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Marrow stimulation techniques

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Summary¹ Due to the very low intrinsic activity of human adult cartilage, healing of chondral and osteochondral defects in patients cannot be expected. In treating symptomatic cartilage damage, marrow stimulation methods belong to the most frequently used methods, along with autologous chondrocyte transplantation (ACT) and mosaicplasty. These arthroscopic procedures are generally easy and the marrow stimulation treatment costs relatively little. In recent years, Pridie drilling has been increasingly replaced by the microfracture technique. This modification relies on the same biological principles of promoting resurfacing with the formation of fibro-cartilaginous repair tissue. For the treatment of smaller cartilage defects (< 2.5 cm²), microfracture still remains the first choice for treatment. The clinical results after microfracture in the knee are age dependent. Younger and active patients (< 40 years) with smaller isolated traumatic lesions on the femoral condyles have the best long-term results. The deterioration of the clinical results begins after 18 months and is significantly more pronounced in older patients with defects on the patella-femoral joint and tibia. The inferior quality of the repair tissue, partially incomplete defect filling and new bone formation in the defect area seem to be limitations of these methods. The AMIC® (autologous matrix induced chondrogenesis) technique was developed to enable treatment of larger defects by the application of a collagen Type III/I membrane (Geistlich Pharma, Wolhusen, Switzerland), in particular when cell-engaged procedures such as ACT cannot be used for financial reasons or because it is not indicated. AMIC® seems to be particularly suitable for treating damaged retropatellar cartilage, which is an advantage because these defects can be hard to treat with standard microfracturing alone. The results of the ongoing studies are awaited to establish whether better results with this technology are achievable in the long term.

Introduction

The use of magnetic resonance tomography has clearly simplified the diagnosis of joint cartilage damage. With the help of cartilage-specific sequences, eg, flash 3-D, a good representation of

the joint surfaces and the subchondral bone plate is possible [2, 5, 27]. Treatment of symptomatic cartilage lesions must be discussed for each patient's individual situation. The response of the organism to damage of the joint cartilage depends on the patient's age as well as on the type and size of the defect. Adults show very low potential for regeneration because the resident differentiated chondrocytes have no mitotic activity. The matrix encapsulated chondrocytes are not able to initiate

¹ Abstracts in German, French, Italian, Spanish, Japanese, and Russian are printed at the end of this supplement.

an effective repair process. Additionally, the cartilage tissue is apparently unable to recruit local sources of progenitor cells at the articular surface and the synovial lining of the joint cavity [10].

The relationship between decreasing numbers of mesenchymal stem cells (MSC) and aging is still unclear [7, 8]. The progression of these defects to osteoarthritis is proven and well documented [26, 35, 40]. Due to the very low intrinsic activity, healing of symptomatic full thickness *chondral* and *osteochondral defects* in adult patients cannot be expected [26]. The treatment of such defects is only successful if the concomitant injuries are treated as well [6, 12, 39].

In treating symptomatic cartilage damage, marrow stimulation methods are among the most frequently used methods, along with ACT and mosaicplasty. These arthroscopic procedures are generally easy and the treatment costs relatively little. In recent years, older techniques such as Pridie drilling [31] or abrasion [18, 19, 20] have been increasingly replaced by the *microfracture technique* [32, 37, 38]. All marrow stimulation methods base on the penetration of the subchondral bone plate at the bottom of the cartilage defect. Different instruments such as the bent awls used in microfracturing create persisting holes in the bone plate. The outflowing bone marrow blood contains the pluripotent stem cells (hMSC) which are stabilised by the clot formation in the defect. The number of these highly proliferative stem cells during this procedure is very low and the concentration in the bone marrow is age dependent [7, 8]. The hMSC which are able to differentiate into fibrochondrocytes, result in fibrocartilage repair with varying amounts of type I, II and III collagen [32, 34, 35, 37, 40].

