SJS SRIWIJAYA JOURNAL OF SURGERY

Sriwijaya Journal of Surgery Volume 3, Issue 1, Page No: 23-29
Available online: www.sriwijayasurgery.com
SJS 3(1) : 23-29

# The Effectiveness of Hyaluronic Acid Injection on Rat Tendon Repair Prognosis as a Model in Achilles Tendon Rupture

Adi Mulya[1], Ismail Bastoni[1*], Erial Bahar[2]

[1] Department of Surgery, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

[2] Department of Anatomy, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

* Correspondence Author Email: ismailbastoni@gmail.com

## Abstract

**Introduction:** Rupture of the Achilles tendon has become an increasingly common case in the last two decades with an incidence of 18% per 100,000 population. The controversy about the best treatment arises because the results are determined by the method of tendon repair and postoperative functional rehabilitation. In recent years, there is a great deal of interest in hyaluronic acid which is found in certain amounts in the soft tissue extracellular matrix and joint fluid. Several experimental studies have shown the application of hyaluronic acid (HA) to heal tendons and stimulate tendon healing and reduce adhesion formation. This research is to find out the effectiveness of injecting hyaluronic acid in behavior changes in mice that have modified Achilles tendon rupture in 21 mice divided into three groups according to their treatment, namely intramuscular HA (IM), Intralesional HA (IL) and NaCl in laboratory animals Sriwijaya University Faculty of Medicine 2019 by seeing changes in behavior every 7 days 3 times.

**Results:** The group with HA-IL treatment had the highest cure success rate, which was 7 (58.3%) good grades, 5 (41.7%) good grades and 2 (100%) very good grades and 5 (33.3%) good and 2 (50%) extraordinary (change behavior 1, 2 and 3, respectively). Then HA-IM 5 (41.7%) Good grades, 7 (58%) Good grades, and 5 (33.3%) and 2 (50%) exceptional grades (change behavior 1, 2 and 3, respectively) and NaCL only have a value of 5 (33.3%) both for behavior change 3.

**Conclusion:** There is a difference in effectiveness between administration of hyaluronic acid

and without administration of hyaluronic acid to behavioral changes in repair of the Achilles tendon.

**Keywords:** hyaluronic acid, achilles tendon rupture, repair tendon, in vivo study in rat

## 1. Introduction

The Achilles tendon is the largest and most powerful tendon in humans. Spontaneous rupture has become the most frequent case lately due to an increase in the elderly population and sports activity in the middle-aged population. Although most Achilles tendon ruptures occur during exercise (44% -83%), changes in intrinsic, biochemical and biomechanical structure also play an important role.[1-2]

Rupture of the Achilles tendon has become an increasingly common case in the last two decades with an incidence of 18% per 100,000 population. A male to female ratio of around 1.7: 1 might illustrate the prevalence of men who are heavily involved in sports. Most studies show a picture of the age distribution with a peak in the fourth decade and follow the second in the 60s and 80s.[3-4] the controversy about the best treatment arises because the results are more determined by the method of tendon repair and post-surgery. Functional rehabilitation. Especially regarding the risks and benefits between closed operations and maintenance are still being debated and safety risks, cost effectiveness is also not a decision.[3-5]

Various pharmacological agents have been used to prevent the formation of adhesions. Prostaglandin inhibitors such as Indometacin and Ibuprofen have been shown to have little benefit. Steroids and antihistamines have shown promising experimental results but cannot be used clinically because of toxicity and interference with wound healing. In recent years, there is a great deal of interest in hyaluronic acid which is found in certain amounts in the soft tissue extracellular matrix and joint fluid. Several experimental studies have shown the application of hyaluronic acid in healing tendons and stimulating tendon healing and reducing the formation / formation of adhesions.[1-4]

Gentile et al. 2016 found that treatment with *platelet rich plasma* (PRP) and hyaluronic acid (HA) for postoperative complications of the Achilles tendon was effective in healing and regenerating soft and hard tissue with rapid healing time, maintaining plantar flexion strength and wrist extension. Foot and restore skin elasticity quickly.[1-5] Kaux et al conducted a *review* article in 2015 that there were successful treatments with hyaluronic acid in 28 articles of

which 13 were in vitro studies, 7 of which were in vivo studies in animals and 8 other studies were studies in humans.[6] This is similar to the in vitro study by Osti 2015 on experiments on human tendons that found increased viability and proliferation and within 24 hours administration of hyaluronic acid destroyed apoptosis compared to treatment without hyaluronic acid.[7]

## 2. Methods

This study was a Randomized Clinical Trial which was tested in mice as a test animal. The study was carried out on 21 mice weighing 150 g which had been divided into three groups according to their treatment (names of the groups in the order of HA-IL, HA-IM and NaCL) to determine whether there was an increase after injection. Hyaluronic acid in animal experiments on behavioral aspects. The dose of HA and NaCL used is 0.05 mg / ml. This research was carried out observations from before the tendon rupture operation, and every 7 days thereafter for 3 times called observation 1, 2, 3 and 4. Rat behavior was assessed by the length of the fasting rat for 6 hours entering a special pipe at the end containing food. The results of observations are called behavioral changes 1, 2 and 3 according to their observations. Behavioral change assessment is assessed from the length of the rat running in a special pipe, if it is faster or the same as before the tendon ruptures, the value is *excellent*, if it takes longer to ≤ 5 seconds then the value is *good* and if the value is > 5 seconds then the value is *fair*.

