Acta Orthop. Belg., 2009, **75**, 433-444

REVIEW ARTICLE

Modalities in prevention of flexor tendon adhesion in the hand : What have we achieved so far ?

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Several modifications in surgical techniques and various pharmacological and non pharmacological modalities have been introduced to prevent adhesions formation in surgery on flexor tendons of the hand. However, most studies have been carried out in animals with very few human trials. Only early post-operative rehabilitation is supported by clinical evidence, while the optimal rehabilitation protocol remains controversial. Innovations in surgical techniques and other modalities need to be tested with adequately powered human trials, before their potential benefit in clinical practice is accepted.

Keywords : hand ; lexor tendons ; adhesions.

INTRODUCTION

Peritendinous adhesions in digital flexor tendons after repair are a major problem in hand surgery. The adhesions are part of the healing process and produce almost inevitably functional disability following the biological response of the tendon to injury (*5,17*). To achieve better gliding function of the digital tendons by reducing peritendinous adhesions without adversely affecting the healing process itself, several options, both 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 should be thoroughly scrutinised before they are widely incorporated into clinical practice (*5*). This article reviews these options, and evaluates the scientific evidence behind them.

No benefits or funds were received in support of this study. Mr Anil Khanna was holding an International DePuy Research Fellowship during completion of this study

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

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promote scarring by various pharmacological agents, introduction of mechanical barriers between the tendons and the proliferating tissue, use of ultrasound and electromagnetic therapy and recent interest in gene therapy have been explored.

1. *Modification 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.

A) 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 2-strand repair (*63*). Increasingly, 4, 6 and even 8-strand repairs are now used (*56,65,72*), 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 (*7,9*). Increased tendon damage and increased external foreign body may increase adhesion formation. Multiple strands may compromise intrinsic healing through ischemia, resulting in adhesion formation. Furthermore, multiple strands and increased external material increase the bulk of the repair. All these factors contribute to reduce tendon glide (*5,7,9,17,47,51,52, 56,63,64,74*). Ideally, a healing tendon should move, but under the minimum load necessary to achieve motion. It is possible to design suture repairs that minimize the friction between tendon and sheath while simultaneously maintaining adequate strength to provide a wide margin of safety during therapy. A looped, four-strand modified Kessler repair is a good example of this type of high-strength, low-friction repair (*5*). Another important element in tendon repair is tendon deformation and formation of gaps depending on the type of suture technique used (*73*). Supplementary sutures increase resistance to 'gapping' *in vitro* (*38*). Reduced 'gapping' is possibly biomechanically important *in vivo*, in the 'middle stages' of tendon healing, allowing active motion exercises with safety.

There is 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 postoperative therapy (*10,11,18,21,30,34,76*). On the other hand, Strick *et al* (*62*) were unable to confirm a difference in adhesion formation and gliding resistance between 2- and 4-strand repairs. In fact most of the studies (table I) on gliding resistance after various suturing techniques are *in vitro* or animal studies and we were not able to identify any human trials (*14,22,62,75*).

B) Tendon sheath : to repair or not to repair ?

Sheath closure following flexor tendon repair is frequently attempted (*5*). This practice is largely based on the concepts that flexor tendons within the region of synovial sheaths are mainly nourished through synovial diffusion (*40*), and that lacerated tendons can heal sufficiently through their intrinsic cellular activities without the necessity of adhesion formation (*40,41*). 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 (*19,20,39,40,41,43*).

The literature offers conflicting views on the advantages of sheath closure (table II). Restoration of sheath integrity in flexor tendons reduces adhesion formation (*62*). However, sheath closure has not proven consistently effective in improving tendon gliding function (*9,20,51,52,56*). For example the sutured sheath may disappear after suturing, and is associated with poor tendon healing (*69*). In a human trial (*52*), no statistical difference between the results of open sheath versus closed sheath in two groups of patients was noticed. Furthermore, the integrity of the vincular system is a determinant of the end result regarding active range of motion in zone II flexor tendon injuries (*5*). Therefore, careful tendon manipulation during repair is an important factor affecting outcome.

