

Matrix-Augmented Bone Marrow Stimulation With a Polyglycolic Acid Membrane With Hyaluronan vs Microfracture in Local Cartilage Defects of the Femoral Condyles

A Multicenter Randomized Controlled Trial

Johannes Glasbrenner,^{*†} MD, Wolf Petersen,[‡] MD, Michael J. Raschke,[†] MD, Matthias Steiger,[§] MD, René Verdonk,^{||} MD, PhD, Claudio C. Castelli,[¶] MD, Giorgio Zappalà,[¶] MD, Daniel Fritschy,[#] MD, and Mirco Herbort,^{**} MD

Investigation performed at the Department of Trauma, Hand and Reconstructive Surgery, University Hospital Münster, Münster, Germany

Background: Microfracture (MF) is an established operative treatment for small, localized chondral defects of the knee joint. There is evidence from animal studies that matrix augmentation of bone marrow stimulation (m-BMS) can improve the quality of the repair tissue formation.

Purpose: To evaluate the therapeutic outcome of a matrix made of polyglycolic acid and hyaluronan as compared with a conventional MF technique.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: Patients between the ages of 18 and 68 years who had an articular femoral cartilage defect of 0.5 to 3 cm² in the weightbearing area of the femoral condyles with indication for MF were included in this study. Patients were randomized and treated with either MF or m-BMS with Chondrotissue. Defect filling, as assessed on magnetic resonance imaging (MRI), at postoperative 12 weeks was defined as the primary outcome measure, with follow-up MRI at weeks 54 and 108. Follow-up data were also collected at 12, 54, and 108 weeks after surgery and included patient-reported clinical scores: visual analog scale for pain, Knee injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee score, and 36-Item Short Form Health Survey.

Results: MRI scans confirmed cartilage repair tissue formation in both groups 12 weeks after treatment. There was no significant difference between the m-BMS and MF groups in the percentage of defect filling at 12, 54, and 108 weeks postoperatively. No significant difference was found in terms of patient-reported clinical scores. Both groups showed significant improvement in 4 KOOS subscales—Pain, Activities of Daily Living, Sport and Recreation, and Quality of Life—at 54 and 108 weeks after treatment.

Conclusion: This is the first randomized controlled trial comparing m-BMS with a polyglycolic acid matrix with hyaluronan with MF. The use of the Chondrotissue implant in m-BMS has been proven to be a safe procedure. No difference was found between m-BMS and MF in terms of patient-reported outcome scores and MRI assessment until postoperative 2 years. Long-term follow-up studies including histological assessment are desirable for further investigation.

Registration: EUCTR2011-003594-28-DE (EU Clinical Trials Register).

Keywords: cartilage defect; microfracture; matrix-associated bone marrow stimulation

Cartilage defects of the femoral condyles can lead to pain and functional impairment of the knee joint and therefore compromise activities of daily living and quality of life.

Since hyaline cartilage has a low intrinsic regenerative capacity,¹⁹ the surgical procedures for cartilage repair are widely used in orthopaedic therapy.²⁴

Marrow stimulation by subchondral drilling was the first technique described in the literature by Pridie in 1959.²⁸ The opening of the subchondral bony layer leads to bleeding in the cartilage defect, where a blood clot

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containing growth factors is formed and enhances the ingrowth of mesenchymal stem cells (MSCs) from the bone marrow, resulting in a fibrocartilaginous repair tissue formation.²² Steadman et al³⁵ developed the microfracture (MF) procedure using an arthroscopic awl instead of a drill bit to avoid heat necrosis from drilling. Since then, MF has become the first-line treatment for small, localized cartilage defects of the femoral condyle in young and middle-aged patients as a single-stage and low-cost arthroscopic procedure.⁸ A variety of studies have focused on the outcome of MF in femoral condyle cartilage defects, demonstrating improvement in pain relief and knee function as well as high return-to-sport rates in athletes up to 11 years after surgery.^{24,33,34} However, complications such as ossification of the repair tissue, osteophyte formation, lack of defect filling, and deterioration of clinical scores after 5 years were also observed in clinical follow-up studies.^{6,8}

Matrix-augmented bone marrow stimulation (m-BMS) is a single-stage surgical procedure that includes the implantation of a membrane into the cartilage defect after MF.⁴ The membrane is designed to induce ingrowth of MSCs and support the formation of the cartilage repair tissue by providing a scaffold for the initial blood clot.²⁰ Furthermore, the presence of a matrix will protect the subchondral bony layer and reduce the risk of excessive bleeding into the joint after MF.¹⁰

There are different implants available for the m-BMS procedure: (1) ChondroGide (Geistlich Biomaterials) is a porcine-derived type I/III collagen membrane consisting of 2 layers. The porous cell adhesive layer aims to attract MSCs, while the covering cell occlusive layer retains the blood clot inside the cartilage defect.^{4,14,20} (2) Hyalofast (Fidia Advanced Biopolymers) is a porous 3-dimensional structure derived from a semisynthetic hyaluronan acid with variable sizes of interstices to entrap MSCs from the bone marrow.^{2,17} (3) Chondrotissue (BioTissue AG) is a pure absorbable polyglycolic acid and sodium hyaluronate. It has been shown that hyaluronic acid induces chondrogenesis of MSCs.¹⁷ A study in a sheep joint defect model demonstrated that the application of Chondrotissue after MF resulted in hemostasis, protection of the underlying tissue, and improvement in regeneration of the cartilage defect with hyaline-like cartilage tissue formation.¹⁰ A clinical case report has also confirmed favorable outcomes after m-BMS with the Chondrotissue implant.²⁷

Gao et al¹¹ performed a systematic review of the literature on m-BMS and found a paucity of high-quality randomized

controlled studies comparing m-BMS with established MF procedures, resulting in insufficient evidence to recommend m-BMS. Only 1 prospective randomized trial has compared m-BMS with MF,³⁸ therefore suggesting the need for further control studies.

