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ORIGINAL ARTICLE

Enhancement of rotator cuff tendon—bone healing using bone marrow—stimulating technique along with hyaluronic acid

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KEYWORDS
Rotator cuff repair;
Tendon bone healing;
Hyaluronic acid;
BMSCs

Abstract *Objective:* The purpose of this study was to investigate the effect of hyaluronic acid (HA) in the tendon—bone healing process after rotator cuff repair in a rabbit model.
Methods: In vitro, rat bone marrow stromal cells (rBMSCs) were cultured in media for cartilage-related and inflammation-related gene expression levels examination at 1.0 mg/mL of HA. In vivo, 48 New Zealand white rabbits underwent rotator cuff repair surgery, and they were randomly divided into three groups: (1) control group (n = 16), (2) microfracture (MF) group accepting MF treatment (n = 16) and (3) MF/HA group accepting MF with HA treatment (n = 16). Four rabbits from each group were sacrificed at 6 and 12 weeks postoperatively for histological evaluation and biomechanical testing.
Results: In vitro experiments reveal that HA significantly decreased inflammation-related mRNA expression (IL-1, TNFα) compared with the control group. At 6 weeks after surgery, there was no significant difference of load-to-failure between groups. At 12 weeks after surgery, the mean failure load of the MF/HA group was significantly higher than that of the control group (100.5 ± 10.1 N vs. 68.0 ± 6.2 N; $p = 0.0115$). The mean failure load of the MF group appeared higher than that of the control group, whereas there was no significant difference ($p > 0.05$). Histologically, more chondrocytes were clustered at the tendon—bone interface, and more extracellular matrixes were produced in the MF/HA group. The interface of the MF/HA group appeared similar with the normal tendon—bone interface.
Conclusion: HA may play a crucial role in the acceleration of tendon-to-bone healing which might be through inhibiting inflammation. Rotator cuff repair using MF along with HA led to better tendon—bone healing and a subsequent increase of biomechanical strength at the repair site.
The translational potential of this article: HA injection is very common for patients with rotator cuff disease because of its antiinflammatory action and adhesion prevention preoperatively. The HA injection during surgery provides an antiinflammatory effect during tendon—bone healing process and leads to better tendon—bone healing postoperatively.

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Introduction

Rotator cuff tear (RCT) in the general population has a high prevalence (approximately 20%), which increased with age [1,2]. Symptomatic RCT causes shoulder pain and limited range of motion over time, which will require surgical repair [3,4]. Generally, rotator cuff repair yields satisfactory clinical outcomes, with long-term relief of pain and recovery of range of motion and function [5]. However, the re-tears of rotator cuff tendon were observed after repair with an incidence of 20%—40%, indicating poor healing of tendon with the bone insertion [6—8].

It has been reported that bone microvascularisation of the footprint plays a role in rotator cuff tendon healing, and a lower rate of microvessels decreases the tendon—bone healing potential after repair [9]. Microfracture (MF) is the cheapest and technically easy method of enhance the repair site vascularisation using a simple MF technique. It affords a potential additional source of growth factor to the repair site and enhances the tendon—bone healing after repairing RCTs [10]. However, Osti et al. [11] reported that MF at the footprint did not result in significantly different outcomes, either clinically or at imaging, compared with traditional rotator cuff repair without MF.

In addition, a growing body of evidence supports use of hyaluronic acid (HA) injection in patients with rotator cuff disease because of its antiinflammatory action and adhesion prevention [12—14]. As reported, inflammation begins during the tendon—bone healing process with lots of inflammatory cells infiltration and may contribute to the formation of a fibrous scar tissue interface rather than to the reformation of a normal tendon—bone insertion site [15,16]. Tendon—bone healing is very difficult at the interface between the tendon and bone in the presence of inflammation. HA, for the antiinflammation effect, has been applied in the promotion of the tendon—bone healing in ligament reconstruction [17]. Moreover, HA is thought to play a crucial role in promoting cell differentiation and growth, and it also promotes a faster mineralisation process [18]. HA can increase the viability and proliferation and can enhance the collagen I expression in tendon-derived cells [19]. Clinically, subacromial injections of HA are effective in treating rotator cuff lesions without complete tears [20].