Table I. — Multistrand repair

Author (reference)	Year	Subjects	Study Design	Results
Zhao C (*75*)	2001	canine model	Sixty flexor digitorum profundus 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 postoperative therapy.
Dinopoulos HT (*14*)	2000	canine model	Twenty-two flexor tendons were repaired using 4- and an 8-strand suture technique, and tested to failure after 10 days of in vivo healing	8-strand repair is significantly more resistant to initial gapping during ex vivo tensile testing than the 4-strand repair
Gill RS (*22*)	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 RT (*72*)	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 MJ (*62*)	2004	Chicken model	The flexor digitorum profundus 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.

C) Post-operative mobilization

Rehabilitation is a critical factor determining the quality of the result after finger flexor tendon repair. Post-operative mobilization decreases adhesion formation and improves function after flexor tendon repair (*5,21,65*). Some studies advocated that tendon loading is beneficial (*17,18*), whereas more recent studies from the same group in the Mayo Clinic showed that it is motion rather than loading that strengthens the tendon (*10,11*). The concept is that the rehabilitation program has to match the specific phase of tendon healing. Therefore a graded therapy program from passive to active motion sounds logical (*5*). There are now several post-operative mobilisation regimes like shortened passive flexion/active extension versus normal passive flexion/active extension (*2*) ; continuous passive motion versus controlled intermittent passive motion (*18*) ; dynamic splintage versus static splintage (*50*) ; active flexion versus rubber band traction (*26*) ; controlled passive flexion with active extension (modified Kleinert) versus controlled passive mobilisation (modified Duran) (*34*) (table III). There is however insufficient evidence from randomised controlled trials to define the best mobilisation strategy. Work from the Mayo Clinic has introduced a new 'synergistic' protocol : It suggests that the proximally directed tendon force applied with simple passive finger flexion with the wrist flexed is minimal (*30*), and that it is not increased by adding synergistic wrist extension (*76*).

Table II. — Tendon sheath : to repair or not to repair ?

Author (reference)	Year	Subjects	Study design	Results
Peterson WW (*52*)	1986	Chicken model	Tendon gliding of flexor sheath excision versus incision/closure following primary flexor tendon repair was examined biomechanically and histologically in forty-one 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.
Strauch B (*61*)	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 MJ (*56*)	1987	Patients with lacerations of both flexor tendons	A modified Kessler suture was used to repair the profundus tendon and the 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 RH (*20*)	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, does not improve significantly the biomechanical, biochemical, or morphologic characteristics of repaired tendons treated with early motion rehabilitation.
Peterson WW (*51*)	1990	Chicken model	Three methods of sheath closure were : I, Primary sheath repair ; II, a fascia patch ; and 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 JB (*71*)	1994	Leghorn chickens	In the left foot the tendon sheath was closed after tendon suture, and in the right 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.

In normal tendons, with a normally lubricated sheath, minimal load can overcome their very low gliding resistance, so that motion occurs. In injured tendons, the increased friction of the laceration and tendon repair makes it unlikely that the higher threshold of friction can be overcome by simple passive finger flexion. Thus combining metacarpophalangeal joint extension with passive wrist extension and passive interphalangeal joint flexion, the generated force should be enough to overcome the higher gliding resistance of the repaired tendon repairs, while remaining well below the gap threshold (*5*).

A survey (*24*) showed that Kleinert-type and Duran-type regimens are widespread and current practice encourages early passive finger motion,

Table III. — Post-operative mobilization

Author (reference)	Year	Subjects	Study design	Results
Adolfsson L (2)	1996	Humans	Injured tendons were repaired within 24 hours and all patients were subjected to mobilization programme 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 RH (18)	1991	Humans	Fifty-one patients were placed randomly into 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.
Percival NJ (50)	1989	Humans	51 patients with isolated flexor pollicis longus tendon repairs were divided into two groups ; one that were kept immobile and second group that controlled dynamic mobilisation	The results of mobilisation were significantly better, 62% achieving good or excellent results compared to 33% treated by fixed splintage.

initiated within 3-5 days (5) and active finger motion within 3 weeks from repair (5,24).

Nevertheless, the location ('zone') of tendon injury is a detrimental factor affecting the choice of rehabilitation program and clinical outcome (65,71).