The aim of this study was to evaluate the safety and efficacy of m-BMS with Chondrotissue in comparison with MF treatment alone. The primary hypothesis of this study was as follows: Arthroscopic m-BMS of cartilage defects with Chondrotissue leads to cartilage repair tissue formation after 12 weeks of treatment. The secondary hypothesis was that arthroscopic m-BMS of cartilage defects leads to a better cartilage repair tissue than MF alone as assessed by magnetic resonance imaging (MRI; Henderson score) and patient questionnaires—International Knee Documentation Committee (IKDC), Knee injury and Osteoarthritis Outcome Score (KOOS), visual analog scale (VAS) for pain, and 36-Item Short Form Health Survey (SF-36)—at 12, 54, and 108 weeks after surgery, without increasing rates of adverse events or postoperative morbidity.

METHODS

Study Design

A multicenter randomized controlled prospective open-label study was performed (Table 1). The study was conducted in compliance with the study protocol, good clinical practice regulations, the applicable regulatory requirements, standards EN ISO 14155-1 and EN ISO 14155-2, the MEDDEV 2.7.1 guidelines, and the Declaration of Helsinki and the International Council for Harmonisation. The study was approved by the respective competent authorities and ethics committees and registered with the EU Clinical Trials Register (study ID EUCTR2011-003594-28-DE).

Inclusion and Exclusion Criteria

Patients between 18 and 68 years old with MF indication attributed to a focal cartilage defect of 0.5 to 3 cm² in weight-bearing areas of the femoral condyles were included in this study. An intact subchondral bone with full-thickness loss of articular cartilage or unstable cartilage covering the defect area was noted in all patients on preoperative MRI.

*Address correspondence to Johannes Glasbrenner, MD, Department of Trauma, Hand and Reconstructive Surgery, University Hospital Münster, Albert-Schweitzer-Campus 1, Building W1, 48149 Münster, Germany (email: johannes.glasbrenner@ukmuenster.de).

†Department of Trauma, Hand and Reconstructive Surgery, University Hospital Münster, Münster, Germany.

‡Department of Orthopedics and Trauma Surgery, Martin Luther Hospital Berlin, Berlin, Germany.

§Institute of Clinical Radiology, University Hospital Münster, Münster, Germany.

||Department of Orthopedic Surgery and Traumatology, Ghent University Hospital, Ghent, Belgium.

¶Department of Orthopaedic and Trauma Surgery, ASST Papa Giovanni XXIII Bergamo, Bergamo, Italy.

#Department of Orthopedic Surgery, Geneva University Hospital, Geneva, Switzerland.

**OCM Munich, München, Germany.

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Ethical approval for this study was obtained from the ethics committee at the University of Münster (2007-476-f-S; study code CHOND1001).

TABLE 1
Study Centers Involved in the Randomized Controlled Trial

University Hospital of Münster
Department of Trauma, Hand and Reconstructive Surgery
Albert Schweitzer Campus 1
48149 Münster, Germany

University Hospital of Ghent
Department of Orthopaedic Surgery and Traumatology
Corneel Heymanslaan 10
9000 Ghent, Belgium

ASST Papa Giovanni XXIII Bergamo
Department of Orthopaedic and Trauma Surgery
Piazza OMS 1
24127 Bergamo, Italy

University Hospital of Geneva
Department of Orthopedic Surgery
Rue Gabrielle-Perret-Gentil 4
1205 Geneva, Switzerland

Patients were excluded when 1 of the following was present: osteochondral defects, general osteoarthritis (≥ 2 compartments), defect of the patellofemoral joint, tibial defect > 2 Outerbridge classification, varus and valgus ($> 5^\circ$ in 30-cm 1-leg standing apical radiograph), joint stiffness (flexion $< 90^\circ$), ligamentary laxity or lesion, meniscal lesions with more than one-third partial resection or adjacent to the symptomatic cartilage defect, history of cartilage surgery (osteochondral transplantation, autologous chondrocyte transplantation, matrix-enhanced autologous chondrocyte implantation [mACI]), history of MF in the symptomatic defect or knee surgery (anterior cruciate ligament or meniscal surgery, osteotomy) in previous 6 months, allergic reactions to polyglycolic acid or hyaluronan, chemotherapy or radiotherapy in past 3 weeks, rheumatoid arthritis or Bechterew disease, obesity (body mass index > 30), and pregnancy or lactation.

Enrolled patients were informed about the study, asked for consent, and randomized to 1 of the 2 study arms of MF or m-BMS by envelope randomization. Patients were blinded throughout the study period. Given the operative procedure, the senior surgeon (W.P., M.J.R., R.V., C.C.C., G.Z., D.F., M.H.), who performed the surgery and the follow-up examination, could not be blinded.