To date, there is no investigation reporting the effect of combined MF and HA in the treatment of RCT. Therefore, the purpose of the present study was to investigate the effect of MF along with HA in the tendon—bone healing process after rotator cuff repair in a rabbit model. The hypothesis was that rotator cuff repair using MF along with HA led to better tendon—bone healing and a subsequent increase of biomechanical strength at the repair site in rabbits.

Materials and methods

In vitro bone marrow stromal cells study

The rat bone marrow stromal cells (rBMSCs) were isolated from the femur of rats (three months old) and cultured in Dulbecco's Modified Eagle's Medium (HyClone, China) supplemented with 10% fetal calf serum (Invitrogen). rBMSCs were respectively cultured placed in 24-cell culture plates at an initial density of approximately 1×10^5 cells with or without HA (1 mg/mL, SOFAST, Bausch&Lomb Freda, China) at 37°C in a humidified atmosphere with 5% CO_2. The effect of HA on the chondrogenic differentiation of the rBMSCs was assessed by the gene expression levels of SOX9, collagen II and Aggrecan. The expression levels of inflammatory cytokine genes (TNFα, IL1β and CCL5 gene) were also analysed at 3 days of culture. The cells were harvested with Trizol reagent (Invitrogen) to extract the RNA based on the manufacturer's protocol. The isolated RNA was reversely transcribed using reverse transcriptase M-MLV (D2640A, Takara) and then amplified using Takara SYBR Premix Ex Taq (DRR041A, Takara) according to the manufacturer's instructions and subjected to polymerase chain reaction using primers (Table 1). The relative expression of genes was normalised to that of β-actin.

Animal experiment

All animal experiments were approved by the Animal Care and Use Committee of the university. Forty-eight adult male New Zealand White rabbits (2.7—3.0 kg) first received anaesthesia preoperatively by pentobarbital (10 mg/kg) intravenously and ketamine (4 mg/kg) intramuscularly. Then, a transverse incision was made over the lateral

Table 1 The primer sequences used for the Real Time Polymerase Chain Reaction (RT-PCR) study.

Gene	Sequences
β-actin	Forward: TAAGAGGAGGATGGTCGCGT
	Reverse: AAGTCAGTGTACAGGCCAGC
SOX9	Forward: TTAATTCCCCAGGCTCTTGGA
	Reverse: AGCCGGGATTTAAGGCTCAAG
Collagen II	Forward: GAAACTTCGCGGCTCAGATG
	Reverse: CAGGTTCACCAGGATTGCCT
Aggrecan	Forward: GGTTGGTTACTTCGCCTCCA
	Reverse: CCAGCCGAGAAATGACACCT
TNFα	Forward: CGGGCAGGTCTACTTTGGAG
	Reverse: ACCCTGAGCCATAATCCCCT
IL-1β	Forward: TGCCACCTTTTGACAGTGATG
	Reverse: CAAAGGTTTGGAAGCAGCCC
CCL5	Forward: CTCGAAGGAACCGCCAAGT
	Reverse: GATGCCCATTTTCCCAGGACC

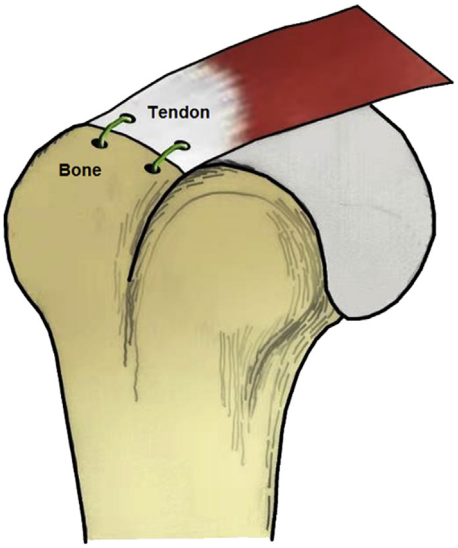

Figure 1 Illustration of rabbit shoulder surgical repair and view of tendon—bone junction.

