Autologous collagen-induced chondrogenesis versus microfracture for chondral defects of the knee: Surgical technique and 2-year comparison outcome study

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ABSTRACT

Objective: Osteochondral lesions of the knee affect patients from all age groups with arthroscopic microfracture being the current gold standard of treatment of such lesions. Autologous collagen-induced chondrogenesis (ACIC) is a novel procedure that has recently been gaining popularity. This study aims to compare the 6 and 24 month post-operative outcomes between patients undergoing microfracture only and microfracture with ACIC. **Methods:** Patients from both groups were assessed pre-operatively, at 6 and 24 months post-operatively for functional outcomes using SF-36 and IKDC scoring (International Knee Documentation Committee Subjective Knee Form).

Results: Both groups showed improved SF-36 and IKDC scores at 6 and 24 months, however patients who underwent ACIC showed better SF-36 mental component and IKDC scores 24 months after surgery.

Conclusion: This demonstrates that ACIC is an effective, single-stage, joint-preserving procedure which is comparable, if not better, in treating chondral defects.

1. Introduction

Osteochondral lesions of the knee are a common cause of knee pain affecting all age groups and at times can be debilitating. Several theories have been postulated for the aetiology of chondral and osteochondral defects, including acute trauma, chronic micro-trauma and degeneration.^{1–3}

At the moment, microfracture is the gold standard of treatment for small articular cartilage defects less than 9 mm in diameter.^{1,4,6} Microfracture, however, has its disadvantages as the cartilage formed consists mainly of fibrocartilage rather than hyaline cartilage. Fibrocartilage has inferior wear characteristics and may lead to poorer clinical outcomes.^{7–9} Defect containment and size are additional limiting factors for regenerating cartilage and the Other techniques utilising osteochondral autograft and allografts recommended for larger defects have significant donor site morbidity or involves a two-stage procedure which increases both cost and post-operative pain.¹⁰

More recently, a novel single-stage procedure has been gaining popularity for repair of cartilage defects. Autologous collagen-induced chondrogenesis (ACIC) is a cost-effective method of treatment of chondral defects.¹² First described by Benthien et al in 2010,² ACIC is a one-step procedure which combines microfracture with subsequent

fixation of a collagen I/III matrix overlying the defect. The matrix covers a prepared microfracture site, providing a conducive environment for released MSCs to differentiate into chondrocytes.^{13,14} Results are promising, with sustained improvement in functional and Magnetic Resonance Imaging Observation of Cartilage Repair Tissue (MOCART) scores at 7 years follow-up in one study.¹⁵

Atelocollagen is a highly purified type I collagen derived from the porcine dermal skin. Atelocollagen combined with commercially available fibrin glue is used in ACIC procedures as treatment for cartilage defects. This scaffold is colonized by the released mesenchymal stem cells from the subchondral bone and creates a solid and stable matrix, resistant to external shear forces, over the cartilage defect.^{16–18}

There is a relative vacuum in the literature on the outcomes of such ACIC techniques, including comparison studies with performing microfracture alone. The aim of this study is to compare clinical outcomes between the ACIC technique and microfracture alone over a 24-month study period.

2. Material and methods

This is a single-centre longitudinal study done by a single surgeon. 11 consecutive patients who underwent chondroplasty using CartiFill™

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procedure were compared with 11 age and sex-matched patients who underwent microfracture-only procedure. Clinically symptomatic patients with MRI (Magnetic Resonance Imaging) proven chondral injuries in a single knee were selected. After excluding patients with concurrent ligament injuries and meniscal injuries, those with chondral injuries with depth more than grade 3 (International Cartilage Regeneration and Joint Preservation Society, ICRS) were isolated. Patients with arthritis due to rheumatological causes and patients who underwent prior invasive procedures in the same knee were excluded. These patients were followed up for a minimum of 24 months, and they were clinically assessed pre and post-operatively at 24 months for International Knee Documentation Committee (IKDC) and Knee Injury, SF-36 and VAS (Visual Analog Scale) scores.

The 8 domains (Physical Functioning, Social Functioning, Role-Physical, Bodily Pain, Mental Health, Role-Emotional, Vitality, and General Health) of SF-36 were transformed into 2 summary scores: Physical Component Score (PCS) and Mental Component Score (MCS).

2.1. Surgical technique

The patients were positioned supine, under general or regional anaesthesia, in a routine arthroscopy setup. A non-sterile pneumatic tourniquet was applied circumferentially around the thigh (Zimmer Biomet, Warsaw, Indiana)

Pre-operatively and inflated to 100 mmHg above systolic blood pressure 10 min after antibiotic prophylaxis is given. All ACIC procedures were performed entirely by arthroscopy via standard anterolateral and anteromedial portals. A standard diagnostic arthroscope (Smith & Nephew, London, UK) with sterile saline irrigation was performed.

