Efficacy and Safety Evaluation of a Novel Cross-Linked Chondroitin Sulfate (SI-449) in Rat Flexor Digitorum Longus Tendon Adhesion Models

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INTRODUCTION:
Adhesion formation following tendon repair is a major cause of poor postoperative outcomes. The resulting decrease in range of motion (ROM) can significantly impair a patient's quality of life. SI-449, a novel cross-linked chondroitin sulfate in powder form, has shown promising anti-adhesion effects in abdominal surgery[1]. This study aimed to evaluate the efficacy and safety of SI-449, specifically its effects on ROM, tendon healing, and mechanical strength, in rat flexor digitorum longus (FDL) tendon repair models.

METHODS:
The study protocol was approved by the Institutional Animal Care and Use Committee of Nagoya University and conformed to national laws and regulations for animal experiments. Study 1 evaluated the efficacy of SI-449 in a rat FDL partial laceration and repair model. Sixty 10-week-old female Sprague-Dawley rats were randomly assigned to one of five groups (n=12 each): Sham (no tendon suture), Control (suture only), and SI-449 at 2, 4, or 8 mg. Study 2 assessed the safety of SI-449 in a rat FDL transection and repair model using a clinically relevant suture technique (2-strand core suture with 7-0 looped nylon and a running suture with 8-0 nylon). Eighty-four 9-week-old female Sprague-Dawley rats were randomized into a Sham group (n=12), a Control group (n=24), an SI-449 4 mg group (n=24), and an SI-449 8 mg group (n=24). In both studies, all rats underwent sciatic nerve transection for foot immobilization. Evaluations included adhesion scoring and ROM measurement at 4 weeks in Study 1, and tensile testing, adhesion scoring, and pathological evaluation at 4 and 8 weeks in Study 2. Statistical analyses were performed using the Williams and Jonckeere-Terpstra tests in Study 1, and Tukey's test for tendon failure load and the Steel-Dwass test for adhesion scores in Study 2. A p-value<0.05 was considered significant.

RESULTS:
In Study 1, the SI-449-treated groups showed dose-dependent improvements in adhesion scores and ROM at 4 weeks, with statistically significant differences observed at 2 mg or greater for adhesion scores and at 4 mg or greater for ROM compared to the control group(Figure1).
In Study 2, due to the death of one rat assigned to the 8-week evaluation in the Sham group, tensile testing and pathological evaluation were performed on 5 limbs each at this time point. Additionally, one tendon sample from the SI-449 4 mg group was inadvertently damaged during harvesting at 4 weeks, resulting in 11 limbs for tensile testing in this group. The failure load of the 8 mg group (mean 1.43 ± 0.303 kg) was significantly lower than that of the control group (mean 1.94 ± 0.335 kg) ($p<0.05$) at 4 weeks, while there were no significant differences among the control (mean 3.13 ± 0.877 kg), 4 mg (mean 2.60 ± 0.709 kg), and 8 mg (mean 2.68 ± 0.613 kg) groups at 8 weeks. Regarding adhesion, at 4 weeks, both the SI-449 4 mg (mean 1.45 ± 0.820) and 8 mg (mean 1.83 ± 0.577) groups showed significantly lower adhesion scores compared to the control group (mean 2.50 ± 0.674) ($p<0.05$).
Histopathologically, at both 4 and 8 weeks, the tendon tissue in both the SI-449 4 mg and 8 mg groups was comparable to that of the control group, with no clear findings suggesting delayed healing or tendon weakening.

DISCUSSION:
This study demonstrates that SI-449 exerts a potent anti-adhesion effect, improves ROM, and does not adversely affect the tendon healing process in rat models. The transient decrease in tendon strength at 4 weeks with the high 8 mg dose—the maximum feasible dose in this model—may be attributed to increased internal pressure from SI-449 swelling, potentially leading to excessive suppression of extrinsic healing. This interpretation is supported by the absence of histological findings suggesting impaired intrinsic tendon healing. Importantly, this reduction in strength was neither severe nor permanent, as it recovered by 8 weeks. Furthermore, the 4 mg dose maintained its anti-adhesion efficacy without compromising tendon strength. In conclusion, SI-449 significantly suppresses postoperative peritendinous adhesions without raising major safety concerns for its clinical use.

SIGNIFICANCE/CLINICAL RELEVANCE:
SI-449, a novel cross-linked chondroitin sulfate in powder form, effectively prevents post-surgical adhesions, a primary cause of poor outcomes in tendon repair. A 4 mg dose of SI-449 appears to be both effective and safe, preserving the mechanical strength of the healing tendon. These findings suggest its potential to improve clinical outcomes in hand surgery.

REFERENCES:
1.Toyama K, Takahashi K, Funayama S, Yoshioka K. Effects of Novel Cross-Linked Chondroitin Sulfate (SI-449) as a Postoperative Anti-Adhesion Barrier. J Surg Res. 2024;304:162-172.

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Figure1. Adhesion score and Range of motion

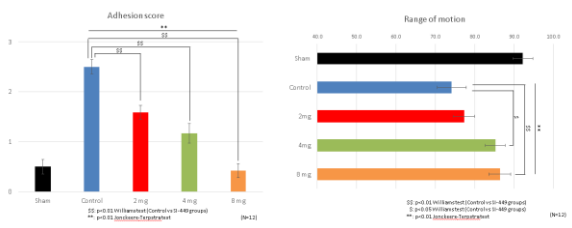

Figure2. Failure load of the tendon