## 3. Results

It can be seen in Table 1 that each treatment group HA-IM, HA-IL and NaCL had 7 samples (33.3%), in observation 2 that had been carried out 7 days after ruptured tendon surgery, it seemed longer to walk in the pipe with a median value of 40 seconds (min.35 - max.47 seconds). On behavior change 1 there were 12 samples (57.15%) good value and 9 samples (42.85%) fair but increased in behavior change 2 with 2 samples (9.5%) excellent and 9 samples (42.85%) good value and on behavior change 3 the excellent value increased to 4 samples and 15 samples (71.5%) good value.

**Table 1.** Characteristics of Samples

| **Variable** | Data Presentation (N = 21) |
|---|---|
| Observation | |
| Observation 1 (before surgery) | 35 (33-38) seconds |
| Observation 2 | 40 (35-47) seconds |
| Observation 3 | 38(35-45) seconds |
| Observation 4 | 38 (34-45) seconds |
| Behavior Change 1 (before surgery and after 7 days of treatment) | |
| *Excellent* | 0(0%) |
| *Good* | 12(57.15%) |
| *Fair* | 9(42.85%) |
| Behavior Change 2 (before surgery and after 14 days of treatment) | |
| *Excellent* | 2(9.5%) |
| *Good* | 9(42.85%) |
| *Fair* | 7(48%) |
| Behavior Change 1 (before surgery and after 21 days of treatment) | |
| *Excellent* | 4(19%) |
| *Good* | 15(71.5%) |
| *Fair* | 2(9.5%) |

* Categorical data is presented with N (%), abnormally distributed data using Saphiro Wilk (P <0.05) presented with a median (minimum-maximum)

There is a very significant relationship difference between each group with changes in behavior that can be seen in Table 2.

Table 2. Comparative Analysis of Each Group Based on Behavior Change

| Group | Bef-*Obs1 | ** p | Bef-*Obs2 | **p | Bef-*Obs3 | ** p | *Obs1-Obs2 | **p | *Obs1-Obs3 | **p | Obs2-Obs3 | **p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HA-IM | 4(3-6) | 0,000 | 2(2-3) | 0,000 | 1(1-1) | 0,000 | 2(0-2) | 0,000 | 2(2-3) | 0,000 | 0(1-2) | 0,000 |
| HA-IL | 2(1-2) | 0,000 | 1(1-2) | 0,000 | 1(1-1) | 0,000 | 1(0-3) | 0,000 | 1(0-1) | 0,000 | 0(0-1) | 0,000 |
| NaCL | 11(9-11) | 0,000 | 9(7-10) | 0,000 | 5(3-7) | 0,000 | 1(1-2) | 0,000 | 1(0-1) | 0,000 | 3(0-3) | 0,001 |

** For the Wilcoxon Test, the p value is significant if p < 0.05. Abnormally distributed data are presented with a median (minimum-maximum value), * Bef = before / before, Obs1 = Observation 1, Obs2 = Observation 2, Obs3 = Observation 3.

## 4. Discussion

In this study treatment 1 and 2 value of HA-IL was superior to HA-IM. While in treatment 3 the value of HA-IL and HA-IM behavior changes are the same. The HA-IL treatment group had the highest cure success rate when seen from the Good score at most, 7 (58.3%) and followed by the HA-IM group who had 5 (41.7%) Good values on behavior change, at behavioral change 2 HA-IL still has the highest level of success where the most Good values are 5 (41.7%) and 2 (100%) Excellent and followed by the HA-IM group which has 7 (58%) Good values and on changes in behavior 3 HA-IL. In behavioral change 3, HA-IL and HA IM have the same wound healing success value with HA-IL and HA-IM good value of 5 (33.3%) and 2 (50%) excellent.

