Arthrozheal®, a Bioactive Fibrin Scaffold for Joint Cartilage, Tendon and Soft Tissue Lesions. Latest Results and Application Perspectives

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ABSTRACT

Treatment of articular cartilage, tendon and soft tissue damage remains a challenge for the practicing orthopaedic surgeon. Due to the multifactorial aetiology of these lesions, there is a narrow therapeutic window within which they can be treated successfully, thus preventing progression to other musculoskeletal tissues. Recently, a new material that combines platelet-rich fibrin with collagen and is applied as a gel scaffold (ArthroZheal®, Vivostat A/S, Allerød, Denmark) has been shown to provide unique results in these patients.

We arthroscopically treated 210 patients (114 knees, 32 hips, 52 shoulders, 12 ankle joints) with ArthroZheal®. The basic idea was to adjust treatment to the individual patient and to repair related and/or contributing problems before or along with treatment of chondral/tendon/ligament injuries. Arthroscopy was our preferred surgical method; the goal was to restore and preserve function, alleviate pain and minimise progression to osteoarthritis. We excluded cases of inflammatory arthropathy, unstable or malaligned joint, "kissing lesions" (bipolar), infection, obesity, massive rotator cuff rupture and multiligament instability.

Our results were more than promising. We observed improved mobility in 93%, reduced pain in 95% at 3 months and further improvement at 6 months, with near-normal ROM (97%) and pain-free status (98%). The MRI at 12 months post application showed cartilage restoration/reformation in 94% of patients, improved cartilage quality (84%)—by 2nd-look arthroscopic confirmation—and normal tendon or ligament reconstruction (without stitching of the affected area)(95%). We were concerned about bone marrow oedema and rehab compliance among elderly patients.

For successful regeneration of tissue lesions and osteochondral defects, natural gel bioscaffolds, combined with platelet rich fibrin (PRF) with chondroinductive and osteoinductive growth factor stimulators (ArthroZheal®) are required. There is no "gold standard" in the treatment of cartilage defect/tissue lesions or preferred

treatment option. Many algorithms are used, which mostly rely on the surface area of the defect/site of lesion and on surgeon experience. An important issue is that rehabilitation depends on the treatment mode used and on the defect/lesion characteristics (classification and qualification). While a return to functional work and sports is possible with all procedures, different lengths of time are needed.

INTRODUCTION

Treatment of articular cartilage lesions as well as tendon and soft tissue damage remains a challenge for the practicing orthopaedic surgeon.[1-3] A wide range of options are currently available, ranging from conservative measures to various types of operations and, recently, the use of growth factors, cell-based techniques and emerging gene therapies.[2] Operative methods vary from simple arthroscopic interventions to marrow tapping techniques, osteochondral auto/allo-grafting, and cell-based and platelet-rich fibrin application therapies.[4-7] At present, autologous cell therapies, growth factor techniques, stem cells and biomaterials offer promising avenues of research to find clinical answers.[6-12]

There are two distinct chondral injury phenotypes according to the contributing factors: focal lesions and degenerative lesions. Focal lesions are well-delineated defects, usually caused by trauma, osteochondritis dissecans or osteonecrosis.[4,9,13,14] Degenerative defects are typically poorly demarcated and are usually the result of ligament instability, meniscal /soft tissue injuries, malalignment or osteoarthritis.[5,11,12,15]

Trauma is the most common cause of osteochondral lesions in sports injuries or accidents. Shearing force creates a stress fracture through the cartilage matrix, and sometimes through subchondral bone. For example, patellar dislocation leads to osteochondral fracture through this mechanism and is responsible for 40–50% of osteochondral lesions around the femoral condyles.[10,14]

Due to their multifactorial aetiology, there is a narrow therapeutic window within which these lesions can be treated successfully, thus preventing progression to other musculoskeletal issues. Recently, a new material that combines platelet-rich fibrin with collagen and is applied as a gel scaffold (ArthroZheal®, Vivostat A/S, Allerød, Denmark) has been shown to provide unique results in these patients.[5,6,16-18]

The purpose of the present study was to evaluate the use of a bioactive fibrin scaffold-ArthroZheal®-for use with all of the above lesions and discuss its future potential applications.

