Thieme

Intra-Articular Injections of Autologous Conditioned Serum to Treat Pain from Meniscal Lesions

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ABSTRACT

Routine use of biological therapies is in its early stages. Techniques involve stem cells, platelet preparations, recombinant growth factors and autologous conditioned serum, often combined with surgery. The objective of this case analysis was to document effects of intra-articular autologous conditioned serum injections in outpatients with knee pain associated with meniscal defects. Autologous conditioned serum was prepared from patients' blood by centrifugal separation from cellular components using a specialized device (EOT®II, Orthokine). Outpatients (n = 47) with heterogeneous knee meniscus lesions (76.6 % traumatic knee injury) were injected once weekly (average 5.2 applications). Average age was 48.6 years (range 21–79). Oxford Knee Score and structural changes with the MRI Boston Leeds Osteoarthritis Knee Score were documented at baseline and 6 months. All analyses were performed retrospectively.
In 83 % patients, surgery was avoided during the 6-month observation period. Oxford Knee Score improved significantly from 29.1–44.3 ($p < 0.001$; best possible score = 48). Structural findings on MRI, measured by Boston Leeds Osteoarthritis Knee Score, showed significant improvement at 6 months (0.82–0.71, $p < 0.001$). This retrospective study implies that intra-articular autologous conditioned serum injection may be an effective treatment option for knee pain associated with meniscal lesions. Controlled studies of autologous conditioned serum treatment for meniscal lesions are advocated.

Introduction

Meniscal lesions, depending on their severity and location, sometimes heal spontaneously or may remain asymptomatic. Osteoarthritis (OA) is frequently associated with both symptomatic and asymptomatic meniscal defects [16]. Treatment of meniscal tears by surgical interventions, including resection, refixation/suturing, scaffold implants and allografts, is the clinical standard; however, there is growing concern that arthroscopic meniscus and/or OA surgical treatment may not be indicated in a substantial subset of patients [27–29, 36, 40]. The recent Osteoarthritis Research Society International (OARSI) guidelines recommend more critical application of surgery [34].

The combination of surgery with augmentation procedures has been proposed to improve clinical outcomes, however, only few controlled clinical studies with biological augmentation techniques for the purpose of improving clinical signs of meniscal injuries have been performed [42]. Such augmentation procedures (experimental and clinical) include recombinant growth factors, platelet concentrates (e. g., platelet-rich plasma), stem cell injections and scaffolds.

Intra-articular injections of autologous conditioned serum (ACS; Orthokine®) are a therapy for symptomatic osteoarthritic knees and has been in use for > 10 years [43]. ACS contains autologous components derived solely from the patient's blood and, because ACS is cell-free, it differs fundamentally from platelets or platelet lysate preparations, which contain cells or cell fragments. Elevated concentrations of cytokines and growth factors have been reported with ACS treatment [43, 44].

▶ **Table 1** Characteristics of patients documented in this report.

Characteristic		Patients (N = 47) (n [%] unless otherwise stated)
Gender	Male	32 (68.1)
	Female	15 (31.9)
Age, years	Mean (range)	49.4 (21–83)
Duration of symptoms, weeks	< 4	26 (55.3)
	≥ 4	15 (31.9)
	Unclear	6 (12.8)
Surgery	No	39 (83.0)
	Yes	5 (10.6)
	Unclear	3 (6.4)
Knee affected	Left	18 (38.3)
	Right	26 (55.3)
	Both	3 (6.4)
Retropatellar cartilage defect	Yes	42 (89.4)
	No	5 (10.6)
Trauma	Yes	36 (76.6)
	No	9 (19.1)
	Unclear	2 (4.3)

Examination of patients with knee pain routinely includes the Oxford Knee Score (OKS) and magnetic resonance imaging (MRI), and MRI often reveals that patients have meniscal lesions, suggesting a retrospective analysis of clinical outcomes in patients receiving knee injections with ACS in the presence of meniscal lesions. The aim of this report was therefore to retrospectively describe a series of cases regarding the clinical effects of intra-articular ACS injections in patients presenting with knee pain associated with MRI-confirmed meniscal defects.

Methods

Patients and ethical procedures

Outpatients presenting at the author's private practice with knee pain, a diagnosis of meniscal lesions and who had undergone ACS treatment were included in this retrospective analysis. Data was obtained in compliance with German law and the Declaration of Helsinki, and an ethical committee was consulted for this retrospective study [1, 4]. Patient anonymity has been carefully protected and data analysis was performed with prior informed consent. This study meets the ethical standards of the journal [25].

