

# Intra-articular adipose-derived stromal vascular fraction (SVF) cells may provide early pain relief compared to adipose tissue-derived mesenchymal stem cells (ADSCs) for the osteoarthritic knee

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**INTRODUCTION:** There has been increased interest in cell based therapy, particularly utilizing adipose-derived stromal vascular fraction (SVF) cells and adipose-derived cultured stem cells (ADSCs) for the treatment of knee osteoarthritis. ADSCs possess differentiation potential with similar properties to bone marrow stem cells (BMSCs) which may aide in treatment of the osteoarthritic knee<sup>1</sup>. However, ADSCs require an interval of a few weeks between harvest and injection for culturing the cells, which is time consuming and expensive. On the other hand, SVF cells are a heterogenous population of cells including ADSCs, macrophages, fibroblasts, and blood cells<sup>2</sup>. Basic science studies have revealed anti-inflammatory properties of SVF cells, which may provide alleviation of knee pain<sup>3</sup>. Only one clinical outcome study exists comparing SVF cells and ADSCs. This retrospective study reported on visual analogue scale (VAS) and Knee injury and osteoarthritis score (KOOS) at baseline, 1 month, 3 months and 6 months following intra-articular injection of either SVF or ADSC<sup>4</sup>. As a result, VAS and KOOS symptoms showed greater improvement in the ADSCs group compared to the SVF cell group at 3 months. However, the study was a short-term follow-up of only 6 months, with no image analysis. The purpose of the current study was to compare clinical and radiographic outcome between SVF and ADSC groups. We hypothesized that there will be no difference in clinical and radiographic outcome between SVF and ADSC groups.

**METHODS:** The current study is a retrospective study of prospectively collected data. Ethical approval was attained for this study. All patients were required to complete at least 3 months of conservative treatment prior to being offered injection with either SVF cells (SVF group) or ADSCs (ADSCs group). After explanation of the benefits and risks of SVF cells and ADSCs, the patients chose which injection to receive. 5ml preparation of SVF (mean  $\pm$  standard deviation;  $2.7 \times 10^7 \pm 1.2$  cells) or 5ml preparation of ADSCs (mean  $\pm$  standard deviation;  $3.9 \times 10^7 \pm 2.1$  cells) purified after liposuction under general anesthesia were injected intra-articular to the patient knees under ultrasound guidance. Inclusion criteria were 1) patients diagnosed with knee OA of any Kellgren-Lawrence (KL) classification 2) have a complete set of outcome data up to at least 1 year post first injection 2) only performed a maximum of 2 injections within 1 year after the 1<sup>st</sup> injection 3) second injection must be performed at least 3 months prior to the post-injection 1 year date from the first injection (fig. 1). Exclusion criteria are previous trauma or surgery to the ipsilateral knee, inflammatory disease, and severe intra-articular bony defect in the knee. Patient background data (sex, age, body mass index, duration of follow-up, hip-knee-ankle (HKA) angle, knee extension/flexion angle and strength, and KL classification) were recorded. Clinical outcome data include, VAS collected at baseline and 12 months (M), and KOOS scores, knee flexion/extension angle, and knee flexion/extension strength collected at baseline, 1M, 3M, 6M, and 12M. Magnetic resonance imaging (MRI) analysis was performed using the MRI osteoarthritis knee score (MOAKS). MOAKS was used to quantify bone marrow lesion, osteophyte formation, cartilage defect, and Hoffa's synovitis in the knee joint. One-way analysis of variance and the Tukey-Kramer post hoc test was used for comparison between groups, and chi-square test for categorical variables. P-values < 0.05 were considered statistically significant.

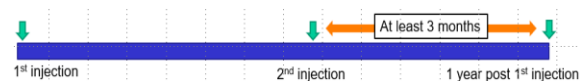
**RESULTS:** 48 knees were included in total. 24 knees (7 males, 17 females) were included in the SVF group and 24 knees (7 males, 17 females) in the ADSCs group. No significant differences were seen between groups in sex, age, BMI, HKA at baseline, KL classification distribution, and number of injections ( $p > 0.05$ ). Follow-up period was longer for the SVF group ( $40.7 \pm 13.4$  M) compared to the ADSCs group ( $29.4 \pm 9.3$  M) ( $p < 0.01$ ). The number of patients with pain (SVF group: 2/24 patients, 8%, ADSCs group: 8/24 patients, 33%) and swelling (SVF group: 1/24 patients, 4%, ADSC group: 12/24 patients, 50%) after the first injection was significantly less in the SVF group compared to the ADSCs group. VAS at 3M post first injection was significantly lower in the SVF group compared to the ADSCs group (Fig. 1). Also, in comparison to pre-operative VAS, no significant difference was seen at all time points in the ADSCs group, and in contrast significant difference was found at all time points in the SVF group (fig. 2) ( $p < 0.05$ ). No differences in HKA, ROM, flexion/extension strength, and were seen between groups. KOOS quality of life (QOL) score was significantly lower in the SVF group at baseline, however, no differences were seen at any other time points, and all other subscores and total score for KOOS. No significant differences were observed in MOAKS scores.

**DISCUSSION:** The most important finding in this study was that SVF group showed greater improvement in VAS compared to ADSCs at 3M after the first injection. No differences were seen in other clinical outcomes and MRI results obtained in the study. The results partially supported the hypothesis that there were no differences in clinical and radiographic outcome besides VAS results which showed greater early improvement in the SVF group compared to the ADSC group. In conclusion, the results suggest that SVF may be advantageous as an initial treatment option based on quicker relief of pain according to VAS scores.

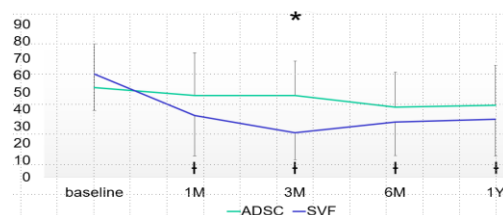
**SIGNIFICANCE/CLINICAL RELEVANCE:** The current study may provide some guidance as to the use of SVF and ADSC in clinical practice and may be a source of evidence when explaining expectations to patients.

**REFERENCES:** 1: Huang SJ et al. Cell Transplantation 2013;701-709. 2: McIntosh K et al. Stem Cells 2006;1246-1253. 3: Fujita M et al. J Cell Physiol. 2033;1-13. 4: Yokota N et al. Am J Sports Med. 2019;2577-2583

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**Fig. 1** Injection protocol for SVF group and ADSCs group. Patients with injections must have their second injection at least 3 months prior to the 1 year mark after the first injection.



**Fig. 2** Visual analogue scale (VAS) scores at baseline, 1, 3, 6 months and 1 year after injection with ADSCs or SVF cells. M: month, Y: year, ADSC: adipose tissue-derived mesenchymal stem cells, SVF: adipose derived stromal vascular fraction cells. \*:significant difference between groups,  $P < 0.05$  †:significant difference to baseline in each group,  $P < 0.05$