aspect of the right shoulder to expose the supraspinatus tendon and its insertion on the greater tuberosity. Then, the supraspinatus tendon was detached from the insertion. Two parallel holes (1 mm in diameter) were drilled from lateral to medial. Subsequently, the detached tendon was sutured again to the insertion site (Fig. 1). Sixteen rabbits those underwent this procedure were considered as the control group. For the MF group (16 rabbits), three to four holes (1 mm in diameter) were drilled before suturing the tendon. On the base of the MF treatment, the remaining 16 rabbits those accepted 0.1 ml HA (SOFAST, Bausch&Lomb Freda, China) injection on the repair site were considered as the MF/HA group. The wound was closed in a layered fashion. The postoperative animals were returned to the animal care facilities. All the rabbits were sacrificed for the following examination at 6 and 12 weeks after surgery.

Histological assessments

Four specimens in each group were fixed in 4% formaldehyde solution for 2 days. These samples were decalcified in 10% ethylenediaminetetraacetic acid and changed twice weekly, for 4—6 weeks, after which they were embedded in paraffin. The samples were sectioned with a thickness of 5 μm perpendicular to the longitudinal axis of the graft. These sections were treated with hematoxylin—eosin and Masson staining for histological evaluation. A semiquantitative grading system (Table 2) was used based on collagen fibre density, collagen fibre orientation, quality of healing at bone

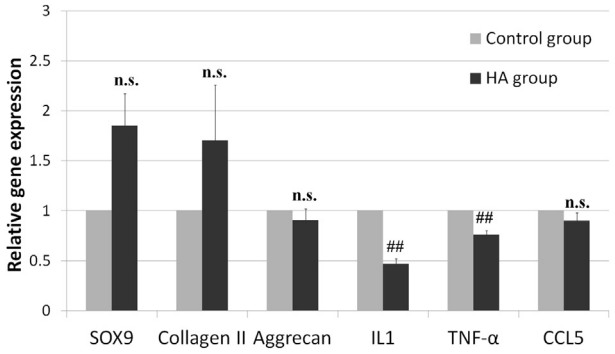

Figure 2 Osteogenic/inflammation-related gene expression of rBMSCs cultured with or without hyaluronic acid. "##" indicates significant difference between HA group and control group. "n.s." indicates no significant difference. HA = hyaluronic acid; rBMSCs = rat bone marrow stromal cells.

tendon interface, vascularity and presence of inflammatory cells according to a previous study [21]. A total was obtained by combining the scores for these five parameters, with a higher score indicating greater healing. Scoring was carried out by an orthopaedic expert who was blinded to treatment details and each other's scores. A minimum of three slides per sample were assessed where the tendon—bone interface could be identified.

Biomechanical testing

Biomechanical testing (AGS-X 5 kN, Shimadzu co., Japan) was conducted immediately after the specimens were taken and the associated muscles were removed, so that only the supraspinatus tendon was left attached on the humeral greater tuberosity. The bone part was fixed firmly in a clamp. The tendon part was sutured by a No. 5 Ethibond suture for traction. Before the tensile test was conducted, the specimen was preloaded with a preload of 1 N for 2 min. Immediately after preconditioning, the ultimate pull-out load was performed with an elongation rate of 2 mm/min. For each specimen, testing was completed when the graft ruptured or was pulled out of the bone tunnel. The maximal failure load (N) was recorded.

Statistical analysis

Data were reported as mean ± standard deviation, and the data analysis was performed using Stata10.0 software (Stata Corp, USA). Analyses of quantitative results were carried out with the one-way analysis of variance or Kruskal—Wallis test according to the data distribution. The statistical significance level was set at 0.05.