All the different bone marrow stimulation techniques rely on the same biological principles of promoting resurfacing with the formation of fibrocartilaginous repair tissue [Fig. 3] with inferior biomechanical qualities [1, 18, 19, 20, 30]. The method can be applied in smaller isolated cartilage defects (1–3 cm²) in young, active patients. Meanwhile, use of this technique in joints other than the knee has been published, ie, in the shoulder, hip and ankle [3, 9, 36].

The mechanism of the repair tissue formation using the microfracture technique is based on the activation of an endogenous stem cell pool [16, 3, 38]. The human mesenchymal stem/progenitor cells (MSPC) are located in the bone marrow in low concentration. They are pluripotent and the precursors for marrow stroma, bone, cartilage, muscle and connective tissues. The potential of human mesenchymal stem cells (hMSC) to differentiate

into various types of mesenchymal tissue, such as chondrocytes, makes them a potential cell source in cartilage repair. Adult human mesenchymal stem cells have been derived from a variety of tissues and have shown the potential to participate in repair processes in vivo and in vitro. This tissue formation has been the subject of numerous animal studies that observed the formation of a fibrous cartilage with diminished biomechanical and limited long-term qualities [15, 16, 28, 32, 33, 35]. Clinical studies in humans showed viable results for the Pridie drillings and the abrasion arthroplasty [13, 25, 31]. Clinically, clearly superior results were published by Steadman for microfracturing [37, 38]. The potential to repair damaged or diseased tissues with an autologous cell source has resulted in a great deal of interest in these cells to provide the basis for strategies in regenerative medicine.

The AMIC[®] (autologous matrix induced chondrogenesis) technique was developed to enable treatment of larger defects by application of a collagen Type III/I membrane (Geistlich Pharma, Wolhusen, Switzerland), particularly when cell-engaged procedures such as ACT cannot be used for financial reasons or because they are not indicated [1, 4]. AMIC[®] is particularly suitable for treating damaged retropatellar cartilage and has become a real alternative, since these defects can be hard to treat with standard microfracturing alone. Our own first pilot cases were done in Freiburg in 2000 and showed good clinical results. A complementary animal study using a sheep model originated from the Nehrer study group in Vienna. In this direct comparison of ACT technology with AMIC[®], the histological superiority of ACT was demonstrated [11].

Microfracturing technique

The destroyed and unstable cartilage is removed arthroscopically in a first step, carefully using the shaver, curette and spoon. In particular, the tidemark zone should not be disturbed and the cartilage should be prepared resulting in a well-contained defect. Microfractures are generated with specially bent awls (Karl Storz[®], Zimmer[®]) by creating V-shaped perforation holes with a diameter of 1.5–2 mm at a distance of 3 mm (3–4 holes/cm²) [Fig. 1]. After shutting off the water influx, bone marrow bleeding from the perforation holes can be checked. In isolated cases, re-reaming of the perforations may be necessary [Fig. 2]. Protruding osseous particles must be removed carefully with the shaver. Insertion of a drainage tube without suction completes the procedure.

AMIC®-Technique

Using minimal open knee surgery with a standard small anterior approach, the destroyed and unstable cartilage is removed using a scalpel, curette and spoon, until a well-contained defect results. Utilising microfracture instruments, V-shaped perforation holes with a diameter of 1.5–2 mm at a distance of 3 mm (3–4 holes/cm²) are created. An imprint of the defect is taken using an aluminium template. The Chondro-Gide® collagen membrane is cut slightly smaller than this template. Application of ringer salt solution to the membrane will later increase the size by approximately 10%. The membrane can be placed precisely with the rough side to the preserved bone plate using fibrin glue (*Tissucoll; Baxter, Vienna*). To prevent delamination, laying the membrane edges over the rim of the cartilage should be avoided. A mixture of commercial fibrin and autologous serum can also be used according to [4]. If the defect is

too large for gluing or the location of the defect is critical from a biomechanical point of view, sutures (6/0 PDS II Ethicon) can be easily used [Fig. 5]. The stable position of the membrane can be established by bending and extending the knee five times. The tourniquet may then be opened if the membrane is still in place. Insertion of a drainage tube, careful haemostasis and suturing of the wound complete the surgery.

