

**St. Vincent’s SportsMed**

**Measuring the effect of Hyaluronic acid (HA) on tendon healing after arthroscopic rotator cuff repair**

**SYNOPSIS**

Protocol title: Measuring the effect of Hyaluronic acid on tendon healing after arthroscopic rotator cuff repair: A prospective randomized double blinded clinical trial.

**Introduction**

The clinical outcome of arthroscopic rotator cuff repair including pain and ROM is generally favourable 1,2

Despite advances in surgical techniques for rotator cuff repair, postoperative non-healing of rotator cuff tendons (tendon re-tear) is a serious issue, with an incidence ranging between 20% and 95%.3,4,5,16,71,76

Given that re-tear rate after cuff repair is a serious issue, a number of approaches have been investigated to improve rotator cuff repair healing including advancements in the fields of repair materials, repair techniques, biological augmentation and rehabilitation protocols.

In this study we examine the healing effect of HA after cuff repair taking in consideration that some in-vitro and animal studies have demonstrated a significant positive effect of HA on tendon healing. Moreover, the efficacy and safety of HA in some abdominal surgeries and as a non-surgical therapy in shoulder disorders has been widely reported.

**Protocol version: Version 1**

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**Summary**

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| --- | --- |
| **Study title:** | Measuring the effect of Hyaluronic acid (HA)on tendon healing after arthroscopic rotator cuff repair |
| **Protocol version** | Version 1 |
| **Objectives** | Primary:  To determine if hyaluronic acid supplementation improves outcomes of arthroscopic repair of complete rotator cuff tears compared to placebo.  Secondary:   1. To compare range of motion (ROM) recovery between the two groups 2. To establish if HA decreases post-operative pain after arthroscopic repair 3. To ascertain if HA decreases re-tear rates in arthroscopic rotator cuff repair 4. To determine if HA improves clinical outcomes in arthroscopic repairs using standard clinical scoring systems |
| **Study design** | Prospective randomized clinical trial |
| **Planned sample size** | 45 patients will be randomly allocated into 2 groups. |
| **Selection criteria** | Inclusion criteria:  Adult patients with complete rotator cuff tear who are admitted for arthroscopic shoulder rotator cuff repair surgery at St. Vincent’s Private Hospital, Nepean Private Hospital and East Sydney Private Hospital in Sydney.  Exclusion criteria:   * Advanced shoulder Arthritis * Patients below 18 years or above 75 years of age 32,33,34,35 * Revision of previous cuff repair * Smokers47-49 * Irreparable cuff tear * Primary Shoulder instability (Bankart labral tear) * Rheumatoid arthritis / Inflammatory arthritis * Chronic pain syndrome |
| **Study procedures** | * Adult patients undergoing arthroscopic rotator cuff repair surgeries at St. Vincent’s Private Hospital, Nepean Private Hospital, and East Sydney Private Hospital will be recruited for the study. * Investigators will conduct the screening of the participants. Eligible patients will undergo preoperative evaluation * Patients who meet the selection criteria will be provided with information sheets and consent forms. * Patients will be randomized into intervention and control groups using a generated list. * Senior Surgeons (ST and WK) will be blinded with regards to the patient allocation. Only the Orthopedic Fellow will know the allocation of the patients. * Patients who are allocated to the intervention group will receive HA in the recovery room 30-60 minutes after surgery, to be administered by the orthopaedic fellow through a catheter placed at the site of cuff repair at the end of surgery. Patients in the control group will receive sterile saline as placebo. * Patients will be evaluated at 2 weeks, 3 months, 6 months and 12 months postoperatively. * Clinical evaluation will be conducted by the surgeon when patients come for their routine visits. * The clinical evaluation includes visual analogue scale (VAS) for pain, passive and active ROM, The constant shoulder score, ASES score (American Shoulder and Elbow Surgeons score). * MRI imaging study will be done at 12 months for evaluation of cuff integrity. |

**Statistical considerations**

Sample size calculation

We based the sample size ion the study of Jeong, et al, who detected a 12.4-point difference in ASES scores postoperatively between HA injected and placebo groups. 88 Using an two-sided significance level of 0.05 and power of 80%, the computed total sample size is 76. Considering a drop-out rate of 20%, the total number of patients needed is 90, to allow for even distribution among groups. 45 patients will be randomly allocated to each group for this study.