METHODS

This study was approved by the institutional scientific board and ethics committee, and all participants provided their informed consent.

We arthroscopically treated 210 patients (mean age 42y) with ArthroZheal®. Group 1 consisted of 114 knees (54F/60M; 55R/59L) with cartilage lesions and meniscus partial tears, Group 2 had 32 hips(20F/12M; 20R/12L) with labral tears and cartilage lesions, Group 3 had 52 shoulders (31F/21M; 35R/17L) with rotator cuff tears and humeral head cartilage lesions, and Group 4 had 12 ankle joints(3F/9M; 4R/8L) with ligament tears, Achilles

Table I
Patient Demographic Data; PRF application

Total Cohort (n)	210
Female (n)	108
Male (n)	102
Age (y)	42.0
Body mass index (kg/m^2)	28.7
Time from trauma to surgery (weeks)	4.2

Data represent means unless otherwise indicated. PRF, platelet-rich fibrin

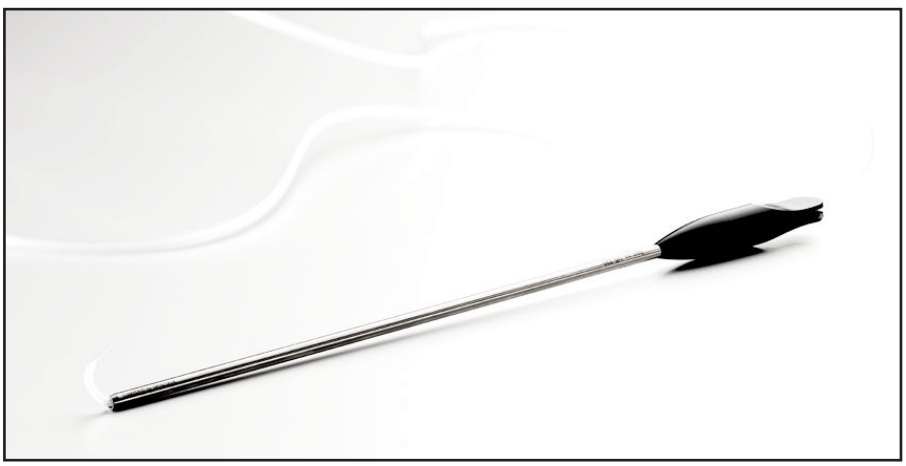

Figure 1. Spray pen applicator with tip.

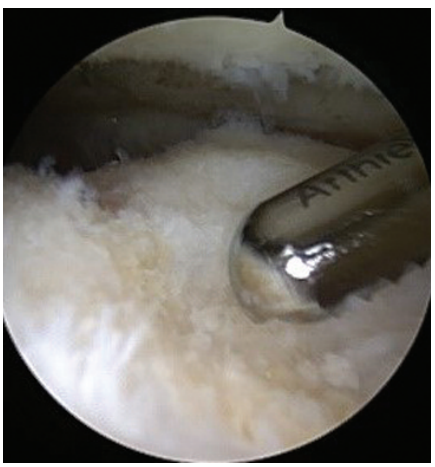

Figure 2. Preparation of the lesion site and dried joint.

tendinopathy and talus cartilage lesions (Table I). The basic idea was to adjust treatment to suit the individual patient, and to address related and/or contributing problems before or along with the treatment of chondral/tendon/ligament injuries. Arthroscopy was our preferred surgical method and was performed by the same senior surgeon in all cases; the goal was to restore and preserve function, alleviate pain and minimize progression to osteoarthritis. We excluded cases of inflammatory arthropathy, unstable or malaligned joint, "kissing lesions" (bipolar), infection, obesity (BMI>32), massive rotator cuff ruptures or multi-ligament instabilities.