2. *Pharmacological modalities*

Given the adhesiogenic nature of tendon healing or repair, improvements in surgical technique alone will help decrease but not prevent adhesion

Table IV. — Pharmacological modalities : Drugs

Author (reference)	Year	Subjects	Mode of hyaluronic acid use	Results
Tanaka T (68)	2007	canine model	Surface treatment of tendons with carbodiimide-derivatized hyaluronic acid (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 in vivo.
Zhao C (77)	2006	canine model	Surface treatment of flexor tendon autografts with carbodiimide-derivatized hyaluronic Acid	Treating the surface of an extrasynovial tendon autograft with a carbodiimide-derivatized hyaluronic acid-gelatin polymer decreases digital work of flexion and tendon gliding resistance in flexor tendon graft model in vivo.
Akasaka T (4)	2005	canine model	Hyaluronic acid injected around the tendon	HA diminishes the excursion resistance after flexor tendon repair.
Hagberg L. (26)	1992	Humans	Hyaluronic acid injected around the tendon	Sodium hyaluronate had no statistically significant effect as evaluated on total active motion at follow-up.

Table IV. — Continuation

Author (reference)	Year	Subjects	Mode of Ibuprofen use	Results
Kulick MI. (*36*)	1984	Cynomolgus monkeys	Group I. Peritendinous injections of 0.1 ml of ibuprofen every 12 hours for 10 days to the 8 flexor digitorum profundus tendons.	In weeks 1 to 3, fewer inflammatory and reactive cells were observed in the ibuprofen-treated digits compared to control and standard digits.
			Group II. Oral ibuprofen, 75 mg/kg, every 12 hours for 10 days and peritendenous injections of 0.1 ml of ibuprofen every 12 hours for 10 days to the 8 flexor digitorum profundus tendons.	The animals treated with supplemental oral ibuprofen revealed a major reduction in peak force in the digits affected as compared to systemic medication alone.
Kulick MI (*37*)	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.
Szabo RM (*67*)	1990	New Zealand white rabbits	Indomethacin solution (1 mg/kg/day) injected subcutaneously 2 hours 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 a suppression of adhesions.
Author (reference)	Year	Subjects	Mode of 5-Fluoro-Uracil (5-FU) use	Results
Moran SL (*45*)	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 ($p < .008$). Overall, a single intraoperative application of 5-FU at concentrations of 25 mg/mL appears to be an effective mechanism for reducing postoperative flexor tendon adhesions.
Akali A (*3*)	1999	Rabbits	5-fluorouracil solution (50 mg/ml)-soaked sponge pledgets	There was a significant reduction in synovial sheath thickening ($p < 0.001$), cell counts ($p < 0.001$) and proportional length of adhesions ($p < 0.001$) in the treated tendons.
Author (reference)	Year	Subjects	Mode of Human amniotic fluid (HAF) use	Results
Ozgenel GY (*49*)	2001	New Zealand adult rabbits	Topical application	Application of HAF immediately after tenorrhaphy was significantly effective in preventing peritendinous adhesion formation without impairment of tendon healing.

Table IV. — Continuation

Author (reference)	Year	Subjects	Other pharmacological agent used	Results
Chang J (*13*)	2000	New Zealand White rabbits	Neutralizing antibody to transforming growth factor (TGF)-beta 1	Intraoperative biochemical modulation of TGF-beta1 levels limits flexor tendon adhesion formation with infiltration of neutralizing antibody to TGF-beta1 improves flexor tendon excursion.
Namba J (*46*)	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 remodeling of collagen fibers was observed in the alginate-treated group, while a random pattern of fibers was observed in the control group.
McCombe D (*44*)	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 ME (*32*)	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 M (*48*)	1996	Chickens	Surface coating of deep flexor tendons with Halofuginone	It was observed that there was 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 DP (*60*)	1985	Lindsay chicken	Topically applied beta-aminopropionitrile base	Results show that topical beta-aminopropionitrile was effective in the control of peritendinous adhesions and, therefore, achieves sufficient depth of penetration topically to affect the peritendinous location. No adverse effects of the topically applied agent were demonstrated.
Porat S (*53*)	1980	Chickens	Surface coating of long flexor tendons with an aqueous solution of enriched native collagen (ECS).	It was suggested that 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.

formation. Adjuvant therapy may be beneficial (*16*). This has led to a massive expansion in search for such pharmacological adjuvants. These adjuvants fall into two main categories, namely drugs and barriers.