Rehabilitation following microfracturing/AMIC®

Rehabilitation begins with 24 hours of bed rest and fixed full-leg extension. Starting on the first post-operative day, mobilisation of the patient includes walking with light foot contact for approximately 6 weeks. The range of motion during this time period



Fig 1: Perforation of the subchondral bone plate during a microfracture procedure.



Fig. 3: Repair tissue one year after microfracture.



Fig 2: Outflow of bone marrow blood after microfracture.

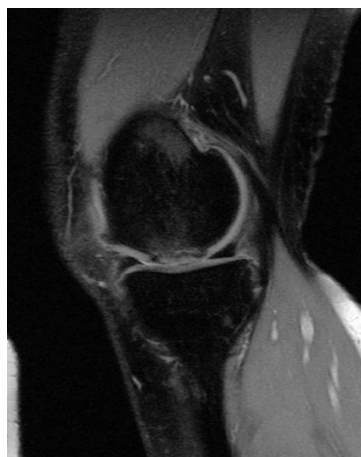


Fig.4: New bone formation in the completely filled defect on the medial condyle one year after microfracture.

is limited as a function of the defect localisation (typically 0/0/90° for the femur condyle/tibia; 0/0/30°, 0/0/60° and 0/0/90° for patella/trochlea, increasing in 2-week steps, respectively). Physiotherapy three times a week with isometric muscle activation and exercises in a closed chain are our standard. Low molecular weight heparin and lymphatic drainage are important in the patient's postoperative management. 6 hours of CPM daily are necessary. This plays an important role in the resulting quality of the repair tissue [32, 37]. After the initial 6-week period with partial weight bearing, the patients increase loading up to full body weight over a further 2 weeks. As would be expected, intensive muscle and coordinative training are required.

Results and discussion

Steadman [38] produced good and very good clinical results in his microfracture study using the Lysholm, Tegner, WOMAC and SF-36 scores with a follow up of 7–17 years (mean 11 years). The average defect size was 2.7 cm² in 72 patients. In this study, only young patients with smaller (< 4 cm²) traumatic cartilage damage were treated. Unfortunately, follow up MRIs and second-look histology were absent in this study of selected patients and no cartilage sensitive score such as proposed by the ICRS (Internationally Cartilage Repair Society) was used.

In the cohort study of Miethöfer [29], clinical and MRI results were analysed in 52 patients over a period of up to 48 months. The average defect size was

4.8 cm². In contrast to the Steadman study, Miethöfer used the ICRS Score for the clinical evaluation. The results showed, that after an initial improvement up to 18 months, the clinical outcome decreased between 18–36 months. In addition to the deterioration of the ICRS score after 18 months, almost half the patients had incomplete defect filling in the MRI and 25% showed new bone formation in the defect [Fig. 4].

In our prospective cohort study [23, 24], with the currently highest number of patients, we also used the sensitive ICRS score and the modified Cincinnati score for patient evaluation. We showed results similar to Miethöfer [29] in our own study of 85 patients with a follow up of 36 months. [23, 24]. Both scores revealed significant improvement 18 months after microfracturing ($P < .0001$). During the second 18 months following surgery, there was a significant deterioration in the ICRS score ($P < .0001$). In addition, patients over 40-years-of-age presented with significantly poorer clinical results after 36 months than younger patients.