Analysis plan

Nominal data will be expressed as means +/- SD, while categorical data will be expressed as mean, frequencies, +/- SD. The Mann-Whitney U-test will be utilized to determine significant difference in outcome measures between two groups. Friedman’s test will be used to determine significant difference in outcome measures over time.

**Study duration**

12 months.

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# BACKGROUND

## Re-tear after cuff repair

The clinical outcome of arthroscopic rotator cuff repair including pain and ROM is generally favourable 1,2

Despite advances in surgical techniques for rotator cuff repair, postoperative non-healing of rotator cuff tendons(tendon re-tear) is a serious issue, with an incidence ranging between 20% and 95%.3,4,5,16,71,76

**1.2Factors affect healing after cuff repair 52**

A number of studies have focused on the risk factors for tendon retear after cuff repair. The most significant factors are: Age32-35, tear size20,36-40, fatty infiltration of the cuff muscle41-43, muscle -tendon unit retraction44-46, smoking47-49, osteoporosis50 and diabetes51.

**1.3 Efforts to augment cuff healing**

Given that re-tear rate after cuff repair is a serious issue, various augmentation approaches have been investigated to improve rotator cuff repair healing. Recent advances can be subdivided into repair materials, repair technique, biological agents and rehabilitation protocol.

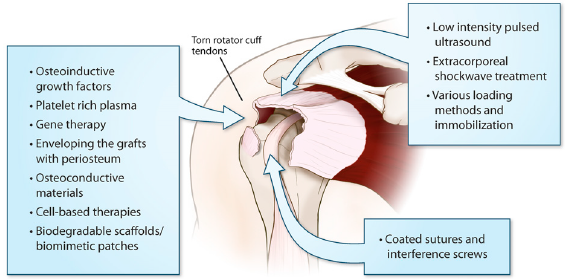
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Fig. 1 Schema summarizing the approaches that have been evaluated for augmentation of tendon-to-bone healing.7

### Repair technique:

Several biomechanical studies of double-row repairs have shown increased load to failure, improved contact areas and pressures, and decreased gap formation when compared to single row repairs.53-57Double-row suture bridge repair has been reported to be associated with significantly higher tendon healing rate compared to arthroscopic single-row repair. 62Another study has shown that the superiority of suture bridge double row technique is only limited to the subcategory of large and massive rotator cuff tears. 63

Although lower re-tear rates have been reported in many studies for double-row compared with single-row repairs 58-60, another report, however, has shown no clinical or MRI differences between the two techniques 61

### Repair material

Various kinds of fixation anchors have been used in cuff repair but there is no evidence that any one is superior to the others. These include but are not limited to,anchorless Trans-osseous sutures,64,65 All suture anchors (ASA) of reduced diameter (1.4 mm), 66,70[suture-less screw anchor,](https://www.ncbi.nlm.nih.gov/pubmed/15650665) 69different types of screw anchors. 67,68

A new anchor augmentation technique with a cancellous screw in osteoporotic rotator cuff repair has been shown to significantly increase the ultimate failure loads in an in vitro biomechanical study on sheep humerus specimens.78

**Rehabilitation protocols:**

 Rehabilitation after cuff repair surgery plays an important role in the final functional outcome and tendon healing as well.80-83Although there is no consensus concerning the rehabilitation protocol following surgery, the process is usually divided in the literature into 4 phases which is aligned with tissue healing as identified in animal studies.79,84

* Phase 1 (1st 6 weeks): Pain control, passive and assistive exercises
* Phase 2 (6-12 weeks) Active functions are regained.
* Phase 3 (month 3 and 4) Strength building including scapular muscle activation followed by isometric and lastly isotonic rotator cuff exercises
* Phase 4: return to sports

Cryotherapy is recommended in the first 3 weeks mainly for pain reduction.30 Based on current published studies, no clear recommendation can be made for or against electrotherapy, aquatic therapy, the application of heat, massages, therapeutic ultrasound or extracorporeal shockwave therapy.84

