹⁰

Acoustic microstreaming is the unidirectional movement of fluids along cell membranes, which occurs as a result of the mechanical pressure changes within the ultrasound field. Microstreaming may alter cell membrane structure, function and permeability.⁹¹ It has been suggested to stimulate tissue repair.⁹⁰ Effects of cavitation and microstreaming *in vitro* include stimulation of fibroblast repair and collagen synthesis,^{92–94,95} tissue regeneration⁹³ and bone healing.⁹⁴

These actions of ultrasound may be used as the basis to explain the mechanism in tendon adhesion prevention.

Supporting evidence

There was a marked regression of peritendinous adhesion between the tendon and skin on Day 30 post-tendon injury and the tendon at the

reconstructive site attained near normal thickness and density.⁷⁷ Treatment with ultrasound increased a range of movements, advanced scar maturation and decreased the amount of inflammatory infiltrate.⁷⁸

Future therapies

Delivery of growth factor genes that may substantially increase the healing rate of injured digital tendons is a new application of gene therapy in the field of hand flexor tendon surgery. Adenoviral, adeno-associated viral and liposome-plasmid vectors have been used to deliver genes to tendons to improve its healing. These may well form part of future treatment modalities for adhesion prevention. However, at the present moment, clinical evidence is lacking.^{96,97}

Conclusion

Both repair with scarring and regeneration can occur within the same animal, including man, and indeed within the same tissue, thereby suggesting that they share similar mechanisms and regulators.⁹⁸ Consequently, by subtly altering the ratio of growth factors present during adult wound healing, one could induce adult wounds to heal with no scars, with accelerated healing and with no adverse effects. Several new surgical techniques and various pharmacological modalities have been proposed. However, most studies have been performed in animals, with very few human trials. The results of mobilization techniques are promising, but inconclusive regarding the most effective technique.

Poor methodological standards in animal studies mean that positive results rarely translate to the clinical domain,⁹⁹ thus questioning whether these chemical adjuvants are really effective in humans. Also, when selecting an appropriate animal model, the major criteria to be considered are closely matched anatomic structure and the ease with which the treatment can be translated to a clinical setting. Adhesions formed after injury to the flexor tendon in primates have the closest resemblance to humans in both surgical technique and physical attributes. The use of rabbits, dogs and chickens, though interesting, may not be directly translatable to human clinical medicine, as their physical and anatomical features do not match the human anatomy.^{100–102}

Therefore, the only thing that appears clinically justified in adhesion prevention is the need for early post-operative mobilization of digits after tendon injury or repair but the best method of mobilization remains controversial. Suggested changes in surgical techniques and

various proposed pharmacological and non-pharmacological modalities need to withstand the test of adequately powered human trials before their potential benefit is accepted in routine clinical practice.

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