In the evidence level I study by Knutsen [21], there was no significant deterioration of the clinical scores seen after 2 years in the direct comparison between ACT-P and microfracture in treating isolated defects on the condyle. Without using the ICRS score, clinical deterioration was not detectable, just as was seen in the Steadman study. In the ACT group a tendency for better histological tissue quality was seen in the histological scoring system compared to the microfracture group. But the detected differences did not reach a statistically significant level because of a too low number of samples with a drop out rate of 20% of the biopsies in the ACT group (32/40). In the Knutsen study [21] as in the Steadman study [38], a MRI follow up was not done. Incomplete defect filling and new bone formation as it was seen in the MRI Study of Miethöfer [29] and Kreuz [23], was not detected,

A new evidence level I Study by Saris [34] with 118 patients presented completely different results from Knutsen. In this study, the histological tissue quality in the ICRS II Histo Score was shown to be significantly superior in the ACT group after one year compared to the microfracture group [34]. Similar to the Knutsen study, no significant differences in the clinical outcome were seen during the short follow up time.

AMIC® combines microfracturing with the application of a porcine collagen type-III/I, bi-layer matrix to host the MSC and to stabilise the blood clot. AMIC® as a 1-step procedure enables the reasonable treatment of larger (> 2 cm²) cartilage defects. Kramer and co-workers [22] showed that from the unique attachment of a Chondro-Gide® collagen membrane

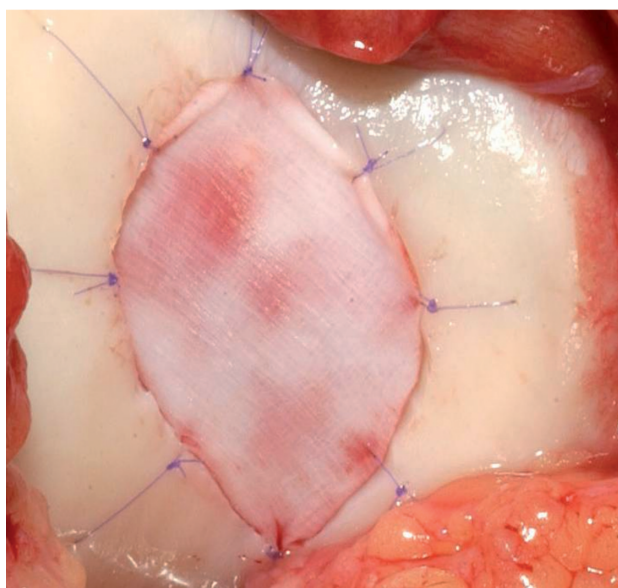


Fig.5: AMIC® procedure on the trochlea.

(Geistlich Pharma, Wolhusen, Switzerland) to the microfractured bone plate, suitable stem cells (hMSC) can be cultivated. With this autologous regenerative approach [22,38], the stem cells (hMSC) available in the bone marrow are brought to the surface by microfracturing and so become available for cartilage repair. The collagen matrix serves as a natural scaffold for cell binding and should stimulate differentiation processes [13]. The first clinical results of 32 patients rating clinical functional improvement, pain reduction and patient satisfaction (ICRS functional status, Cincinnati score, Lysholm score, VES) as well as the demonstrated good defect filling in MRI are promising [1] [Fig. 6]. The outcome was evaluated with a follow-up of 6–24 months. The mean defect size was 3.9 cm² (1.0–6.8 cm²). Microfracturing in combination with a collagen matrix (AMIC[®]) is a minimally invasive, effective technique for the repair of focal cartilage defects of the knee joint.

Conclusion

The clinical results after microfracturing in the knee are age dependent. Younger, active patients (< 40 years) with smaller isolated traumatic lesions on the femoral condyles have the best long-term results. The deterioration of the clinical results begins after 18 months and is significantly more pronounced in older patients with defects on the patella-femoral joint and tibia. For the treatment of smaller cartilage defects (< 2.5 cm²), microfracturing is a good



Fig. 6: Complete defect filling one year after AMIC[®] procedure on the patella.

first line procedure because it is a minimal invasive method which does not interfere with other cartilage repair techniques. The AMIC[®] procedure seems to be a promising, cost effective method with good clinical results in the short term follow up. This procedure possibly enables better clinical long-term results in the treatment of larger cartilage defects of the patello-femoral joint.

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