**Biological agents**

Many reports have been published regarding the effect of various biological agents(fig.1) on tendon healing after cuff repair including: Platelet-rich plasma (PRP) 6,8,9Mesenchymal stem cells10,11Cytokines and growth factors.72

Charles et al 72 have recently published a systemic review in which they concluded that:

* Platelet-rich plasma (PRP) overall has no significant impact on functional outcomes and repair integrity but may have benefit in small tears.
* Mesenchymal stem cells have demonstrated improved healing rates without an impact onclinical outcomes so further studies are needed.
* Cytokines and growth factors show promise in animal models but require human trials to further evaluate effectiveness.
  1. **Rationale for the study**

Many in-vitro studies have examined the effect of HA on tendon healing 14,15,22,31. One of them has shown a good evidence that HA accelerates the chondrogenic differentiation of cultured MSCs.15

The same study has shown a significant improvement in tendon healing on MRI after cuff repair in rabbits.

Up to our knowledge 2 clinical trials have examined the healing effect of HA after cuff repair.

The 1st one published by  Jeong, et al in 2017 which showed that the incidence of retears was 2.7% (n ¼ 1) in the injection group and 11.8% (n ¼ 4) in the control group. Although not statistically significant, there was a tendency to have a higher incidence of retears in the control group than in the injection group (p = 0.192).89

The main limitation for this study is that it’s not a randomised trial.

The second study was published by Oh CH et al which examined the healing effect of HA as a secondary objective and the anti-adhesive effect of HA as the primary objective, but it has failed to prove either.16

This study has the following limitations

1. Postoperative images could only be obtained in approximately 50% of patients, which might weaken the statistical power regarding cuff healing after surgery 16.
2. MRI is superior to US and CT arthrogram which have been used in this study for evaluation of tendon integrity.

3.HA injection was performed without guidance16 and so may have missed the targeted repair site.

We believe further studies are needed as the evidence from the relevant animal study 15 and many invitro studies 14,15,22,31 is promising.Moreover,we hope we can avoid the limitations of the above mentioned clinical studies.

**2. STUDY OBJECTIVES**

**2.1 Primary OBJECTIVE:**

To determine if hyaluronic acid supplementation improves outcomes of arthroscopic repair of complete rotator cuff tears compared to placebo.

**2.2 Secondary OBJECTIVES:**

1. To compare range of motion (ROM) recovery between the two groups
2. To establish if HA decreases post-operative pain after arthroscopic repair
3. To ascertain if HA decreases re-tear rates in arthroscopically repaired rotator cuffs
4. To determine if HA improves clinical outcomes in arthroscopic repairs using standard clinical scoring systems

3.STUDY Design\*

3.1 Design: a prospective randomized double blinded clinical trial as shown in table 1

|  |  |  |
| --- | --- | --- |
|  | **Treatment** | **Outcome measures** |
| Coordinating investigator (Orthopedic Fellow) | Non-blinded | Non-blinded |
| Senior Surgeons (ST and WK) | Blinded | Blinded |
| Study participants | Blinded | Blinded |
| Radiologists | Blinded | Blinded |

3.2 Study Groups

2 groups,one for the patients who receive HA after surgery and the other group is the control who receive saline postoperatively.

3.3 number of participants

We based the sample size ion the study of Jeong, et al, who detected a 12.4-point difference in ASES scores postoperatively between HA injected and placebo groups.88 Using an two-sided significance level of 0.05 and power of 80%, the computed total sample size is 76. Considering a drop-out rate of 20%, the total number of patients needed is 90, to allow for even distribution among groups. 45 patients will be randomly allocated to each group for this study.

3.4 study sites:

1- St vincent’s Private Hospital,Sydney

2- Nepean Private Hospital

3- east Sydney Private Hospital

* 1. duration: 12 months

4. Participant section

**4.1 Inclusion criteria:**

Adult patients with confirmed rotator cuff tear who will undergo arthroscopic shoulder rotator cuff repair surgery at St. Vincent’s Private Hospital, Nepean Private Hospital and East Sydney Private Hospital.