Table 2 Histological grading system used to determine the rotator cuff healing outcomes.

Score	Collagen fibre density	Collagen fibre orientation	Tendon—bone interface	Vascularity	Inflammation
0	None	None	0—24% interdigitation	Abundant vascular network	Abundant inflammatory cells
1	Low	Disorganised fibres	25—49% interdigitation	Moderate vascular network	Moderate inflammatory cells
2	Medium	Moderate alignment	50—75% interdigitation	Minimal vascular network	Minimal inflammatory cells
3	High	Highly aligned	>75% interdigitation	No vascular network	No inflammatory cells

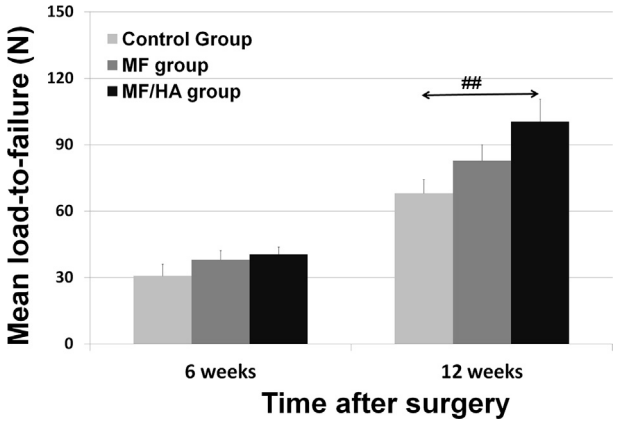

Figure 3 Results of biomechanical testing of the control group, MF group and MF/HA group. MF = microfracture. HA = hyaluronic acid. "##" indicates significant difference between MF/HA group and control group.

Results

In vitro analysis of rBMSCs, the mRNA expression levels of type II collagen, SOX9, TNFα, IL-1β, CCL5 and aggrecan genes were evaluated after the exposure to 1.0 mg/mL HA. Compared with the control, HA increased the expression of the mRNAs of collagen II and SOX9, while no significant difference was detected between the HA group and the control group ($p > 0.05$). Meanwhile, HA significantly decreased the expression of the mRNAs of IL1 ($p = 0.004$) and TNF-α ($p = 0.013$) (Fig. 2).

In vivo study, no rabbits died before they were sacrificed. No rabbits underwent recurrent tearing or wound infection. In all the groups, the gross observations showed an intact tendon—bone interface with synovial tissue covered on the surface at each time point.

During biomechanical testing, all the specimens failed at the tendon—bone interface area without fixture-specimen slipping. The results of load to failure tests are presented in Fig. 3. The failure loads of all groups increased significantly from week 6 to week 12 (control group, $p = 0.0064$; MF group, $p = 0.0015$; MF/HA group, $p < 0.001$). At 6 weeks after surgery, there was no significant difference between groups (Control group, 31 ± 5 N; MF group, 38 ± 4 N; MF/HA group, 41 ± 3 N) ($p > 0.05$). At 12 weeks after surgery, the mean failure load of the MF/HA group was significantly higher than that of the control group (101 ± 10 N vs. 68 ± 6 N; $p = 0.0115$). The mean failure load of the MF group (83 ± 7 N) appeared higher than that of the control group (68 ± 6 N), whereas there was no significant difference ($p > 0.05$).

Histological results were shown in Figs. 4 and 5. At 6 weeks, the control group had some inflammatory reaction