Surgical Procedure

In both groups, arthroscopic evaluation and debridement of the femoral cartilage defect were performed, and the presence of intact subchondral bone was macroscopically confirmed. The defect area was measured and perforated with an arthroscopic awl. In the control group (MF), no further operative treatment was performed. In the intervention group, m-BMS was performed via implantation of the Chondrotissue after MF (Figure 1). To restore the elastic properties of the freeze-dried Chondrotissue, the patient's autologous blood serum was used, as prepared from 8 to 15 mL of blood. The implant was cut to fit the size of the defect area, arthroscopically implanted into the defect, and fixed with resorbable pins made of polylactic acid (SmartNail; Conmed).

Rehabilitation Protocol

The rehabilitation protocol was identical in both groups, including early mobilization without weightbearing in the first 6 weeks after operation. Flexion was limited to 60° until the end of the third week and to 90° until the end of the sixth postoperative week to reduce contact pressure in the patellofemoral contact area of the femoral condyles. Two weeks after surgery, swimming and aqua gymnastics were permitted. Cycling was allowed after 6 weeks, running after 6 months, and return to contact sport after 18 months.

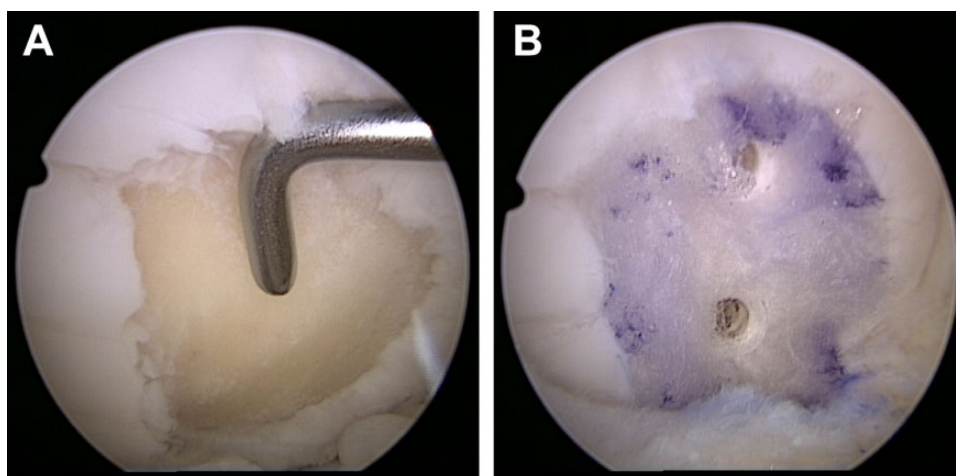


Figure 1. Cartilage defect after (A) arthroscopic debridement and (B) matrix-augmented bone marrow stimulation.

Follow-up and Assessments

All outcome parameters were assessed according to the intention-to-treat-method. The patients were seen at 1, 2, and 6 weeks after surgery for clinical postoperative safety control. Range of motion and events such as effusion, allergic reaction, swelling, redness, and joint stiffness were assessed and classified by the senior surgeon.

Defect filling with cartilage repair tissue was assessed by MRI at postoperative 12 weeks and defined as the primary outcome measure. Further MRI assessment was performed at 54 and 108 weeks after surgery. Clinical outcome scores—KOOS for Pain, Symptoms, Activities of Daily Living, Sport and Recreation, and quality of Life; IKDC for knee function; and VAS for pain—were also obtained at 12, 54, and 108 weeks after surgery. Quality of life was evaluated with the SF-36 score, with emphasis on general health condition.

MRI scans were blinded and evaluated by an experienced radiologist (M.S.) with expertise in traumatology and musculoskeletal radiology. Defect filling was evaluated according to a scoring system by Henderson et al,¹⁸ which consists of 4 subcategories (defect filling, signal intensity, effusion, and edema). Each subcategory is graded from 1 to 4, with lower scores indicating a better result. Different studies have shown a close correlation of the total Henderson score with clinical outcome after cartilage repair procedures in the knee joint.^{5,18}

Statistical Analysis

Data were tested for normality using the Kolmogorov-Smirnov test, and statistical significance was assessed by the nonparametric Kruskal-Wallis test (1-way analysis of variance on ranks). Differences between groups were analyzed with the Dunn post hoc test, while comparisons between 2 groups (delta of scores) were evaluated with the nonparametric Mann-Whitney rank sum test. Significance was accepted if $P < .05$.

A power analysis was performed beforehand and based on a significance level of $\alpha = .05$ with an expected dropout rate of 25%, which yielded the required number of patients ($n = 30$) to achieve a $\geq 80\%$ power to detect a difference in the formation of cartilage repair tissue of at least 25% of the defect size. Sample size calculation was performed on the basis of the expected standard deviations, and differences in efficiency were computed according to histological scores after m-BMS in the ovine model of Erggelet et al.¹⁰

RESULTS

Patient Characteristics

The study was initiated on June 1, 2009, and the final patient follow-up was performed on September 11, 2017. Thirty patients were screened and enrolled in the study. Two patients withdrew their informed consent after surgery. Four patients were lost to follow-up. Therefore, 24 patients were monitored throughout the study (Table 2,