120 mL of blood was drawn in the OR after induction of anaesthesia, to prepare the ArthroZheal®, and before antibiotic prophylaxis. The ArthroZheal® device is a closed system that consists of a preparation unit and a processor unit. The blood aspirate is placed in the automated preparation chamber and, after approximately 30 min, an autologous PRF solution is ready for application. A mixture of PRF/collagen polymerizes immediately upon application by a simple change in pH at the tip of the spray pen (Fig. 1). At the end of each arthroscopic procedure in all groups, joints were dried and emptied of arthroscopic fluid (Fig. 2), and PRF (5-6 mL) was sprayed using a special application device (Fig. 3) , which is part of the ArthroZheal® system, over the lesion site (cartilage, tendon or ligament) and also in areas where bleeding was expected (Fig. 4).

SPSS software (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. The Student t-test was used to evaluate the significance of differences in quantitative variables between groups.

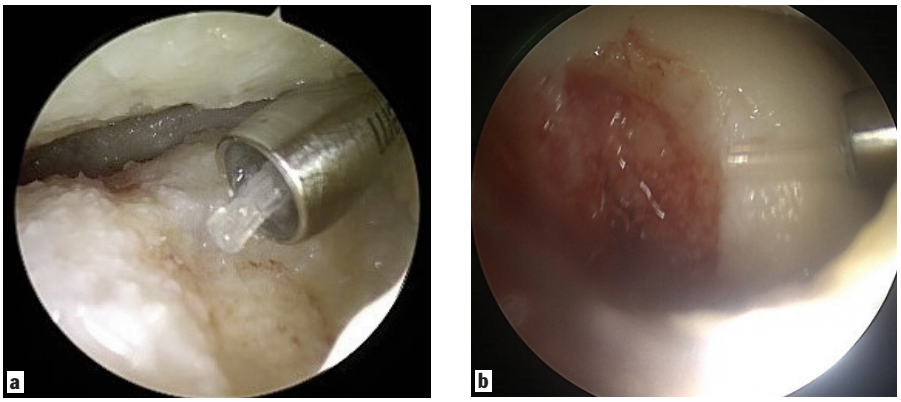

Figure 3. (a,b) ArthroZheal© System applicator device (Vivostat A/S, Allerød, Denmark).

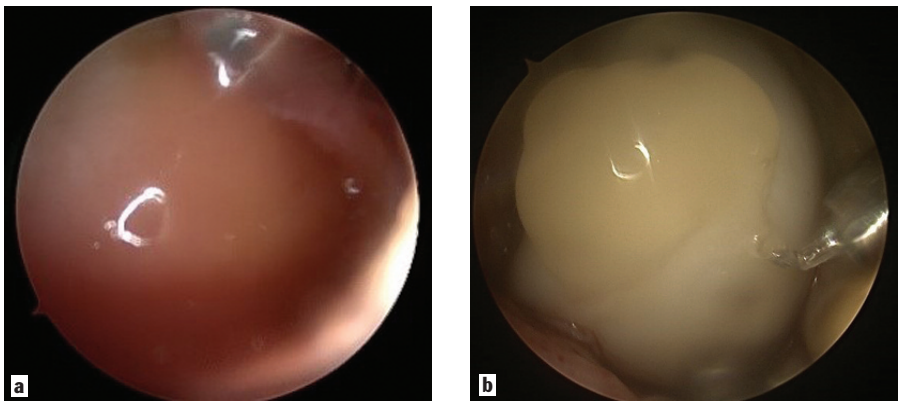

Figure 4. (a) ArthroZheal© gel bubble formation and (b) filling of the lesion site.

Data are expressed as mean ± SD. The chi-square test and Fisher exact test were used for the analysis of categorical variables where appropriate. A P value <.05 was considered statistically significant.