A) Drugs

Several drugs have been tried not only to influence the inflammatory phase of the healing process but also to inhibit fibroblast proliferation and suppress pro-adhesion formation growth factors. These include use of hyaluronic acid, nonsteroidal anti inflammatory drugs (Ibuprofen and Indomethacin), 5-fluorouracil, human amniotic fluid, alginate solution, collagen synthesis inhibitor (CPHI-I), enriched collagen solution, plant alkaloid halofuginone, human-derived fibrin sealant, topical beta-aminopropionitrile and transforming growth factor

Table V. — Barrier methods

Author (reference)	Year	Subjects	Type of Barrier used	Results
Hanff G (*29*)	1998	Rabbits	Application of poly tetrafluoroethylene (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 found to be similar in e-PTFE and control groups.
Peterson WW (*52*)	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.
Siddiqi NA (*58*)	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 as well as 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 NA (*57*)	1995	Chickens	Application of hydroxyapatite (Hap) and alumina sheath to injured Profundus tendons in zone II	Decreased severity of postoperative adhesions in the HAp as well as in the alumina groups in comparison with the sheath repair and controls.
Isik S (*31*)	1999	Leghorn chickens	Application of hyaluronic acid sheath to repaired flexor profundus tendons at zone II in the second, third and fourth toes	There were few adhesions in hyaluronic acid treated group microscopically at the third month as compared to control group.
Karakurum G (*33*)	2003	Chickens	Seprafilm (a combination of carboxymethylcellulose membrane and hyaluronate)	Seprafilm was effective in preventing adhesions after tenolysisas compared to control group.
Kobayashi M (*35*)	2001	Domestic fowl	Application of PVA-H sheath to injured deep flexor tendon of the 3rd 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 N (*66*)	2006	Chickens	Application of bovine pericard to injured flexor tendons in chicken toe	Significantly less adhesion formation in the bovine pericardia treated group.

beta-1 inhibitors (table IV) (*3,4,13,27,32,39-41,4346,48, 49,53,60,67,68,77*). Again, most of these studies are animal studies with insufficient human trials to support their clinical relevance.

B) Barriers

The cellular activity of intrasynovial tendons may be specially adapted to intrasynovial environments. Thus, 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 (*1,8,9,15*). This concept has led to the development of several chemical barriers to prevent adhesion in digital tendons. Polytetrafluoroethylene,

hydroxyapatite, hyaluronic acid membrane, polyvinyl alcohol hydrogel and bovine pericard have been tried (table V) (*28,29,31,33,35,57,58,66*). Most of these studies are animal studies, with insufficient human trials to support their clinical relevance.

3. *Other modalities*

Other modalities such as ultrasound therapy (*42*) and pulsed electro-magnetic field (*23, 54*) have also been tried but only animal studies with controversial results are available.

4. *Future therapies*

Delivery of growth factor genes which 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 (AAV), and liposome-plasmid vectors have been used to deliver genes to tendons to improve their healing. These may well form part of future treatment modalities for adhesion prevention. However, at the present moment, clinical evidence is lacking (*70,78*).

CONCLUSION

The goal of flexor tendon repair and rehabilitation is to achieve a gliding and functioning tendon : the repair should be strong enough to allow rehabilitation, and the rehabilitation method should respect the mechanical limits of the chosen technique.

Repair with scarring and regeneration can both occur within the same animal, including man, and indeed within the same tissue, thereby suggesting that they share similar mechanisms and regulators (*16*). Several new surgical techniques and various pharmacological and non pharmacological modalities have been proposed. However, most studies have been carried out in animals with very few human trials. The results of mobilisation techniques are inconclusive.

Poor methodological standards in animal studies mean that positive results rarely translate to the clinical domain (*25*), thus questioning the fact whether these chemical adjuvants are really effective in humans. 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 (*12,55,59*).

Thus, the only clinically justified intervention in adhesion prevention is early post-operative mobilisation of digits after tendon injury or repair, but the best method of mobilisation remains controversial. Suggested modifications of surgical techniques and 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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