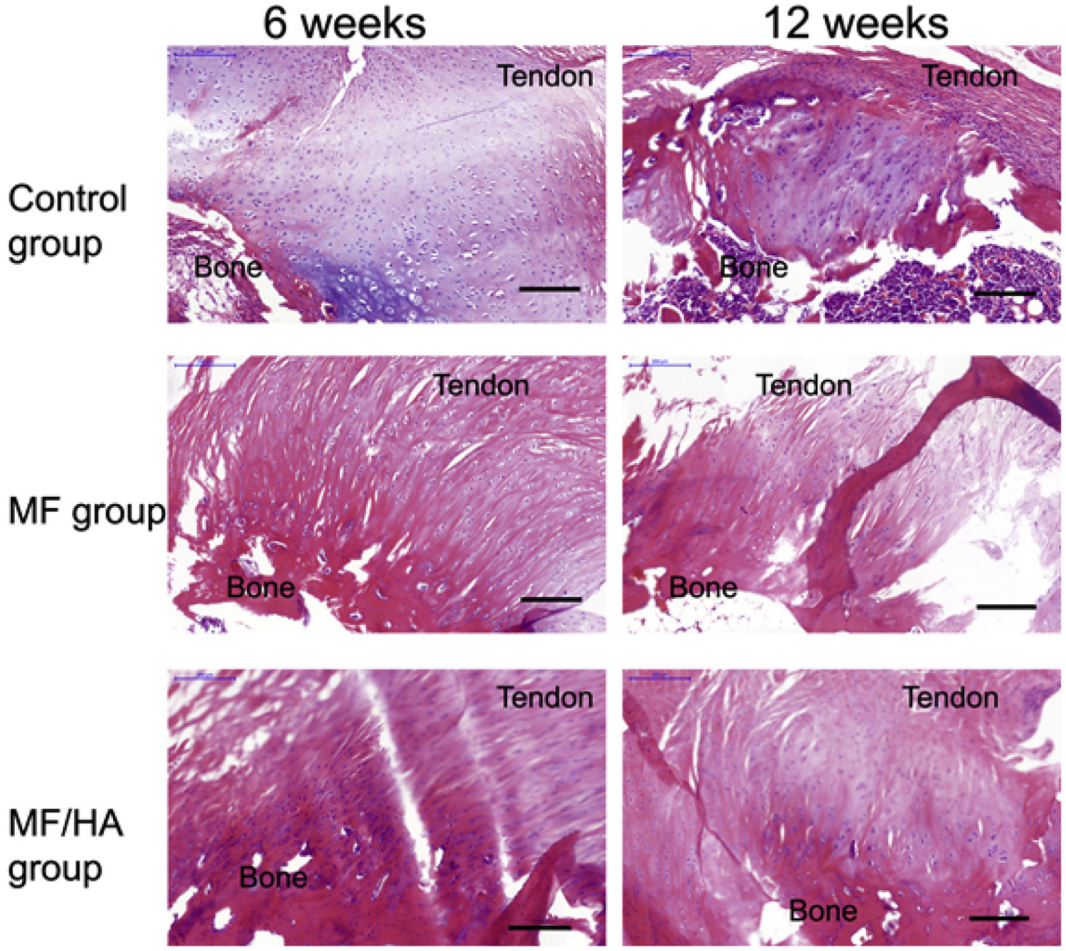

Figure 4 Histological images (H&E staining) of the control group, MF group and MF/HA group at 6 and 12 weeks. MF = microfracture. HA = hyaluronic acid; H&E = hematoxylin—eosin.

at the tendon—bone interface with much lymphocytes and eosinophils found in the bone marrow. In the MF and MF/HA group, the collagen fibres extended into the cancellous bone naturally with the cartilage cells in columns. A transition of tendon-to-bone was gradually formed. Some immature chondrocytes were clustered at the tendon—bone interface, but the chondrocytes were not aligned. Compared with those of the MF group, the collagen and chondrocytes of the MF/HA group appear denser, and the collection of the tendon to bone became more close and tight.

At 12 weeks, the control group still have some inflammatory reaction at the interface, and a transition of bone to tendon was gradually formed at the interface. The cartilaginous tissue was more aligned, while the collagen fibres tissue was distributed horizontally in the control group. In the MF group, although no evidence was present of acute inflammatory reactions, the proliferation of fibroblasts was dominant at the tendon-to-bone interface instead of chondrocytes and new bone formation. In the MF/HA group, more chondrocytes were clustered at the tendon—bone interface, and more extracellular matrixes were produced. Sharpey's-like fibres were observed anchoring the tendon to bone, and chondrocytes were arranged in columns. The interface of the MF/HA group appeared similar with the normal tendon—bone interface, which consisted of four different regions: the tendon, unmineralised fibrocartilage, mineralised fibrocartilage and bone.

