Evaluating the Effectiveness of Commercially Available Anti-Adhesion Tendon Protector Sheets in Tendon Repair Surgery versus Tendon Repair Surgery Alone: A Preclinical Model Study

Rou Wan[1], Gongyin Zhao[1, 2], Elameen Adam[1], Omar Selim[1], Aida Sarcon[1], Ramona Reisdorf[1], Alexander Meves[1], Chunfeng Zhao[1], Steven L. Moran[1]
[1] Mayo Clinic, Rochester, MN, USA [2] The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou, Jiangsu, China.
Zhao.Chunfeng@mayo.edu, Moran.Steven@mayo.edu

INTRODUCTION:

Injuries to the flexor tendon of the hand and wrist are common. Reportedly, postoperative adhesions can occur in up to 40% of cases, resulting in reduced range of motion, tendon rupture, re-operations, and significant disabilities, despite advances in both surgical techniques and rehabilitation practices over the years. There are currently a very limited number of products in the market for reducing peritendinous adhesions. The effective components of these products include hyaluronic acid (HA), collagen, gelatin, oxidized cellulose, hyaluronate carboxycellulose, polyester-urethane, and glycosaminoglycans (GAGs), 16-20. Unfortunately, their therapeutic benefits are inconsistent, and these products are also costly (rough range, $200-$1200 per box). In practice, the routine use of anti-adhesion commercial products remains up for debate as no consensus on their application. We did not find these products being tested on a large animal model. Hence, the purpose of this study was to employ a previously established turkey flexor tendon model to compare the differences in anti-adhesion outcomes achieved by two frequently used materials (type I Collagen-Cartilage glycosaminoglycan and hyaluronic acid) in clinical practice. We hypothesized that the application of commercially available anti-adhesion agents would outperform tendon repair alone.

METHODS:

Twenty-four adult Bourbon Red turkeys were randomized to three groups: (1) control, (2) TenoGlide®, Type I Collagen-Cartilage Glycosaminoglycan (Collagen-GAG), and (3) VersaWrap®, Hyaluronic Acid (HA). The flexor digitorum profundus (FDP) tendon of the middle digit was sharply lacerated and repaired. All operated feet were immobilized until sacrifice six weeks after the surgery. After euthanasia, the repaired and normal third digit on the contralateral limbs were collected for analysis. This included normalized work of flexion (nWOF), repair strength and stiffness, adhesion scores, histology, and adhesion-related gene expression. The study design is shown in Fig. 1.

A sample size of 6 birds in the biomechanical test would be sufficient to detect a significant difference of one-half of a standard deviation with a 90% power at a significance level of $p<0.05$ based on our previous studies. Quantitative data are presented as mean value ± SEM. Kruskal-Wallis one-way analysis of variance (ANOVA) was used for comparison among groups. Tukey's multiple comparisons test was followed for pairwise differences if ANOVA results showed significance.

RESULTS:

All turkeys except one recovered on Day 42. One female turkey did not reach the study end date and was sacrificed on Day 14 due to an injury from mating, which was unrelated to the study. No other significant postoperative events occurred.

At 42 days after tendon repair, the nWOF was the lowest in the Collagen-GAG group with an average of 2.67±1.18 N-mm/degree versus control (4.87±2.45 N-mm/degree) and HA (6.02±1.99 N-mm/degree) groups ($P=0.028$). Amongst the groups, the Collagen-GAG group had the lowest gross adhesion score ($P=0.002$) (Fig. 2). The Collagen-GAG group had a statistically significant lower gross adhesion score in zone II versus control (4.29±0.95 versus control 6.67±0.82, $P=0.001$). The HA group (6.00±1.29) also had a slightly lower score versus control, but it was not statistically significant ($P=0.43$). No significant difference was found between the treatment groups and the control group in repair failure strength or stiffness. The healing scores were 2 in all the groups which corresponded to 25-50% disorganized, separated, and deteriorated fiber structures under microscopy. The scores of cellularity, vascularity, and cartilage formation were 0 in all groups. The tendons in the Collagen-GAG group were smoother at the repair site, whereas those in the control and HA were rougher due to higher adhesions. The Collagen-GAG sheets appeared intact and visible around the tendon on Day 42. Further H&E analysis revealed that the mesenchymal cells grew into the remaining Collagen-GAG matrix (Fig. 3). In addition, microscopically, all tendons healed without gaps between the repaired ends and the Collagen-GAG group had a significantly lower histological adhesion score than the control group ($P=0.02$) (Fig. 4). Gene expression levels of WNT3A, WNT5A, WNT7A, and Teneurin-3 were significantly suppressed in the Collagen-GAG group ($P<0.001$).