ACS

ACS was prepared with venous blood drawn using the Orthokine device (EOT®II-syringe, Orthogen Lab Services, Germany), which contains glass beads. Patients' blood was incubated in the device for 6 h at 37 °C. The conditioned, cell-free serum was then recovered by centrifugation and injected into the patient at weekly intervals [18, 43].

Data generation

All patients were routinely examined clinically by MRI and the self-administered Oxford Knee Score (OKS) questionnaire, which consists of 12 questions [2]. The answers are scored from 0–4 (range from 0–48; worst–best). The recommended scoring system for OKS includes a sub-analysis for a functional score and a pain score [3]. The functional subscore consists of OKS questions 2, 3, 7, 11, 12 (highest possible summed score of 20). Examples for the questions for the functional subscore included 'Could you kneel down and get up again afterwards?', 'Could you do household shopping on your own?', and 'Could you walk down a flight of stairs?'. The OKS pain subscore consists of OKS questions 1, 4, 5, 6, 8, 9, 10 (highest possible summed score of 28), examples of which are 'How would you describe the pain you usually have in your knee?', 'For how long are you able to walk before the pain in your knee becomes severe?', and 'How much has pain from your knee interfered with your usual work (including housework)?' [2]. OKS questionnaires were completed before start and again after 6 months of treatment. Data of patients diagnosed with meniscal defect were selected for analysis. For analysis, subscores were standardized from 0–100 by multiplying OKS function by 5 and multiplying OKS pain by 3.57 [3].

MRIs were retrospectively evaluated by an independent radiologist using the Boston Leeds Osteoarthritis Knee Score (BLOKS) [19, 32]. In addition, patients were asked for a subjective evaluation of pain and function, and responses were classified as pain free, mostly pain free, undecided, dissatisfied/unchanged, no/unclear information (for pain); fully functional, mostly functional, improved, unclear information (for function).

Statistics

Data were tabulated using MS Excel, which was also used to produce basic statistics and graphs. Based on the data for all patients before and after treatment, paired t-tests (2-sided) and effect sizes with 95 % confidence intervals (CI) were computed using programs written in Visual Basic for Applications by S. Cleveland. The effect size (Cohen's d) is a dimensionless measure of change due to an intervention and is independent of sample size. It is computed as the difference between pre- and post- treatment, divided by the common standard deviation of these groups. Cohen's d is expressed as small (0.2–0.5), medium (0.5–0.8), large (0.8–1.2), very large (1.2 –2.0) [12].

Results

A total of 47 outpatients (male/female 32/15; mean age 49.4 years [range 21–83]) with knee pain, and diagnosed with meniscal lesions, were included in this analysis (▶ **Table 1**). Patients presented over a period of 4 years. All patients reported knee pain (left/right/both 18/26/3) of diverse etiology (9 with trauma, 36 without trauma, 2 unclear) and duration (1 day– > 1 year). 89 % of selected patients showed retropatellar cartilage defects (▶ **Table 1**). The mean total number of weekly injections with 2 mL ACS each was 5.2 (range 3–8), and 42 patients had a femoropatellar cartilage defect. Five patients requested meniscal surgery (10.6 %) and 3 patients (6.4 %) were lost to follow-up. The remaining 39 patients (83 %) completed the OKS

▶ **Table 2** OKS and BLOKS at baseline and after 6 months of ACS treatment.

	Summed OKS Score				BLOKS			
	Baseline n = 39	**6 months n = 39**	**p-value**	**Effect size d**	**Baseline n = 40**	**6 months n = 40**	**p-value**	**Effect size d**
Mean (SD)	29.2 (9.1)	44.3 (4.3)	< 0.001	2.13	0.81 (0.35)	0.71 (0.39)	< 0.001	0.28
Median (min, max)	30 (11, 47)	46 (31, 48)	–	–	0.83 (0.17, 1.67)	0.67 (0, 1.67)	–	–
ACS: autologous conditioned serum; BLOKS: Boston Leeds Osteoarthritis Knee Score; OKS: Oxford Knee Score; SD: standard deviation								
The OKS score consists of 12 questions for evaluation of functional and pain symptoms, each scored out of 4. The best possible score is 48. All OKS questions are answered according to severity grade: None [4], Very mild [3], Mild [2], Moderate [1], Severe [0]								

▶ **Table 3** Function and pain OKS subscores at baseline and after 6 months of ACS treatment.