RESULTS

Patients were assessed at 3, 6 and 12 months follow-up. Overall, the mean operating room time was 69 minutes. In all groups, mobility improved was seen in 93% of patients. Pain was reduced in 95% of patients at 3 months and reduced further at 6 months, with near-normal ROM in 97% and pain-free status in 98% (Fig. 5). The MRI at 12 months post application showed cartilage restoration/reformation (94%) (Fig. 6), improved cartilage quality (84%)-as confirmed by 2nd-look nano-arthroscopy in Groups 1 and 3-and normal tendon or ligament reconstruction (95%) (without stitching of the affected area). We were concerned about bone marrow oedema (15% in Group 1 and 5% in Group 4)

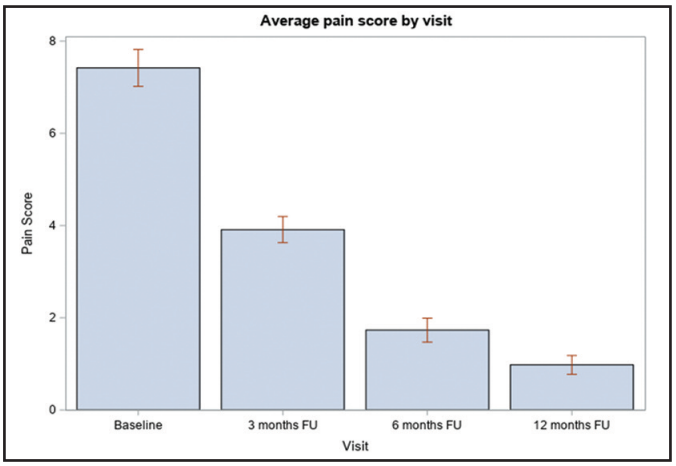

Figure 5. Average pain score over time.

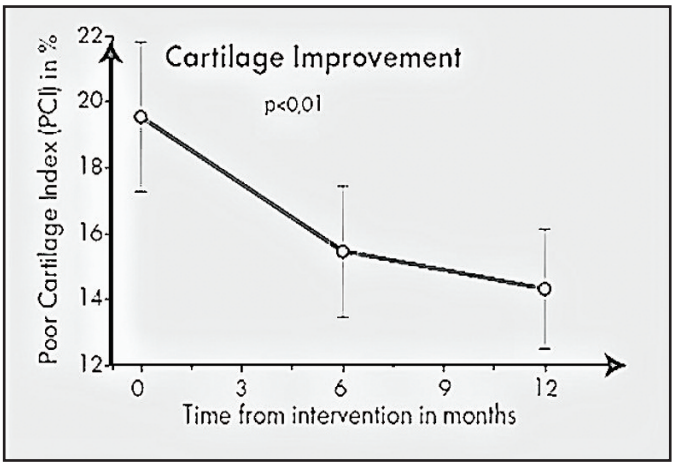

Figure 6. Improvement in cartilage over time.

Table II
Adverse Events

		N=210	%
Blood and lymphatic system disorders	Bone marrow oedema	8	4
General disorders and administration site conditions	Application-site erythema Application-site oedema Application-site pain	2 8 2	1 4 1
Musculoskeletal and connective tissue disorders	Tendonitis	2	1

and rehab compliance among elderly patients (age 65>, 30% of all groups) (Table II).

Thus, our results were more than promising. No significant differences in postoperative analgesia requirements were detected between groups. No statistically significant difference between group outcomes was detected in clinical measurements, calculated at the end of the first postoperative year. The IKDC score was used for Group 1, the Oxford hip score was used for Group 2, the Shoulder Pain and Disability index was used for Group 3, and the AOFAS score was used for Group 4. Pain was evaluated using a VAS. Overall, improvements in function, pain, and tissue and cartilage quality were significant at 3 months post-op, and this continued for up to 12 months post-op, with a high patient satisfaction rate.

