Intraarticular Application of Autologous Conditioned Serum (ACS/Orthokine) reduces bone tunnel widening and improves clinical outcome after ACL reconstructive surgery

+1 Moser, C; 2 Darabos, N; 3 Hundai-Haspl, Z; 4 Haspl, M; 5 Markotic, A; 6 Darabos, A

+1 Groenemeyer Institute for Microtherapy, 44799 Bochum, Germany; 2Department of General Surgery and Traumatology, General Hospital Varazdin, 1 Mestrovica bb, 42000, Varazdin, Croatia; 3 Croatian Institute of Transfusion Medicine, Petrova ulica, 10000, Zagreb, Croatia; 4Department of Orthopaedic Surgery, School of Medicine, University of Zagreb, Salata 3b, 10000, Zagreb, Croatia; 5The Scientific Unit, University Hospital for Infectious Diseases, Rockfellerova ulica, 10000, Zagreb, Croatia; 6The Scientific Unit, General Hospital Varazdin, 1 Mestrovica bb, 42000; Varazdin, Croatia; 7Centre for Molecular Orthopaedics; Dusseldorf, Germany

Senior author: moser@microtherapy.de

INTRODUCTION:

According to available literature, there are 10-25 % of unsuccessful results after an ACL reconstruction due to different possible causes. A number of biological and mechanical aetiologies have been discussed. The role and exact aetiology of tunnel bone tunnel widening (TW) is still controversial. It results in potential higher knee laxity that could be an early sign of a bad postoperative outcome.

Based on what is known so far about the mechanisms involved in processes leading to inflammation or bone tunnel enlargement following anterior cruciate ligament reconstruction, the inhibition of catabolic cytokines, the local administration of autologous anabolic growth factors, or both together appear to be logical and promising approaches to therapy.

A new treatment option is to administer Autologous Conditioned Serum (ACS/Orthokine) containing endogenous anti-inflammatory cytokines including Interleukin-1 receptor antagonist (IL-1Ra) and growth factors like insulin like growth factor-1 (IGF-1), platelet derived growth factor (PDGF) transforming growth factor beta (TGF-ß1), produced from venous patients blood.

The purpose of this trial was to establish whether the postoperative outcome could be affected by intra-articular application of ACS, thus resulting in a reduced tunnel widening, potential decrease of knee laxity and representing a better postoperative outcome in comparison to saline treatment.

METHODS:

In a prospective, randomized, double-blind, saline-controlled trial with two parallel groups, 62 patients were treated. Bone tunnel width was measured by CT-scans on postoperative Day 1, and 6 and 12 months after surgery by CT-scans and two independent experts.

Clinical efficacy was assessed by patient administered outcome instruments (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]) and IKDC following the ACL-reconstruction in patients receiving ACS (Group A) or Saline (Group B). At 6 and 12 months, patients completed the same questionnaires as at baseline and the blinded orthopaedic surgeon performed a physical examination of the knee, completed the surgeon part of the IKDC 2000, checked for adverse events and changes in analgesic use.

All patients underwent a surgical reconstruction of traumatic rupture of ACL of a knee joint, using autografts of m. semitendinosus and gracilis tendons (HS), as well as the patellar ligament (BTB). For the ACS production all patients whole blood was taken with special syringes (Orthokine EOT Syringe, Orthogen, Duesseldorf, Germany) with increased inner surface area. Processing included incubation for six to nine hours, centrifugation, microfiltration and aliquoting into four 2ml portions. Samples from patients receiving saline injections were discarded. Subsequently, an injection regime of four injections was started on a rigid scheme comprising injections on day 0 (day of surgery), 1, 6 and 10. After undergoing surgery all patients underwent an identical standard Rehabilitation regimen lasting 6 months (Lyon and Zagreb protocol).

Each patient was fully informed about the purpose of the trial, expected benefits, possible risks and signed the Informed Consent. The approval for this study was obtained by the Ethics Committee, School of Medicine, University of Zagreb, prior to performing the study.

RESULTS:

Baseline disease characteristics were to be comparable in the two groups according to the WOMAC index and IKDC 2000 Form. Both ACS and saline-treated patients showed a significant improvement on all outcome measures (P < 0.001), as compared to baseline values. ACS-treated patients scored consistently better as compared to saline-treated patients. With respect to improvement over time, ACS resulted in significantly more improvement for WOMAC stiffness (p=0.047, 12 months), as compared to saline treatment. However, most differences between the two treatment groups were small. It seems that, with respect to effusion and functional tests, one can measure better results faster and earlier.

Postoperative (femoral and) tibial tunnel diameters in both groups (BTB or HS) were significantly larger than directly after surgery. There was a significant difference in the degree of tunnel widening with respect to the graft type used. Irrespective of treatment modality (ACS or Saline), tunnel widening is marked in the HS group. The mean increase in the tibial tunnel area was 33.17% (range 6 to 105%) after six months and 41.74 (range 8 to 108%) after 12 months in the HS group. In the BTB group it was only 11.1% (range -2 to 48%) after six months and 17.1% (range 3 to 69%) after 12 months. With respect to the treatment groups (ACS vs. Saline), the increase within the ACS group, when compared with Saline outcome measurements, was significantly lower at follow-up in the HS (ACS vs. Saline 6 months: p=0.032, 12 months: p=0.048) and in the BTB group (ACS vs. Saline 6 months: p=0.061 [n.s], 12 months: p=0.001; Figure).

Figure shows the effect of ACS and Saline treatment over time on the bone tunnel widening (TW in millimeter) following ACL-reconstructive surgery.

In general, all IA injections were well tolerated. Adverse events were only mild to moderate and were mostly attributable to a subjective pain or pressure sensation directly after the IA injections and revealed in a few hours without secondary damage. There was no statistically significant difference in the prevalence of adverse events between the two groups. However, we were unable to detect correlation between the tunnel widening and clinical results or laxity of the BTB and HS procedures. Tunnel widening did not correlate with the clinical findings, knee scores (WOMAC, IKDC 2000), effusion grade, range of motion or other examination results.

DISCUSSION:

The statistically significant reduction of bone tunnel enlargement, the statistically significant improvement of WOMAC Stiffness together with the consistently higher, though non-statistically significant, improvement of most other parameters demonstrates that ACS clearly induces a fast biological response different from saline treatment and warrant future investigations into the possible protective effects of ACS.