**4.2 Exclusion criteria:**

* Advanced shoulder Arthritis
* Patients below 18 years or above 75 years of age 32,33,34,35
* Revision of previous cuff repair
* Smokers47-49
* Irreparable cuff tear
* Primary Shoulder instability (Bankart labral tear)
* Rheumatoid arthritis / Inflammatory arthritis
* Chronic pain syndrome

**5. HA safety and clinical applications**

**5.1 What is Hyaluronic acid (HA)?**

Hyaluronic acid is a high–molecular weight glycosaminoglycan composed of repeating disaccharide units of glucuronic acid and N-acetyl-glucosamine.73,74 present in the extracellular matrix of soft connective tissue and synovial fluid,12 exerting different physiological roles in different tissues.13The viscoelastic properties of HA in synovial fluid play a critical role in joint mechanics. 73,74

**5.2 What is Monovisc?**

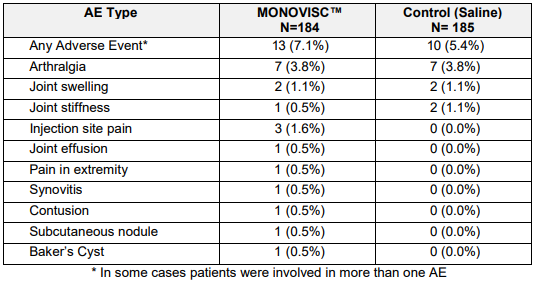
Monovisc™ is a sterile, non-pyrogenic, viscoelastic solution of hyaluronan contained in a single use syringe. Monovisc™ consists of high molecular weight, ultra-pure, natural HA. The HA in Monovisc™ is derived from bacterial cells and is cross-linked with a proprietary cross-linker.

**5.3 Surgical safety of HA**

The efficacy and safety of HA in abdominal and gynaecologic surgery has been widely reported.23,24,25

The safety of Monovisc in particular has been studied and only two mild injection site reactions (2.5%) has been reported. These reactions were described as a light swelling of the injected knee for 48 hrs that resolved without therapy. No subjects experienced a serious adverse event (SAE).87

Another study reported a group of mild to moderate adverse events as shown in the table 2 which all resolved without sequelae and again there were no Serious Adverse Events.88

Table 2: Adverse events related to Monovisc treatment.88

**5.4 HA injection as a non-surgical therapy in shoulder disorders**

The use of HA as a non-surgical therapy in shoulder disorders has been reported.17,18,19,75

**5.5 HA and wound healing**

Several studies have demonstrated that HA may stimulate wound healing in different ways 26,27,28,29

# Study Outline

## 6.1 Study Flow Chart

**Patient selection**

Patients will have a face-to-face interview with one of the consulting investigators (A/Prof. Tan and Dr. Kuo) when he is booked for surgery to check whether he/she fulfils the inclusion and exclusion criteria for the study.

**Randomisation**

* Patients will be assigned a candidate number and will be randomized into two groups using a computer randomisation software (Urbaniak, G. C., &Plous, S. (2013). Research randomizer, version 4.0)
* patient allocation will be recorded in the research Master logbook, which can be only accessed by the coordinating investigator.

**Informed Consent and pre-op assessment**

* If the patient fulfils the study criteria and agrees to participate in the study, they will be given a Participant Information and Consent Form, the VAS pain score and the constant shoulder score prior to surgery.
* The ASES shoulder score (American Shoulder and Elbow Surgeons shoulder score) and ROM will be evaluated and documented by the consulting investigator (A/Prof. Tan and Dr. Kuo)

**Day of Surgery**

**Before surgery:**

the coordinating investigator will collect the consent and related paperwork from patients making sure all forms are complete.