At 6 weeks postoperatively, the MF/HA group had a significant higher histological scoring compared with the control group (4.7 ± 1.0 vs. 3.0 ± 0.5; $p = 0.008$). At 12 weeks after surgery, the histological score of the MF/HA group was significantly higher than that of the control group (5.2 ± 0.2 vs. 3.8 ± 0.3; $p = 0.002$), and the histological score of the MF group was also significantly higher than that of the control group (6.9 ± 0.6 vs. 3.8 ± 0.3; $p = 0.02$) (Fig. 6).

Discussion

It is well known that successful repair of RCT requires the repaired rotator cuff tendon—bone healing [22,23]. To date, various approaches have been tried to enhance the tendon—bone healing after rotator cuff repair, including bone marrow stromal cells [24], growth factors [25] and scaffolds [10]. Previous recent study [26] revealed that HA accelerated tendon-to-bone healing in the rotator cuff repair model, enhancing the biomechanical strength and increasing chondroid formation and tendon maturity at the tendon—bone interface. In this study, MF combined with HA was applied in the tendon—bone healing process after rotator cuff repair in a rabbit model. It was demonstrated rotator cuff repair using MF along with HA led to better tendon—bone healing at the repair site because of antiinflammatory effect.

In this study, the histological score of the MF group was also significantly higher than that of the control group. The mean failure load of the MF group appeared higher than that of the control group, while there was no significant