After a general assessment of the joint's ligamentous and meniscus integrity, the chondral defect was identified and classified according to the ICRS classification. After determining the size and location of the lesion, the exposed bone was prepared with probe, curettes and shavers till stable, smooth and perpendicular borders were defined. Microfracture was performed with standard microfracture awls as described by Steadman et al⁵. The angled awl was used to penetrate the subchondral bone perpendicularly to a depth of 6 mm, with each hole a minimum of 3–4 mm apart (Figs. 1 and 2).

The second part of the surgery is performed under dry arthroscopic conditions. The normal saline irrigation was stopped and remaining fluid in the knee joint was removed via the shaver or angled suction tube. A carbon dioxide insufflator (UHI-3, Olympus Medical Systems Corp, Tokyo, Japan) was connected and the joint was distended with carbon dioxide at a pressure of 20 mmHg, at a flow rate of 20 L/min. This pushes surrounding synovium away and allow a dry prepared site

Fig. 2. Post-debridement and microfracture.

for the Cartifill™. The chondral lesion can be further dried using surgical Rayon patties inserted through the arthroscopic portal with an artery forceps. At this point, the Cartifill™ (Regenerative Medicine System, Seoul, South Korea) was prepared on the bench. Two 1 ml syringes, one filled with 1 mL of fibrinogen (Tissel™, Baxter, Deerfield, IL, USA), one filled with 0.9 ml of Atelocollagen (Cartifill™, Regenerative Medicine System, Seoul, South Korea) and 0.1 ml of thrombin. Cartifill™ was combined with the fibrin glue in a 1:1 ratio with the aid of a Duploject Double-Barreled Syringe Applicator device (Baxter, Deerfield, IL, USA) and an 18G blunted drawing-up needle (Terumo, Hamburg, Germany).

The needle was introduced into the joint through an appropriate arthroscopic portal and the mixture was applied over the lesion until it was equal in height to that of the surrounding cartilage. The gel mass was shaped in-situ using a McDonalds dissector. The mixture was allowed to polymerize for a minimum of 5 min. The intra-articular space was kept dry with a combination of suction and surgical Rayon patties during the polymerization process. Once complete polymerization has occurred, the CO₂ inflow was shut off and fluid irrigation of the joint was restarted. To confirm that the mixture was stable and adherent to bone, the lesion was probed and the knee was gently mobilised through a full range of motion. The pneumatic tourniquet was deflated to promote bleeding from the microfracture sites. The arthroscopic portals were closed with Ethilon 4-0 (Ethicon Inc, Somerville, New Jersey, USA) and waterproof dressings were applied (Figs. 3 and 4).

All patients underwent a standard rehabilitation protocol. Patients were discharged either on the day of surgery or the following day. To protect the ACIC scaffold, postoperative range of motion of the knee

Fig. 1. Arthroscopic view of femoral condyle osteochondral lesion, Pre-debridement.

Fig. 3. Injection of Cartifill™ onto prepared site during dry-scope.

Fig. 4. Final view of articular surface.

Table 1

Demographic data.

Demographic Data		Microfracture	CartiFill
Gender (%)	Male	7 (63%)	7 (63%)
	Female	4 (37%)	4 (37%)
Mean Age (Range)		49.6(39–55)	46.3(23–60)
Side of the Surgery (%)	Right	8 (73%)	7 (63%)
	Left	3 (27%)	4 (37%)

was limited to 0–90° by a hinged knee brace. Patients were told not to bear weight on the operated limb for the first three weeks and to start partial weight-bearing after three weeks. Full weight-bearing and full range of motion of the operated limb was allowed at 6 weeks post-operation.

3. Results

The Micro-fracture groups had 11 patients with 7 males and 4 females with an average age of 49.6 years old (39–55). The surgeries were performed on 8 right knees and 3 left knees. The CartiFill™ groups had 11 patients with 7 males and 4 females with an average age of 46.3 years old (23–60). The surgeries were performed on 7 right knees and 4 left knees (Table 1).

In the Micro-fracture group there were 10 chondral defects on the medial femoral condyle (5 mm–20 mm) and one trochlear chondral defect (15 mm). In the CartiFill™ group there were 8 chondral defects on the medial femoral condyle (10 mm–30 mm), 1 on the lateral femoral condyle (10 mm) and there were 2 trochlear chondral defect (10 mm–15mm). All chondral defect gradings were ICRS 3 to 4. Locations of the chondral defects were recorded and illustrated accordingly (Figs. 5–7).

Both the groups demonstrated significant improvement in SF-36 and

IKDC scores at 24 months after surgery. The microfracture group demonstrated a SF-36 PCS score improvement from 42.3 to 73.6 ($p = 0.006$). SF-36 MCS score improved from 46.8 to 61.4 ($p = 0.022$). IKDC total score improved from 55.7 to 68.5 ($p = 0.002$). Further breakdown of IKDC scores showed significant improvement in symptoms ($p = 0.014$) and functional activities of daily living (ADLs, $p < 0.001$) but not for sports activities ($p = 1.0$). VAS pain score was reduced from 7.4 to 4.5 ($p = 0.001$) at 24 months (Table 2).