TABLE 2
Patient Characteristics (N = 24)^a

	MF (n = 12)	m-BMS (n = 12)	P
Age, y			
Mean (range)	36.7 (18-51)	47.9 (35-68)	.017 ^b
Median	40.5	46.0	
Sex, No.			
Female	3	6	
Male	9	6	
Body mass index, kg/m ²			
Mean (range)	24.7 (22.2-29.1)	25.1 (22.1-29.6)	.69
Median	24.5	24.5	
Operated site, No.			
Right	5	7	
Left	7	5	
ICRS classification, No.			
III	8	10	
IV	4	2	
Baseline scores, mean \pm SD			
Henderson	2.8 \pm 0.7	3.3 \pm 0.8	.171
VAS for pain	2.4 \pm 2.0	4.8 \pm 2.7	.372
KOOS subscale			
Pain	66.9 \pm 20.9	41.9 \pm 17.6	.006 ^b
Symptoms	71.1 \pm 14.6	50.0 \pm 15.8	.003 ^b
Activities of Daily Living	78.2 \pm 18.9	53.0 \pm 18.8	.003 ^b
Sport and Recreation	43.8 \pm 13.8	31.7 \pm 27.7	.004 ^b
Quality of Life	39.6 \pm 14.2	31.3 \pm 18.3	.115
IKDC	38.0 \pm 10.4	47.8 \pm 15.6	.028 ^b

^aICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; m-BMS, matrix-augmented bone marrow stimulation; MF, microfracture; VAS, visual analog scale.

^bSignificant difference between groups ($P < .05$).

Figure 2). The MRI follow-up rate was 20 of 24 (83%) at 6 weeks, 18 of 24 (75%) at 54 weeks, and 19 of 24 (79%) at 108 weeks postoperatively (Table 3).

The median age in the group treated with m-BMS was 46.0 years (range, 35-68 years), while the group treated with MF was 40.5 years (range, 18-51 years) ($P = .017$). The median body mass index was 24.5 kg/m² in both treatment groups. Cartilage degradation in the defect area was arthroscopically characterized according to the ICRS classification and resulted in 75% of patients with grade III and 25% with grade IV. The mean treated defect size was 1.7 cm² in both groups.

Safety Analysis

There was 1 severe adverse event in each treatment group. In the m-BMS group, an infected hematoma was managed by repeat arthroscopy with joint lavage and administration of specific intravenous antibiotics. Complete recovery from the severe adverse event was achieved, and the patient remained in the trial.

In the MF group, severe pain related to the cartilage defect was reported 1 year after surgery in a 24-year-old

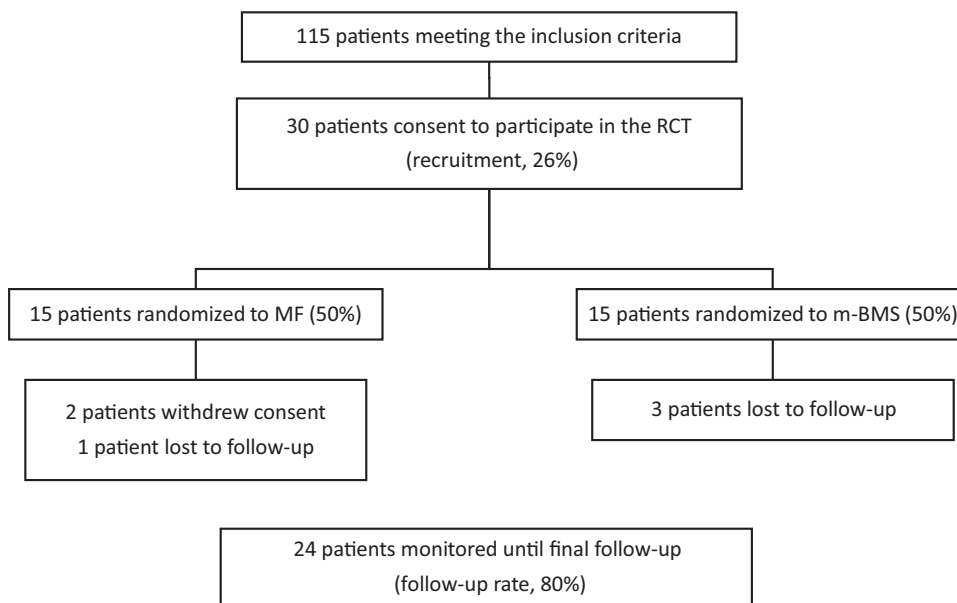


Figure 2. Flowchart regarding inclusion, randomization, and follow-up. m-BMS, matrix-augmented bone marrow stimulation; MF, microfracture; RCT, randomized controlled trial.

TABLE 3
Grade of Defect Filling After MF and m-BMS Treatment at 12, 54, and 108 Weeks Postoperatively^a

Defect Filling, %	MF			m-BMS		
	Week 12	Week 54	Week 108	Week 12	Week 54	Week 108
76-100	3	6	7	1	5	7
50-75	8	2	3	2	4	2
<50	2	0	0	4	1	0
0	0	0	0	0	0	0

^am-BMS, matrix-augmented bone marrow stimulation; MF, microfracture.

man. Repeat arthroscopy revealed instable fibrous cartilage in the original defect, and mACI conversion treatment was initiated. The patient therefore had to be withdrawn from further follow-up.