**During surgery:**

* All arthroscopic procedures will be performed by one of the 2 consulting investigators who are Fellowship trained shoulder surgeons (A/Prof. Tan and Dr. Kuo) from St. Vincent’s SportsMed centre.
* Glenohumeral joint pathologies are to be addressed first.
* Then Subacromial decompression with acromioplasty will be performed
* Rotator cuff repair will be performed in a single row manner.
* A catheter (On-Q Pain Relief System, Halyard) will be introduced under arthroscopic vision using a separate needle puncture going through the deltoid leaving the tip at repair site between the repaired cuff tendon and the footprint on GT.(Alternatively, we can use the same manner used in jeong et al sudy: a spinal needle attached with a syringe containing HA was inserted into the lateral sub-deltoid and acromion)
* The catheter will be then marked at skin level, capped and secured by tapes to ensure it stays in the desired position.

**After Surgery**

**Group I: HA group**

30-60 minutes after surgery (to allow time for drainage of the arthroscopic surgical fluid) while the patient is still at the post-op recovery room, 4ml of Monovisc HA will be administered through the catheter by the coordinating investigator (the orthopaedic fellow) who is the only unblinded investigator in the whole process. The catheter will be then removed without violation of the surgical dressing.

**Group II: Control group**

30-60 minutes after surgery (to allow time for drainage of the arthroscopic surgical fluid) while the patient is still at the post-op recovery room, 4ml of sterile saline will be administered through the catheter by the coordinating investigator (the orthopaedic fellow) who is the only unblinded investigator in the whole process. The catheter will be then removed without violation of the surgical dressing.

**Rehabilitation**

All patients will follow the same 4-phase rehabilitation protocol mentioned previously in this project protocol (point 1.3, page 8)

**3-months visit**

The passive and active ROM, the constant shoulder score, the ASES score and the manual strength testing using MRC grading (0-5) will be documented by one of the consulting investigators (A/Prof. Tan and Dr. Kuo)

**1st visit (10-14 days after surgery)**

the visual analogue scale (VAS) for pain will be documented by one of the consulting investigators (A/Prof. Tan and Dr. Kuo)

before taking off the stitches if needed.

**Radiological assessment**

* An independent, blinded musculoskeletal radiologist will read the MRI studies for all participants and will report cuff healing using the 5-stage Sugaya assessment system.86

**12 months visit**

* The passive and active ROM, the constant shoulder score, the ASES score and the manual strength testing using MRC grading (0-5) will be documented by the consulting investigator (A/Prof. Tan and Dr. Kuo).
* MRI report will be checked by the consulting investigator and the Cuff tendon integrity will be documented according to the 5-stage Sugaya assessment system.86

**6-months visit**

* The passive and active ROM, the constant shoulder score, the ASES score and the manual strength testing using MRC grading (0-5) will be documented by one of the consulting investigators (A/Prof. Tan and Dr. Kuo)
* An MRI request for the Shoulder will be given to the patient to be done 12 months after surgery. The referral will request that the radiologist report cuff healing using the 5-stageSugaya assessment system.86

**6.2 Investigation Plan**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| List Interventions | Enrolment Visit | Preop assessment (Day of surgery) | 1st post op visit (10-14 days) | 3-months visit | 6-months visit | 12-months visit |
| Inclusion / Exclusion criteria | ✓ |  |  |  |  |  |
| Informed consent and preoperative assessment papers to be given to the patient | ✓ |  |  |  |  |  |
| Preoperative assessment papers will be collected making sure all complete |  | ✓ |  |  |  |  |
| Randomisation |  | ✓ |  |  |  |  |
| VAS pain score |  | ✓ | ✓ | ✓ | ✓ | ✓ |
| Passive ROM(active ROM is part of the constant score) | ✓ | ✓ |  | ✓ | ✓ | ✓ |
| Constant shoulder score | ✓ | ✓ |  | ✓ | ✓ | ✓ |
| ASES shoulder score | ✓ | ✓ |  | ✓ | ✓ | ✓ |
| Strength(manual testing in 4 directionsusing MRC grading 0-5) | ✓ | ✓ |  | ✓ | ✓ | ✓ |
| MRI request |  |  |  |  | ✓ |  |
| Checking MRI result (tendon integrity scoring) |  |  |  |  |  | ✓ |
| Adverse Event Assessment |  |  | ✓ | ✓ | ✓ | ✓ |

## 6.3 Study Procedure Risks

The administration of either HA or sterile saline is a low to negligible risk treatment modality and theoretically, it should add nothing to the normal reported risks of arthroscopic shoulder cuff repair surgery.