DISCUSSION:

Our data showed that around 42 days after flexor tendon repair, the Collagen-GAG sheet had significantly greater histological anti-adhesion properties compared to HA or no treatment. In the biomechanical function tests, nWOF in the Collagen-GAG was significantly lower than that in the HA group. The prevention of adhesion histologically is well-proved while the restoration of digit function needs further evaluations. Neither of the products showed effects on tendon regeneration. Our study had a few limitations. First, the sample size was small due to animal availability, cost, housing space, and the season of avian flu. Additionally, we did not evaluate the expression of more traditionally tested tendon adhesion-related genes (COL1A1, COL3A1, TGF-b, α-SMA, fibronectin, tenomodulin, Scleraxis) also due to the number of animals and the hypocellular nature of the tendon tissue.

SIGNIFICANCE:

There are currently very limited commercially available products to reduce postoperative peritendinous adhesions. In addition, the routine use of anti-adhesion implants remains a subject of ongoing debate, with a lack of consensus in the field. A product possessing both lubricating properties and the capacity to function as a physical barrier, simulating the tendon sheath, may offer superior performance compared to materials solely serving as lubricants.

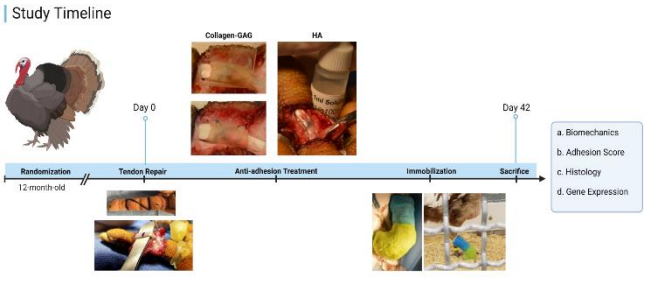

Figure 1. Study design. FDP repair surgery and intraoperative anti-adhesion treatments occurred on Day 0. In the Collagen-GAG group, the sheet was inserted under the tendon with a piece of rigid plastic membrane for ease of application. After securing the Collagen-GAG sheet circumferentially around the repair site, the plastic membrane was removed. In the HA group, the sheet was provided dry with stiffness and placed to cover the whole repair site. It did not need to be sutured. A solution of alginate was dropped onto the dry sheet, immediately turning it into an ultrathin, uniform gelatinous layer. The HA sheet in the photo was before the application of the solution, as it becomes less visible after wetting. Repaired digits were then wrapped in gauze and cotton pads and casted in a flexion position for 6 weeks until sacrifice.

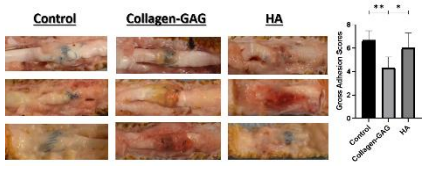

Figure 2. Gross adhesion scores.

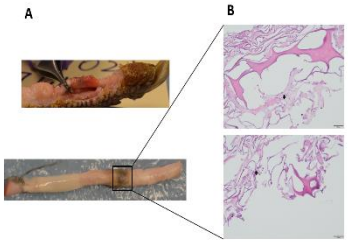

Figure 3. Morphology of the repaired tendons in the Collagen-GAG group at 42 days. (A) A visible sheet around the tendon. (B) Mesenchymal cells incorporated into the matrix. Scale bars represent 500 μm. All cuts were longitudinal.

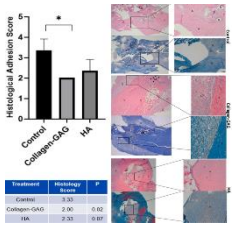

Figure 4. Histological analysis. Representative histology images of H&E and Masson trichrome staining showed the area of the presence of adhesion tissue. The Collagen-GAG group showed organized and dense tendon tissue covered and protected in the sheet. (T: Tendon, C: Collagen-GAG, A: Adhesion tissue, H: HA, S: Stitches). Scale bar represented 500 μm. (*$p < 0.05$)