There was only 1 severe effusion after 6 weeks in the MF group. Mild swelling was present in 3 patients 2 weeks after surgery in the m-BMS group, which vanished after 6 weeks in all cases. There was 1 moderate and 1 severe case of restricted range of motion 1 week after surgery in the m-BMS group, which became a light restriction after 6 weeks, and only 1 case of slightly restricted range of motion remained. Moderate or severe allergic reactions were not observed in both groups.

Defect Filling Assessment Through MRI

MRI scans revealed cartilage repair tissue formation, with no significant difference between the m-BMS and MF groups in terms of defect filling at 12 weeks after surgery. MRI revealed progressive defect filling in both treatment groups (Figures 3 and 4), showing >50% of defect filling at postoperative 108 weeks.

Total Henderson score showed a similar significant ($P \leq .01$) decrease from weeks 12 to 108 in both treatment groups, without a significant difference between groups at each time point. However, the changes in overall Henderson score were significantly higher at week 12 and week 108 in the m-BMS group as compared with the MF group (Figure 5).

Clinical Assessments

There was no significant difference in terms of pain intensity between treatment groups at each follow-up (Figure 6). Nevertheless, as compared with the preoperative situation, patients reported better pain relief at 6, 12, 54, and 108 weeks after treatment with m-BMS in contrast to MF.

The m-BMS group showed a gradual increase in the IKDC score, from 38 points before treatment to 75 points at 108 weeks after treatment (Figure 7). In the MF group, the increase in IKDC score was from 48 to 73 points. Increases in the IKDC scores were significant ($P < .05$) only at weeks 54 and 108 for both treatment groups but not between groups at all follow-up time points.

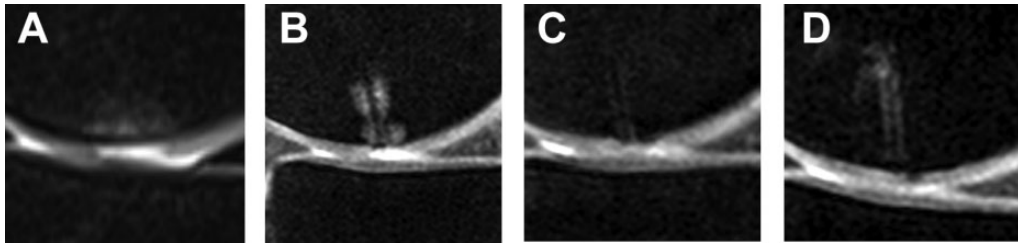


Figure 3. Magnetic resonance imaging scans of cartilage defect filling in the medial femoral condyle: (A) preoperatively and at (B) 12, (C) 54, and (D) 108 weeks after matrix-augmented bone marrow stimulation treatment.

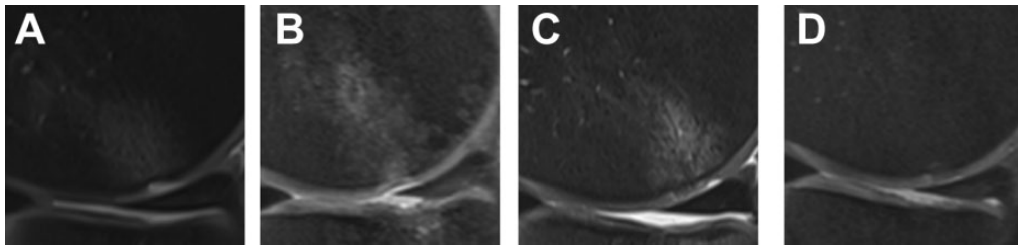


Figure 4. Magnetic resonance imaging scans of cartilage defect filling in the medial femoral condyle: (A) preoperatively and at (B) 12, (C) 54, and (D) 108 weeks after microfracture treatment.

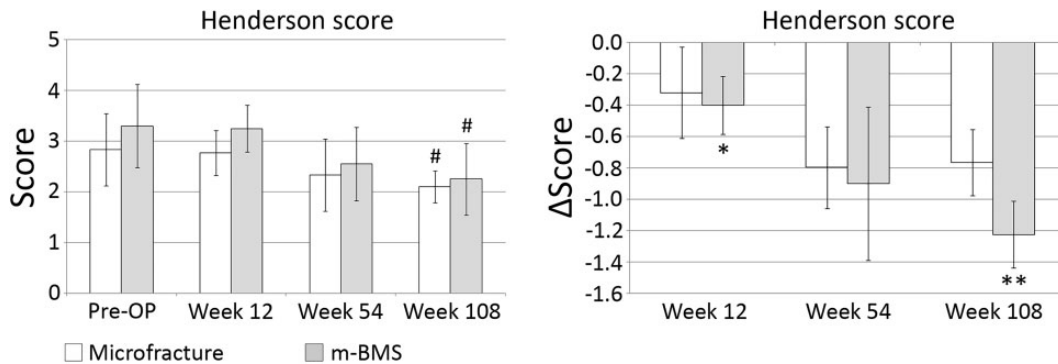


Figure 5. Henderson score and delta score in microfracture and m-BMS treatment groups. Values are presented as mean ± SD. #Significant difference as compared with baseline scores. * $P < .05$ and ** $P < .01$ between groups. m-BMS, matrix-augmented bone marrow stimulation; pre-OP, preoperative.