## 6.4 Recruitment and Screening

All adult patients to undergo arthroscopic rotator cuff repair surgery at St. Vincent’s private Hospital-Sydney, Nepean private hospital and East Sydney private hospital will be recruited for the study. Initial patient screening based on study inclusion and exclusion criteria, will be conducted by the consulting investigator to determine whether the patient is suitable for the study.

## 6.5 Informed Consent Process

All patients who have met the inclusion criteria will be presented with the Participant information and Consent form prior to enrollment to the study. The consent form will be countersigned by another person other than the patient and Research Investigator to serve as a witness. The patient has the right to decide whether to be a participant or not. Patients who will give consent will be included to the randomisation procedure. Patients who decline to sign the consent form will be excluded.

## 6.6 Enrolment Procedure

The participant will be enrolled into the study after the informed consent process has been completed and the participant has met all inclusion criteria and none of the exclusion criteria. The participant will receive a study candidate number which will be documented in the research project Master logbook.

## 6.7 Randomisation Procedure

The participant will be randomized when the coordinating investigator meets him/her on the day of surgery to study Group A (HA group) or Study Group B (control group). Patients will be allocated to treatment groups using online computer-generated software (SealedEnvelope TM) for simple randomisation. The record and concealment of patient randomisation will be stored in the study logbook.

# Safety

## 7.1 Adverse Event Reporting

An adverse event can be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

## 7.2 Serious Adverse Event (SAE)Reporting

For medicines, also referred to as serious adverse drug reaction, any untoward medical occurrence that at any dose:

* results in death;
* is life-threatening;
* requires in-patient hospitalisation or prolongation of existing hospitalisation;
* results in persistent or significant disability/incapacity;
* is a congenital anomaly/birth defect; or
* is a medically important event or reaction.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.

## 7.3 Data Safety and Monitoring Board

The guidelines for monitoring approved research are outlined in Chapter 5.5 of the National Statement on Ethical conduct in Human Research.

## 7.4 Early Termination

Subjects will be withdrawn from the study if he/she failed to adhere to the protocol or has severe adverse reactions. Every participant has the right to refuse further participation in the study at any point of the study. A subject’s participation is terminated immediately upon request of the patient. The reason for withdrawal should be determined and recorded. The subject may be withdrawn from the study at any time in discretion of the investigator or in any time the patient requests. The following situations are reasons for immediate termination of participation of the patient:

a. Severe adverse event

b. If patient declines further study participation.

For patients that were initially included in the study but have failed to comply to the protocol in either treatment group for any reasons, the patient’s data will still be included in the study. However, the analysis of their data will be included in the Intention to treat analysis. Statistical analysis of data obtained from these patients will follow the Bonferrini analysis.

# BLINDING AND Unblinding

The study is a prospective, randomized trial in which the coordinating investigator is the only one who will be unblinded. The patients, radiologists and all other investigators will be blinded.

# STATISTICAL Consideration

**Sample size calculation**

Based on a power calculation from a similar study that demonstrated a significant positive effect of mesenchymal stem cells on tendon healing after cuff repair, 90 patients will be recruited into this study. 45 Patients will be assigned randomly to the intervention group (HA) and 45 to the control group (saline placebo).10

**Analysis plan**

Nominal data will be expressed as means +/- SD, while categorical data will be expressed as mean, frequencies, +/- SD. The Mann-Whitney U-test will be utilized to determine significant difference in outcome measures between two groups. Friedman’s test will be used to determine significant difference in outcome measures over time.

# CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY Documents

All patient data will be used confidentially and in accordance with the Australian Medical Association guidelines for patient information handling. The information will only be used by the primary investigators. As per the guideline for archiving periods of Interventional studies conducted under the TGA CTN Scheme, the study documents will be archived indefinitely.

# Other study documents

* Selection Criteria Form.
* Patient Information sheet and consent.
* Randomisation list
* Clinical evaluation forms: Preoperative, 2 weeks after surgery,3 months after surgery,6 months after surgery,12 months after surgery.
* Adverse events reporting

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