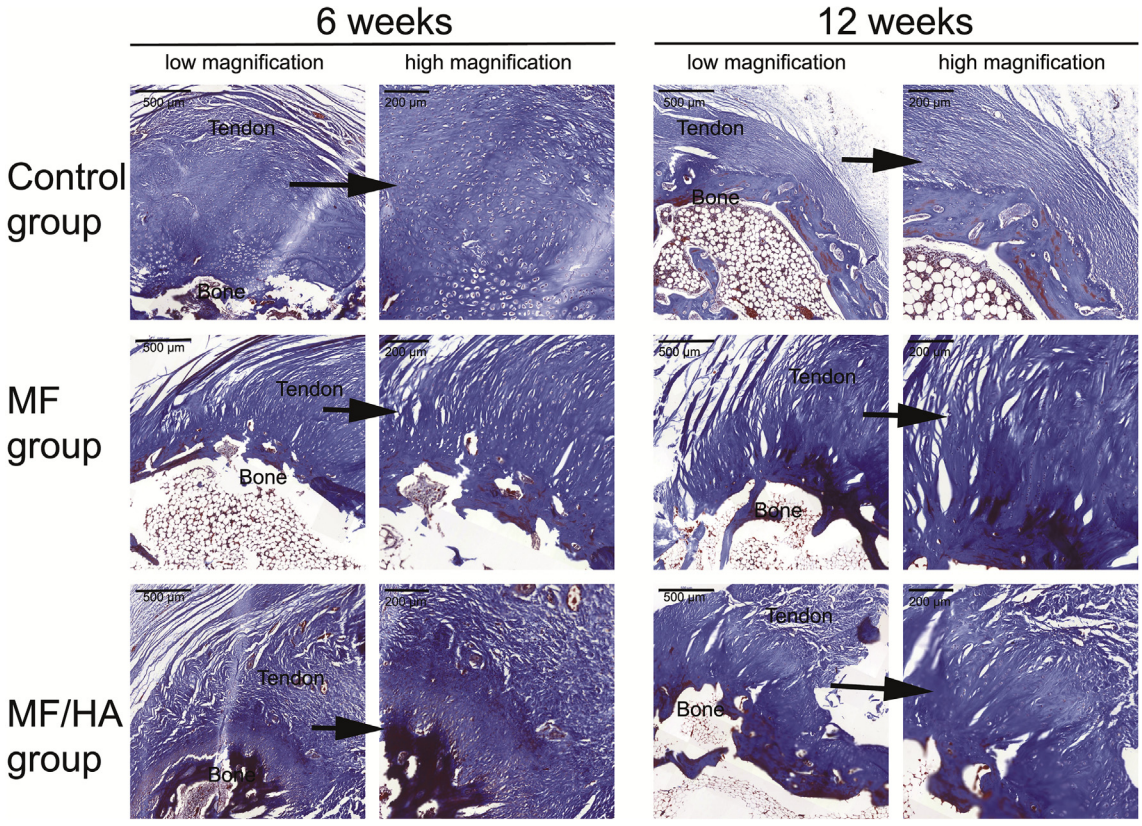

Figure 5 Histological images (Masson staining) of the control group, MF group and MF/HA group at 6 and 12 weeks. MF = microfracture. HA = hyaluronic acid.

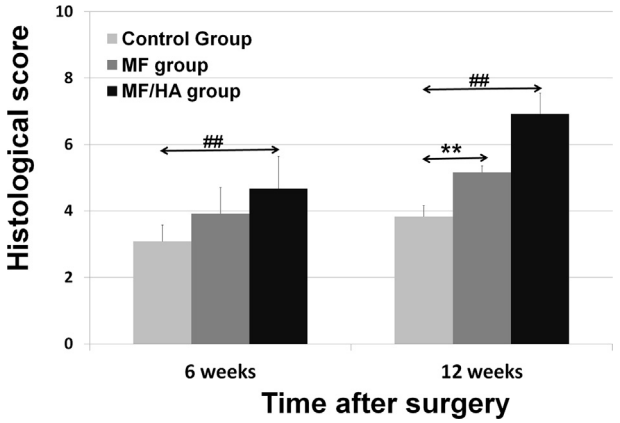

Figure 6 Histological scores of the control group, MF group and MF/HA group. MF = microfracture. HA = hyaluronic acid. "##" indicates significant difference between MF/HA group and control group. "**" indicates significant difference between MF group and control group.

difference. Previous study has shown that MF will produce a fibrin clot to cover the denuded tuberosity and repaired rotator cuff tendon. This fibrin clot, containing mesenchymal stem cells and growth factors, serves as a temporary scaffolding material and encourages cells migration and proliferation [10]. MF also enhances the vascularisation at the tendon—bone interface, which is important for the tendon—bone healing [27].

The elevation of inflammation may be responsible for the eventual tendon degeneration and inferior tendon tissue quality, resulting poor tendon—bone healing [28]. In this study, HA, for its antiinflammation effect, was applied in the rotator cuff repair. It was observed that MF/HA treatment led to better tendon—bone healing regarding the biomechanical property and histological scores compared with pure MF treatment. In a previous investigation [29], HA was injected to the rotator cuff repair in rats, and it was found that there was no significant difference of biomechanical load-to-failure between the HA group and the control group. It was presumed that the pure HA might have limited effect to enhance rotator cuff tendon—bone healing. Thus, MF combined with HA was applied in the rotator cuff repair in the present study.

Conclusion

In this study, HA played a crucial role in the acceleration of tendon-to-bone healing which might be through inhibiting inflammation, and it was found that MF along with HA led to better tendon—bone healing and a subsequent increase of biomechanical strength at the repair site. It was believed that HA injection postoperatively could be the good option for patients who have undergone rotator cuff repair.

Authors' contributions

Yuzhou Chen and Hong Li performed the animal experiments. Shiyi Chen gave the experiment guidance during this study. Hong Li analysed and interpreted the data regarding the biomechanical and histological results and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All animal experiments were approved by the Animal Care and Use Committee of Shanghai JiaoTong University Animal Department.

Conflicts of interest statement

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jot.2019.01.001.

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