DISCUSSION

The present results suggest that ArthroZheal® treatment is ideal for the successful regeneration of tissue lesions and osteochondral defects. ArthroZheal® is a natural gel bio-scaffold combined with platelet-rich fibrin (PRF) with chondro-inductive and osteoinductive growth factor stimulators. There is no "gold standard" in the treatment of cartilage defect/tissue lesions or even a preferred treatment option. Many algorithms are used that rely on the surface area of the defect/site of the lesion and on surgeon experience. An important issue is that rehabilitation depends on the treatment mode used and on defect/lesion characteristics (classification and qualification). In all groups, clinical outcomes lead to similar function and stability at 1 year. Platelet-derived growth factors, including TGF-ß, PDGF, and VEGF, have been shown to have positive effects on soft tissue proliferation, neovascularization, healing, and regeneration.[6,15]

A limited number of studies have examined the use of growth factors for cartilage, tendon and ligament reconstruction. Anderson et al.[15,19] demonstrated the effects of osteoinductive growth factors on tendon healing in rabbit models, while Yoshikawa et al.[15,20] reported that the addition of exogenous VEGF to tendon grafts in sheep models promotes angiogenesis and diminishes the stiffness of the grafted tendon.

Evaluation of the integration, restoration and reconstruction of lesion sites is important. Uchio et al.[15,21] conducted an MRI study 2 years after ligament reconstruction, with 2nd-look arthroscopy and histopathology examination.

Sanchez et al.[18] evaluated the morphology of ACL grafts with a platelet-rich plasma preparation rich in growth factors (PRGF) by 2nd-look arthroscopy and reported excellent outcomes in 57.1% of the PRGF group. PRGF-treated grafts had a significantly better maturity index and histological image, together with newly formed connective tissue enveloping the graft in 77.3%.

The PRF-collagen gel that is obtained with the ArthroZheal® system protects against degradation of endogenous fibrogenic factors, facilitating enhanced wound healing.[22] Agren et al.[15,23] demonstrated that the application of PRF reduced MMP-9 by 139-fold while concentrating the presence of a variety of growth factors that enhance tissue regeneration by 1.6- to 75-fold. Moreover, the nonactivated platelets in ArthroZheal® stimulated wound healing far more effectively than the activated platelets in most other platelet-rich plasma products, by enhancing fibroblast differentiation and stimulating their contractile function.[15,24]

PRF is effective in the treatment of talar osteochondral lesions, according to Giannini et al.[4] and Buda et al.[13,15]

This study is the first to show that the application of an autologous PRF-collagen gel scaffold (ArthroZheal®) to different patient groups led to similar successful results. Dry arthroscopy was used with the special ArthroZheal® 5mm arthroscopic applicator. MRI scans for evaluation were used in all cases at 12 months. Fibrin matrix can maintain the platelets in place longer, making it possible to deliver the maximum amount of growth factors to the affected surface. Also, the haemostatic effect of ArthroZheal® should be emphasized. Buda et al.[13] showed that the clotting factors in autologous platelet-rich fibrin regulate intra- and postoperative bleeding, leading to significantly less hemarthrosis. All groups demonstrated an earlier return to sports or special lifestyle activities.

This study has several strong points, including a histological analysis through 2nd-look arthroscopy, evaluation of all groups prospectively, T2 mapping MRI performed in all cases at 12 months and quantification of growth factors through flow cytometry.

On the other hand, there are also some limitations due to the fact that cartilage and tissue regeneration was evaluated by T2 mapping MRI at only a single time point (12 months).

CONCLUSION

Our results suggest that the application of autologous PRF for the treatment of joint cartilage, tendon and soft tissue lesions by means of dry arthroscopy results in better MRI, pain management and functional results at 3 months post-op, and these improvements can persist for up to 12 months. For the good regeneration of tissue lesions and osteochondral defects, chondroinductive (TGF) and osteoinductive (BMP) growth factors and stimulators are required. Concomitant problems, ligament tears and/or ligament instabilities should be treated

before or simultaneously with cartilage resurfacing. There is no "gold standard" in the treatment of cartilage defect/tissue lesions or even a preferred treatment option. Rehabilitation depends on the treatment mode used and on the defect/lesion characteristics (classification and qualification). While a return to functional work and sport is possible with all procedures, this can take different lengths of time. Improved MRI findings can be associated with better clinical outcomes and a reduction in the need for analgesics. ArthroZheal® has a beneficial haemostatic effect, resulting in less postoperative hematoma. STI

AUTHORS' DISCLOSURES

The author declares that there are no conflicts of interest.

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