Kaux et al conducted an article *review* in 2015 that there were successful treatments with hyaluronic acid in 28 articles of which 13 of them were in vitro studies, 7 of them were in vivo studies in animals and 8 other studies were studies in humans.[6] this is similar to the in vitro study by Osti in 2015 on trials in human tendons found increased *viability* and *proliferation* and within 24 hours administration of hyaluronic acid has broken down apoptosis compared with treatment without hyaluronic acid.[7]

This is similar to the study of Zhao et al. Which identified the effect of using HA in 14 dog samples to reduce adhesion and increase reconstruction of tendon repair. Zhao found a significant improvement in injection of 1% HA to have optimal recovery after 6 weeks.[8] This is similar to the study of Oryan et al in 40 rabbits, in addition to using HA, Oryan et al also use NaCl and show significant results even though the histoPA administration of NaCL has not shown significant tendon improvement such as an increase in tenoblast but it is still small and collagen fibrils have not been erected perfect.[9]

Oryan et al. conducted a study of 40 rabbits on HA cusps that showed a significant change and healing success by significantly decreasing the diameter of tendon wounds that had increased the number of Tenoblasts and densities in collagen fibrils.9 Yoshida et al conducted studies on mice and found similar results, in 40 mice given HA in an 8-week trial found a significant cure rate where histoPA results showed good tendon scale improvement.10 whereas Liang et al found a tendon repair in 28 tendons Achilles rat on healing at 26 weeks.[11]

In this study the comparison between surgical wound healing with HA-IM injection, HA-IL injection and administration (NaCL) in mice undergoing modification of the Achilles tendon rupture has the results: There is a very significant difference between each treatment

group based on changes in behavior with a P value = 0,000; There is a significant difference between behavior change with the comparison of HA-IM with HA-IL, as well as HA-IM and NaCL with p value < 0.05; and There was a significant difference in changes in observational behavior 1 with the comparison of HA-IM with HA-IL, and also HA-IL and NaCL with p < 0.05.

Oryan et al found a significant difference between HA use and the group using the NaCL placebo, this was also supported by Yoshida et al and Liang et al who found a significant differencebetween the recovery rate and repair of rat tendons in the HA administration group and the length of time observed.[9 -11]

## 5. Conclusion

The use of hyaluronic acid in tendon rupture showed an increase in the value of behavior change and there was a very significant difference between each treatment group based on changes in behavior with a value of P = 0,000.

## 6. References

1. Thevendran, G., et al. “The Ruptured Achilles Tendons: a Current Overview from Biology of Rupture to Treatment.” Musculoskeletal Surgery, vol. 97, no. 1, 2013, pp. 9–20., doi: 10. 1007/s12306-013-0251-6.
2. Özgenel, G. Y. “The Effects of a Combination of Hyaluronic and Amniotic Membrane on the Formation of Peritendinous Adhesions after Flexor Tendon Surgery in Chickens.” The Journal of Bone and Joint Surgery. British Volume, 86-B, no. 2, 2004, pp. 301–307., doi:10.1302/0301-620x.86b2.14435.
3. Lin, Tony W., et al. “Biomechanics of Tendon Injury and Repair.” Journal of Biomechanics, vol. 37, no. 6, 2004, pp. 865–877., doi:10.1016/j.jbiomech.2003.11.005.
4. Singh, Dishan. “Acute Achilles Tendon Rupture.” British Journal of Sports Medicine, vol. 51, no. 15, 2017, pp. 1158–1160., doi:10.1136/bjsports-2016-h4722rep.
5. Gentile, Pietro, et al. Use of platelet rich plasma and hyaluronic acid in the treatment of complications of achilles tendon reconstruction. World journal of plastic surgery, 2016, 5.2: 124. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5003947/
6. Kaux, Jean-François; Samson, Antoine; Crielaard, Jean-Michel. Hyaluronic acid and tendon lesions. Muscles, ligaments and tendons journal, 2015, 5.4: 264.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4762636/pdf/264-269.pdf

7. Osti, Leonardo, et al. Hyaluronic acid increases tendon derived cell viability and collagen type I expression in vitro: Comparative study of four different Hyaluronic acid preparations by molecular weight. BMC musculoskeletal disorders, 2015, 16.1: 284.
8. Zhao C, Wei Z, Kirk RL, et al. The Effects of Bio-Lubricating Molecules on Flexor Tendon Reconstruction in a Canine Allograft Model in Vivo. Plast Reconstr Surg. 2014; 133: 628e637e.
9. Oryan A, Moshiri A, Meimandi Parizi AH, Raayat Jahromi A. Repeated administration of exogenous Sodium-hyaluronate improved tendon healing in an in vivo transection model. J Tissue Viability. 2012; 21:88-102.
10. Yoshida M, Funasaki H, Kubota M, Marumo K. Therapeutic effects of high molecular weight hyaluronan injections for tendinopathy in a rat model. J Orthop Sci. 2015; 20(1):186-195.
11. Liang JI, Lin PC, Chen MY, Hsieh TH, Chen JJ, Yeh ML. The effect of tenocyte/hyaluronic acid therapy on the early recovery of healing Achilles tendon in rats. J Mater Sci Mater Med. 2014; 25: 217-227.