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ORIGINAL ARTICLE

Effect of recombinant human growth hormone on rotator cuff healing after arthroscopic repair: preliminary result of a multicenter, prospective, randomized, open-label blinded end point clinical exploratory trial

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Background: This study evaluated the effect of systemic injection of recombinant human growth hormone (rhGH) on outcomes after arthroscopic rotator cuff repair.
Methods: This multicenter, prospective, randomized, comparative trial, randomized patients who underwent arthroscopic repair of large-sized rotator cuff tears into 3 groups: rhGH 4 mg group (n = 26), rhGH 8 mg group (n = 24) , and control group (n = 26). Sustained release rhGH was injected subcutaneously once weekly for 3 months postoperatively. The healing failure rate (primary end point), fatty infiltration, and atrophy of the supraspinatus muscle, and functional scores (Constant and American Shoulder and Elbow Surgeons scores) were evaluated at 6 months. Range of motion, pain visual analog scale, and serum insulin-like growth factor-1 level were measured at each follow-up.

This study was conducted in accordance with the principles of the Declaration of Helsinki, with appropriate regulatory and ethical approval, and was approved by the Institutional Review Board of each author's institution.

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Results: The healing failure rate was similar between groups (rhGH 4 mg group, 30.8%; rhGH 8 mg group, 16.7%; and control group, 34.6%; all $P > .05$) The proportion of severe fatty infiltration (Goutallier grade ≥3) was 20.8% in the rhGH 8 mg group, 23.1% in the rhGH 4 mg group, and 34.6% in the control group ($P > .05$). Functional outcomes, range of motion, and pain visual analog scale were similar between groups (all $P > .05$). The rhGH 8 mg group showed more increased peak insulin-like growth factor-1 level (279.43 ng/mL) than the rhGH 4 mg group ((196.82 ng/mL) and control group (186.31 ng/mL), which was not statistically different (all $P > .05$). No rhGH injection-related major safety issues occurred.
Conclusions: This preliminary study showed no statistically significant improvement in healing or outcomes related to the treatment of rhGH after rotator cuff repair. However, further study with more enrolled patients after resetting the rhGH dose or daily administration protocol would be mandatory.
Level of evidence: Level II; Randomized Controlled Trial

Keywords: Recombinant human growth hormone; insulin-like growth factor-1; rotator cuff, healing; healing failure; fatty infiltration; atrophy

Healing failure after rotator cuff repair remains one of the most common and well-known complications, and recent studies have reported an unacceptably high failure rate independent of the procedures used, especially in larger tears.[7,9] In addition, chronic rotator cuff tears lead to the fatty infiltration of the rotator cuff muscles, and fatty infiltration is one of the most important prognostic factors for anatomic and functional outcomes after rotator cuff repair. Unfortunately, some have suggested that surgical repair alone may not be able to halt or reverse the progression of fatty infiltration.[17,33]

Several growth factors, such as insulin-like growth factor-1 (IGF-1), transforming growth factor-β, vascular endothelial growth factor, platelet-derived growth factor, and basic fibroblast growth factor, are known to be involved in the healing process.[36,37] Among these, IGF-1 is a major mediator in all stages of healing, especially in the inflammatory phase. IGF-1 has been shown to directly regulate tenoblastic function by stimulating tenoblastic activity, migration, and proliferation[1] and to inhibit the enzymatic degradation of perilesional matrix molecules during tendon healing.[12] This action of IGF-1 would certainly aid the tendon healing process.[31] In addition, IGF-1 is also known to be able to regenerate skeletal muscle mass through satellite cell activation[6] and is associated with a reduction in the body mass index and visceral fat.[14,16] On the basis of these properties, it can be assumed that IGF-1 may lead to the decrease of fatty infiltration and improvement of muscle atrophy in cases of chronic degenerative rotator cuff tear.

Sustained-release recombinant human growth hormone (rhGH) has been commercially developed and is being used to treat patients with growth hormone (GH) deficiency. It acts mainly by increasing the systemic levels of IGF-1. Besides the effect of rhGH in treating GH deficiency, it can be hypothesized that the exogenous systemic administration of rhGH/IGF-1 may enhance collagen synthesis and stimulate healing after rotator cuff repair, considering that the circulating GH and collagen content are reduced in the elderly, in whom rotator cuff tears are prevalent.[31] Moreover, because IGF-1 can mediate loading-induced collagen synthesis, it is more plausible that an increase of IGF-1 may enhance tendon healing under the mechanically reloaded condition after rotator cuff repair. The effect of exogenous rhGH/IGF-1 on rotator cuff healing has not been proven, however, and well-designed prospective randomized clinical trials are lacking.

Thus, the current study was conducted to evaluate the effect of commercial sustained-release rhGH on outcomes after arthroscopic rotator cuff repair in patients with large-sized rotator cuff tears. We hypothesized that systemic administration of sustained-release rhGH would enhance healing and might improve functional outcomes after rotator cuff repair with the increase of serum IGF-1 level.

Materials and methods

Patient enrollment and allocation

This was a multicenter, randomized, prospective, controlled trial. Written informed consent was obtained from all patients.

The inclusion criteria were as follows: large-sized posterosuperior rotator cuff tears (tear size 3-5 cm) according to the rating system introduced by Cofield,[10] planned arthroscopic repair surgery, and age between 40 and 75 years. Tear size was initially measured in preoperative magnetic resonance imaging (MRI) and confirmed arthroscopically by using a calibrated probe at the time of surgery.

The exclusion criteria were as follows: diabetes mellitus (fasting plasma glucose level ≥126 mg/dL and hemoglobin A_{1c} level ≥6.5%),[4] malignant tumor, total bilirubin >3 mg/dL, alanine transaminase >100 units/L, aspartate transaminase >100 units/L, alkaline phosphatase >300 units/L, serum creatinine >1.6 mg/dL, Cushing syndrome or acromegaly, steroid injection or medication history within 3 months before the operation, GH injection or medication history within 3 months before the operation, thyroid function abnormality, oral estrogen treatment, hypersensitivity to GH, preoperative stiff shoulder,[42] systemic inflammatory disorder, acute multiple trauma requiring cardiopulmonary or abdominal surgery, acute respiratory distress syndrome, alcohol abuse or drug intoxication within 1 year before the operation, previous surgery on the same shoulder, severe glenohumeral arthritis (stage 3 according to Hamada classification[20]), workers' compensation status,[30] and refusal to participate in the study. Also excluded from the study were patients who underwent concomitant repair surgery for intra-articular lesions, such as superior anterior and posterior labral lesions or Bankart lesion, and those with