There was significant improvement over time in both groups concerning the KOOS but not between groups (Figure 8). In the m-BMS group, a significant improvement could be observed at week 54 and week 108 in 4 KOOS subscales: Pain, Symptoms, Sport and Recreation, and Quality of Life. In the Activities of Daily Living subscale in the m-BMS group, a significant improvement was demonstrated at postoperative weeks 12, 54, and 108. The MF group showed a significant increase in 3 KOOS subscales—Pain, Activities of Daily Living, and Sport and Recreation—at weeks 54 and 108. A significant increase in the Quality of Life subscale was observed in the MF group at week 54, with a slight decrease at week 108.

There was no significant difference in SF-36 outcome (general health condition) between treatment groups. Physical functioning was significantly increased in the

m-BMS treatment group in 2 subcategories, physical role limitations and pain relief, at weeks 54 and 108. Treatment with MF did not show a significant improvement in any of the subcategories of physical health. The m-BMS group showed a significant ($P < .05$) increase in social functioning and emotional role limitations after 54 and 108 weeks and at 12, 54, and 108 weeks, respectively. In contrast, MF led to a significant increase in only emotional role limitations after 54 and 108 weeks.

DISCUSSION

The most important finding of the present study was that newly formed cartilage repair tissue was seen as early as 12 weeks after treatment in both groups. However, the results

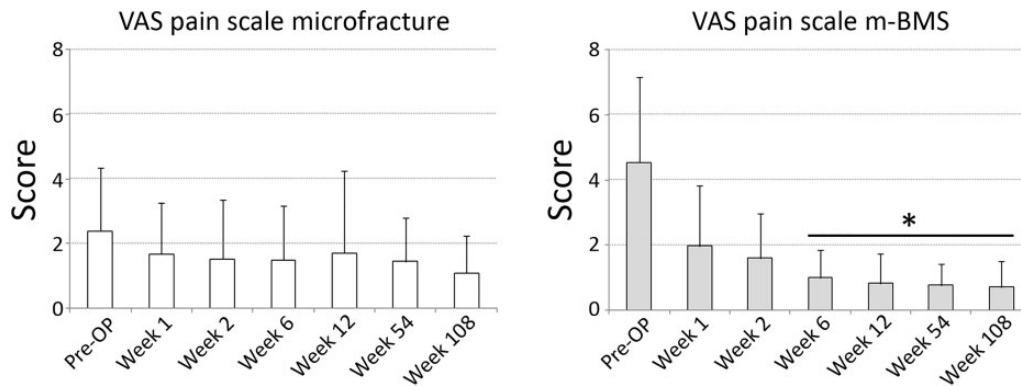


Figure 6. Visual analog scale (VAS) for pain in microfracture and m-BMS treatment groups. Significant pain relief in comparison with baseline data is shown in the m-BMS group. Values are presented as mean ± SD. **P* < .05. m-BMS, matrix-augmented bone marrow stimulation; pre-OP, preoperative.

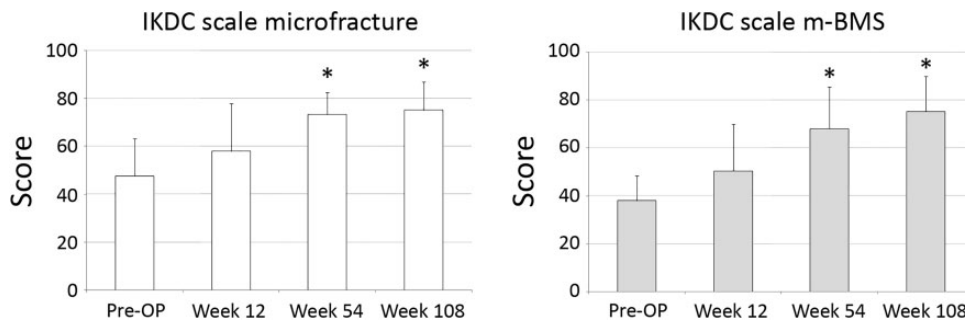


Figure 7. IKDC scale (knee function) in both treatment groups. *Statistically significant difference over time (*P* < .05). Values are presented as mean ± SD. IKDC, International Knee Documentation Committee; m-BMS, matrix-augmented bone marrow stimulation; pre-OP, preoperative.

of this study did not reveal an advantage in terms of quantity of defect filling at 12 weeks after m-BMS treatment. There was a tendency toward accelerated formation of cartilage repair tissue after MF when compared with m-BMS at 12 weeks postoperative, whereas at 1 or 2 years after treatment, there was no difference in the quantity of repair tissue. No significant difference was found in terms of patient-reported clinical scores at 12, 54, and 108 weeks after surgery, although there was a significant difference in baseline IKDC and KOOS subscale scores between groups (see Table 2).

This study proved that the use of the polyglycolic acid membrane with hyaluronan (Chondrotissue) in m-BMS of cartilage defects of the femoral condyles is a safe procedure without an increase of adverse events as compared with MF.

