Implantation of an acellular, bioresorbable, ultra-purified alginate gel after discectomy for lumbar intervertebral disc herniation: An interim analysis of a first-in-human pilot study and comparison with a control cohort study.

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INTRODUCTION: Herniated nucleus pulposus (NP), one of the most common diseases of the spine, is surgically treated by removing the sequestered NP. However, intervertebral disc (IVD) defects may remain after discectomy, which leads to inadequate tissue healing and predisposes patients to IVD degeneration. An acellular, bioresorbable, ultra-purified alginate (UPAL) gel implantation system can be used to fill any IVD defects to prevent IVD degeneration after discectomy (Figure 1). This first-in-human pilot study aimed to determine the feasibility, safety, and postoperative outcomes of combined treatment or herniated NP with discectomy and UPAL gel implantation compared to a control group that underwent only discectomy.

METHODS:

We designed a single-arm, double-center, open-label pilot trial. The study started in November 2018 and recruitment of patients ended in September 2020. Patients aged 20–49 years, diagnosed as having isolated lumbar IVD herniation, and scheduled for discectomy represented the suitable candidates. All eligible participants who provided informed consent underwent standard discectomy, followed by UPAL gel implantation (Figure 1). The primary outcomes of the trial were the feasibility and safety of the procedure. The secondary outcomes included self-assessed clinical scores for evaluating pain and health-related quality of life (QOL), and magnetic resonance imaging (MRI)-based measures of morphological and compositional qualities of the IVD tissue. The initial outcomes were published at 24 weeks, with prospective follow-up at 96 weeks postoperatively. The patients who underwent discectomy only without UPAL implantation were recruited as a comparative historical control group. The historical control study started in January 2021 after all surgeries in the UPAL implantation group had been completed.

RESULTS:

Forty patients (30 men, 10 women; mean age: 36.3 y) were enrolled in the UPAL group and all patients completed the initial 6-month postoperative follow-up. All patients underwent discectomy and underwent UPAL gel implantation, suggesting that the feasibility of UPAL gel implantation was 100%. No adverse events related to UPAL occurred after the operation. After 6 months postoperatively, 28 of the 38 patients, excluding 2 cases with hernia recurrences, were followed up for 2 years postoperatively.

Thirty-three patients (19 men, 14 women; mean age: 37.3 y) who underwent discectomy only were enrolled in the control group. Patient backgrounds in the control group were comparable to those in the UPAL group. All patients completed the initial 6-month postoperative follow-up, excluding one patient who underwent re-operation due to a recurrent herniation at 4 weeks postoperatively, after which 24 of the 32 patients were followed up at 2 years postoperatively, except for one patient with a recurrence of herniation after 48 weeks postoperatively.

The secondary outcome of pain assessment showed that the visual analog scale (VAS; 0-100 mm, with higher scores representing worse pain) scores for low back and leg pains were equivalent between the groups (Figure 2). The Japanese Orthopedic Association (JOA) score and the self-assessed clinical scores including the JOA Back Pain Evaluation Questionnaire (JOABPEQ) score, Oswestry Disability Index (ODI) and Roland-Morris Disability Questionnaire (RDQ) were better in the UPAL group than in the control group (JOA: post-op 1,3,12 weeks, ODI: post-op 1,4 weeks, RDQ: post-op 4 weeks, JOABPEQ [Lumbar dysfunction]: post-op 4,12 weeks, $p<0.05$, respectively), but were equivalent at 2 years postoperatively (Figure 2).

MRI analysis showed that the Pfirrmann disc degeneration grade in the UPAL group was significantly lower than in the control group at 24 and 96 weeks postoperatively (Figure 3). In quantitative MRI analysis for IVD, normalized T1rho and T2star values of lesioned IVD were comparable between groups at preoperative, 24 and 96 weeks (Figure 3). Diffusion-weighted imaging (DWI) showed a significant increase in the normalized apparent diffusion coefficient of lesional IVD in the control group compared to the UPAL group at 24 weeks postoperatively, but was comparable at 96 weeks postoperatively (Figure 3).

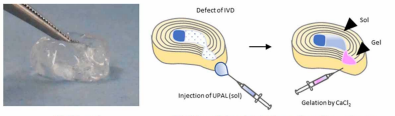
DISCUSSION AND CONCLUSION:

In vivo studies have shown that UPAL gel optimizes the repair environment within the IVD and that residual NP cells and progenitor cells accumulate and increase in the gel, allowing the disc to repair spontaneously (Tsujimoto et al. eBioMedicine, 2018), and that UPAL gel suppresses the production of inflammatory cytokines and pain-related behaviors (Ura et al. SciRep2021).

This first-in-human pilot study confirmed the feasibility and safety of UPAL gel implantation for herniated NP after discectomy, and demonstrated that UPAL gel implantation improves early postoperative pain and health-related QOL

compared to the control group. Furthermore, MRI indicated the possibility of preventing IVD degeneration after discectomy. The methodology and design of the study needed for the extensive clinical trials that are being planned will be implemented based on the results of this study.

Figure 1.
Acellular, bioresorbable ultra-purified alginate (UPAL) gel



UPAL gel UPAL gel implantation after discectomy

Tsujimoto et al. EBioMedicine 2018

Figure 2. Clinical scores

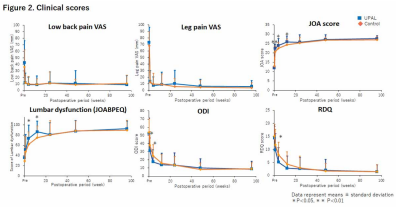


Figure 3. MRI analysis