	OKS Function Score *				OKS Pain Score *			
	Baseline n = 39	**6 months n = 39**	**p-value**	**d**	**Baseline n = 39**	**6 months n = 39**	**p-value**	**d**
Mean (SD)	65.4 (18.7)	92.6 (10.1)	< 0.001	1.81	57.1 (20.8)	92.0 (8.5)	< 0.001	2.20
Median (min, max)	65 (35, 100)	95 (60, 100)	–	–	60.7 (10.7, 96.4)	96.4 (67.9, 100)	–	–
ACS: autologous conditioned serum; OKS: Oxford Knee Score; SD: standard deviation								
All OKS questions are answered according to grade: None [4], Very mild [3], Mild [2], Moderate [1], Severe [0]								
The OKS functional subscore consists of questions 2, 3, 7, 11, 12; highest possible score = 20. The OKS pain subscore consists of questions 1, 4, 5, 6, 8, 9, 10; highest possible score = 28								
* Normalized: Both pain and function subscores were normalized to 0–100 (0 = worst, 100 = best) by multiplying OKS function by 5 and multiplying OLS pain by 3.57								

before and after 6 months of ACS treatment. The mean summed OKS score (SD) at baseline was 29.2 (9.1), increasing significantly to 44.3 (4.3) after 6 months of ACS treatment (34 %, p < 0.001). Cohen's d was very large (2.1 [95 % CI 1.4–2.8]) (▶ **Table 2**).

The OKS functional subscore increased from 65.4 ± 18.7 to 92.6 ± 10.1 (29 %, p < 0.001), Cohen's d 1.81. OKS pain subscore increased from 57.1 ± 20.8 to 92.0 ± 8.5 (38 %, p < 0.001), Cohen's d 2.20 (▶ **Table 3**).

MRI BLOKS score was available for 40 patients both at baseline and after 6 months of treatment. Of these patients, 17 (49 %) had improved scores at 6 months, 17 were unchanged, and 1 patient had a worse score. Overall, the mean score decreased from 0.81 to 0.71 (p < 0.001, paired t-test), but with a small Cohen's d of 0.28 (95 % CI 0.17–0.39) (▶ **Table 2**).

Subjective pain and function evaluation was not available for all patients. Of the available statements, 27/47 reported being pain-free and mostly pain-free, and 31/39 reported being fully functional and mostly functional (▶ **Table 4**).

▶ **Table 4** Patients' subjective evaluation of pain and function.

Evaluation	Statement	Patients (n [%])
Pain	**Statement available**	**47**
	Pain-free	22 (46.8)
	Mostly pain-free	5 (10.6)
	Undecided	6 (12.8)
	Dissatisfied/unchanged	7 (14.9)
	No information	7 (14.9)
Function	**Statement available**	**39**
	Fully functional	21 (53.8)
	Mostly functional	10 (25.6)
	Improved	2 (5.1)
	Unclear information	6 (15.4)
Surgery	**Statement available**	**47**
	Not required	39 (83.0)
	Surgery performed	5 (10.6)
	No information	3 (6.4)

Discussion

Meniscal abnormalities in asymptomatic patients have been previously described [30]. Although a long-term correlation between meniscal lesions and cartilage degeneration, with and without surgical intervention, appears established [17, 26], surgical intervention for meniscal lesions has been under critical review for some time [27–29, 36, 38, 40]. Publications speculating on the potential of biological augmentation of meniscus therapy have popularized less invasive procedures, and research on biological therapy for meniscal lesions has been performed by several groups. Approaches include recombinant growth factors, stem cells of different origin (e. g., fat, bone marrow), PRP and, as discussed here, ACS. Furthermore, combinations of surgical repair plus subsequent biological augmentation have been discussed in the literature [35]. In a case-control study of patients under 40 years of age, Pujol et al. [37] showed a moderate difference after 12 months between groups of open surgery meniscal repair with or without augmentation, in favor of PRP, using the Knee injury and Osteoarthritis Outcome Score (KOOS), the International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form and MRI. Griffin et al. [24] reported a case-control study of PRP-augmented and non-augmented arthroscopic meniscus surgery, with no significant differ-

ence between the two groups at 24 months post-surgery. In this case, the main measurement instruments were IKDC and the Tegner-Lysholm score. In a randomized clinical trial, Vangsness et al. [42] compared injections of allograft mesenchymal stem cells (MSC; 50×10^6 cells vs. 150×10^6 cells vs. vehicle control) following partial medial meniscectomy. Using a visual analog scale, they showed intra-group symptomatic improvement and a statistically significant difference in pain between MSC groups and the control group at 24 months. The Tegner-Lysholm score improved significantly in all groups (17–19 patients in each), however no statistically significant differences were detected between groups. For a recent review of meniscus repair using MSC, see Yu et al. [45]; case reports of single cases have also been published [15], and a clinical trial combining surgical meniscus repair with PRP was announced in 2009, but aborted ahead of recruitment [11].

No final assessment has been reached regarding biological augmentation in meniscal repair; nevertheless, a biological approach is thought to have potential in this indication.