It has been confirmed by many authors in large case report series that MF of focal cartilage defects in the femoral condyles leads to clinical improvement, especially in the short term,^{††} which is very important for professional athletes.²³ In the majority of clinical studies, clinical scores decrease at mid- and long-term follow-up.^{23,36} It has also been shown that the outcome of MF is much better in small

defects (<2-4 cm)^{2,8,24,37} and has a worse outcome in localized cartilage defects >4.5 cm.^{2,8}

Volz et al³⁸ found a superiority of m-BMS over MF in cartilage defects with a mean size of 3.6 cm² (inclusion up to 10 cm²) after a follow-up of 5 years. In the present study, a continuous improvement was found in the Henderson score, VAS, IKDC, KOOS, and SF-36 at 12, 54, and 108 weeks after MF. Although it should be emphasized that preoperative KOOS subscale scores (Pain, Symptoms, Activities of Daily Living, Sport and Recreation) were significantly lower in the MF group, in our findings, MF did not lead to a significant improvement in pain relief, which is in contrast to Volz et al. In the present study, there was a tendency toward accelerated defect filling after MF at 12 weeks as compared with m-BMS, with further improvement at 54 weeks and a steady state from 54 to 108 weeks. The MRI findings of the present study are according to the results of MF in published prospective cohort studies of smaller defects.^{1,23,37}

Previous studies have shown that the complications after m-BMS are not increased in comparison with MF,^{3,4,7,12,21,26,31} which is confirmed by our study. Besides 1 case, the absence of hematoma or hemarthrosis underlines the hemostatic properties of the Chondrotissue implant in the ovine animal model by Erggelet et al.¹⁰

††References 1, 8, 13, 16, 23, 24, 33, 34, 36.

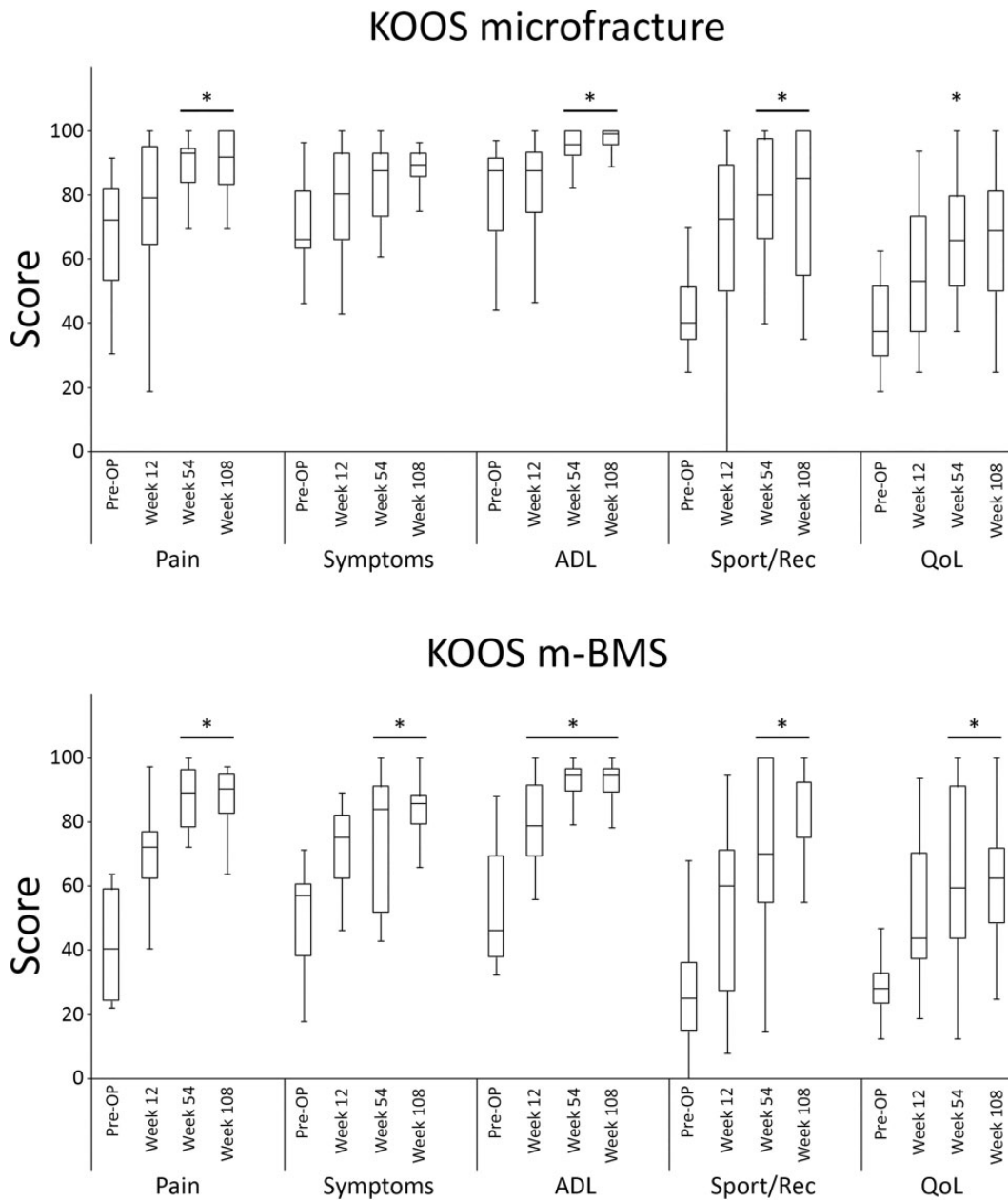


Figure 8. KOOS subscale scores in microfracture and m-BMS treatment groups. Values are presented as median (line), interquartile range (box), and 95% CI (error bars). *Statistically significant difference in comparison with baseline data for each group ($P < .05$). ADL, Activities of Daily Living; KOOS, Knee injury and Osteoarthritis Outcome Score; m-BMS, matrix-augmented bone marrow stimulation; pre-OP, preoperative; QoL, Quality of Life; Sport/Rec, Sport and Recreation.