Results of an animal study indicated a significant clinical and histologic improvement in osteoarthritis-affected joints of horses following treatment with ACS, compared with placebo treatment [21]. A recent publication by de Girolamo et al. discussed the possible involvement of the blood/bone marrow-derived growth factor PDGF (platelet-derived growth factor; a major component of both PRP and ACS [43]) in improved meniscal healing associated with anterior cruciate ligament (ACL) reconstruction surgery [13]. In vitro studies showed that growth factors including PDGF, TGFb1, IGF1, bFGF and EGF may play a beneficial role in meniscal cell or tissue development [39]. The standardized production and resulting composition of ACS have been described [43, 44], however, to name one compound as the active component of ACS would be speculative; it is possible that there may be further known and unknown blood components involved, such as extracellular vesicles (exosomes) and their contents.

ACS is a complex mixture of biologically active signaling substances, with the preparation method optimized for anti-inflammatory and pain-reducing clinical action, which avoids some of the drawbacks associated with intra-articular PRP injections [43]. Published data show that platelets, as found in PRP, can exert strong pro-inflammatory effects in joints [9], such as complement activation [14] and release of Interleukin-1 (IL-1) [31, 41]. Plasma injections may lead to joint problems, resulting in intra-articular coagulation with associated complications, such as the necessity of clot removal by proteinases (e. g., plasmin) possibly damaging articular collagen [23]. Mice expressing an anticoagulant pro-thrombin protein are partially protected from collagen-induced arthritis. This supports the interpretation that clot formation in a joint, as seen with PRP injections, may have negative effects [20].

Elevated concentrations of biologically active – and potentially regenerative – components in cell-free ACS generated according to standard specifications have been reported [43]. Intra-articular ACS injections have been shown to be effective in OA [8, 22] and radicular pain [8]. Interestingly, ACS has also been described to have positive effects on tendon repair [33] and muscle healing [44]. ACS treatment success of knee OA may be independent of OA grade, age or BMI [5]. Taken together these results lend support to the hypothesis that augmentation of meniscus regeneration may be a clinical target for intra-articular injections of ACS.

In this retrospective data analysis, the improvement in symptoms shown by OKS correlates with a structural improvement in 49 % of patients seen using the BLOKS MRI evaluation. There is a small but significant ($p < 0.001$) improvement in MRI-based meniscus morphology over all patients. Further examination should reveal a possible correlation with injury types more or less likely to respond. It remains to be shown in controlled studies if this effect can be reproduced and whether it is superior to other therapies. The OKS pain improvement is more pronounced than the OKS functional improvement. This is consistent with the WOMAC results from a previous study [5]. Regeneration of fibrous tissues such as tendons/ligaments is notoriously slow, and it is possible that to show on MRI regenerative/reparative effect caused by ACS requires longer than 6 months. Moreover, the possible effect of physiotherapy cannot be evaluated from this set of results and it should be considered that patients may prematurely return to their usual sports activities, due to their reduced pain, thereby jeopardizing tissue healing.

Limitations

This is an unblinded, uncontrolled retrospective case analysis with a small number of patients. The degree and type of meniscal lesions and the number of injections were not standardized, and the follow-up period was short (6 months). Such cohorts are representative of what is found in "real-world" practice and, since the mean OKS improvements are much higher than the MCID of 5.0, controlled studies are justified to validate these findings. Additionally, studies are recommended to determine if postsurgical ACS may improve healing of complex meniscal tears following arthroscopic meniscal repair.

Due to the lack of a control group in this retrospective case analysis of routine patients, the possibility of a placebo effect contributing to the results needs to be acknowledged. Osteoarthritis injection therapy studies have demonstrated that a placebo effect could contribute to approximately 20–30 % of parameter improvement [6], whereas in this study, OKS score improvements range from 29–38 %, so there is reasonable evidence that the improvement is most likely not simply due to a placebo effect.

Conclusion

The data presented here are derived from a retrospective analysis of an uncontrolled case series. The mean magnitude of OKS improvement in this study is ~15 points, higher than the minimally detectable difference (MID) of 4.15 points previously published [7], but comparable to that reported by Clement et al. [10]. Although spontaneous healing can occur in meniscal injuries, an effect of the magnitude like the one reported here is most likely not attributable to a spontaneous process, and the prevention of surgery in the majority of patients (83 %) during 6 months of follow-up is meaningful.

A randomized, controlled clinical study is required to generate further evidence for the ability of ACS to contribute to meniscal repair; however, this retrospective cohort study implies that intra-articular ACS injection may be an effective treatment option for knee pain associated with meniscal lesions.

Conflict of Interest

The author declares no conflict of interest.

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