The majority of published studies on m-BMS treatment in localized cartilage defects of the femoral condyles reported an improvement based on clinical scores (VAS pain, Lysholm, Tegner, and KOOS, including subscales) and MRI findings up to 5 years after surgery^{†‡}; however, only 1 controlled high-standard study compared m-BMS

with other treatment options.³⁸ Furthermore, the published studies differ by quite heterogeneous patient cohorts and operative procedures, such as arthroscopic³⁰ versus open surgical³⁸ and fixation of the implant by suture, glue, or pin, as well as by enhancing substrates, including platelet-rich plasma⁹ or an additional periosteal transplantation.³²

In the randomized controlled trial by Volz et al,³⁸ m-BMS was performed in localized cartilage defects of the knee with a porcine-derived type I/III collagen membrane

††References 3, 7, 9, 12, 13, 15, 21, 30-32, 38.

(Chondroglide) in an open surgical approach and compared with MF. The authors compared fibrin glue or suture fixation with MF alone. The follow-up rate was <70% after 5 years, and the study examined cartilage defects up to 10 cm². After solid defect filling in all groups at postoperative 1 year, a constant decrease in defect filling was observed at 2 and 5 years postoperative in m-BMS (vs MF) according to MRI scan and other clinical assessments. Nevertheless, 9 of 23 patients had no defect filling at all after 5-year MRI assessment. The clinical scores remained stable from postoperative 2 to 5 years, and the implant fixation technique had no influence on the outcome.

In the present study, continuous improvement in defect filling was found up to 108 weeks after surgery in MF and m-BMS treatment. The comparison of relative changes in Henderson score (delta score) revealed a significant increased quality improvement in the m-BMS group as compared with the MF group at week 108, which indicates that m-BMS might lead to a slower repair but ultimately may result in better final defect filling.

In the present study, m-BMS treatment showed continuous improvement in knee-related pain and symptoms reduction up to postoperative 108 weeks. Knee function was increased after m-BMS and MF, as demonstrated by patient self-reported IKDC and KOOS from 12 to 108 weeks after treatment. All reported KOOS subscale scores in the m-BMS group were >10 points and therefore can be interpreted as being clinically relevant.^{25,29} In the MF group, a meaningful clinical change was not observed for the Pain, Symptoms, and Activities of Daily Living subscales at week 12, although significantly higher baseline subscale scores for the Pain, Symptoms, Activities of Daily Living, and Sport and Recreation subscales were detected in the MF group. The tendency toward better outcome after m-BMS in terms of cartilage-related pain, as shown by VAS for pain and as well 2 KOOS subscales (Pain and Symptoms), was not accompanied by significant advantage in functionally based clinical scores until 24 months postoperatively.

No conversion to invasive treatment, such as mACI or osteochondral transplantation, was required during the 2 years after m-BMS in the present study. However, in a 24-year-old man, mACI was performed 12 months after MF, owing to persisting intra-articular complaints in the absence of sufficient fibrous cartilage repair tissue, which was rated as a treatment failure. Adverse events found in the m-BMS group were all evaluated as procedure and not device failure.

Several limitations have to be considered when discussing the results of the present study. The senior surgeons who performed the surgery were responsible for the follow-up examinations. Although the evaluation of the clinical outcome was based on subjective scores, the single-blind design could lead to an objective bias. The radiologist (M.S.) was not involved in the design of the study to avoid bias at the analysis of the MRI; nevertheless, the presence of resorbable pins or bone marrow edema might have revealed a surgical measure before the MRI.

A significant difference was detected between groups in terms of age ($P = .017$), baseline IKDC score ($P = .028$), and

4 KOOS subscale scores: Pain ($P = .006$), Symptoms ($P = .003$), Activities of Daily Living ($P = .003$), and Sport and Recreation ($P = .004$). Furthermore, generalizability of the results might be compromised by the relatively high mean age in both treatment groups. The regenerative potential of cartilage has been shown to be age dependent⁸; therefore, younger patients might expect better results than those shown in the present study. Cartilage lesions of the femoral condyles are often associated with axis deviation or meniscal or ligamentary lesions of the knee. Given the strict exclusion criteria, patient recruitment was more challenging than expected. In the period of patient recruitment, 26% of patients who met inclusion criteria gave their consent to participate in the trial.

The correlation of MRI with clinical outcome in cartilage surgery has been discussed critically in the past.⁵ Histological assessment of the cartilage repair tissue is desirable to prove the difference in its quality, although radiological follow-up can support an indirect judgment on this issue.

CONCLUSION

The use of the polyglycolic acid membrane with hyaluronan in m-BMS of cartilage defects has proven to be a safe procedure. No difference was found by comparing m-BMS and MF in terms of patient-reported outcome scores and MRI assessment until 2 years postoperatively. Long-term follow-up studies including histological assessment are suggested for further investigation.

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