The CartiFill™ group demonstrated 24 month SF-36 PCS improvement from 40.0 to 78.2 ($p = 0.003$), SF36 MCS score improved from 47.7 to 84.1 with a ($p < 0.001$). IKDC scores improved from 58.0 to 80.6 ($p < 0.001$). Further breakdown of IKDC showed significant improvement in all 3 subcategories, symptoms ($p = 0.001$), functional activities of daily living (ADLs, $p < 0.001$) and for sports activities ($p = 0.019$). VAS scores improved from 6.8 to 2.4 ($p < 0.001$) at 24 months (Table 3).

When comparing the 2 groups, at 24 months there was statistical significance in the mean difference comparing CartiFill™ vs Microfracture-only in both SF-36 MCS ($p = 0.017$) and IKDC scores ($p = 0.001$). Although there was no statistical difference in the improvement of SF-36 PCS score between in the two groups, the values in the CartiFill™ group demonstrated higher values (Table 4).

We had no immediate or late complications in the two groups. 1 patient in the Micro-fracture group underwent a second arthroscopic debridement and 2 patients underwent total knee replacement over the 24-month follow-up period.

4. Discussion

With a more active population, the incidence of articular cartilage lesions is expected to increase, which can result in significant functional disability due to its limited capability of spontaneous healing.^{1,2,19,20} Surgical management of chondral defects in young active patients is divisive amongst orthopaedic surgeons. Treatment generally focuses on the stimulation of mesenchymal stem cells and formation of fibrocartilage, which is not as robust and durable as hyaline cartilage. Several surgical techniques have been described to improve the quality of cartilage regenerated which include microfracturing,³⁰ osteochondral autografts and allografts, autologous chondrocyte implantation³¹ and autologous matrix induced chondrogenesis (AMIC).^{23,32} In some patients, a partial knee replacement might even be indicated, but this comes with a compromise; a permanent reduction of activity level in order to preserve the longevity of the implants.³

Microfracture is a single-stage cost effective arthroscopic procedure with low morbidity that was developed in early 1980s by Steadman.^{5,11,21} It is currently the first-line treatment of grade III or IV chondral injuries which employs marrow-based strategy for cartilage

Microfracture			
Location	Frequency	Size (ave. mm)	Depth (ave) ICRS Grade
5	5	9.6 (5-15)	III
8	1	10	III
2,5, and 8	2	17.5(15-20)	IV
5 and 6	2	16 (12-20)	IV

CartiFill™			
Location	Frequency	Size (ave. mm)	Depth (ave) ICRS Grade
5	3	11.7(10-15)	III
8	1	15	IV
2,5, and 8	3	21.7(15-30)	IV
5 and 6	1	20	IV

Fig. 5. Location of chondral defects on the medial femoral condyle

Fig. 6. Location of chondral defects on the lateral femoral condyle

Fig. 7. Location of chondral defects on the trochlear.

Microfracture			
Location	Frequency	Size (ave. mm)	Depth (ave) ICRS Grade
N/A			

Cartifill™			
Location	Frequency	Size (ave. mm)	Depth (ave) ICRS Grade
5	1	10	IV

Microfracture			
Location	Frequency	Size (ave. mm)	Depth (ave) ICRS Grade
2	1	15	IV

Cartifill™			
Location	Frequency	Size (ave. mm)	Depth (ave) ICRS Grade
2	2	12.5(10-15)	III

Table 2

Clinical outcomes: Microfracture.

Microfracture					
	Pre-operative Mean (SD)	6 Month post-operative Mean (SD)	Significance compared to pre-op	24 Month post-operative Mean (SD)	Significance compared to pre-op
SF36 Physical Function	42.3 (21.5)	69.4 (20.1)	0.019	73.6 (23.1)	0.006
SF36 Mental Function	46.8 (9.0)	58.6 (20.0)	0.43	61.4 (23.4)	.0223
Total IKDC Score	55.7 (7.8)	69.0 (8.6)	0.001	68.5 (6.9)	0.002
Symptoms	16.9 (4.5)	23.9 (3.9)	0.002	22.6 (4.8)	0.014
Sports activities	29.4 (4.4)	30.8 (4.6)	1.0	31.1 (4.3)	1.0
Functional ADLs	2.2 (0.88)	5.27 (0.79)	< 0.001	5.9 (1.8)	< 0.001
VAS	7.4 (1.6)	4.1 (2.0)	< 0.001	4.5 (1.4)	0.001

Table 3

Clinical outcomes: Cartifill™.

Cartifill™					
	Pre-operative Mean (SD)	6 Month post-operative Mean (SD)	Significance compared to pre-op	24 Month post-operative Mean (SD)	Significance compared to pre-op
SF36 Physical Function	40.0 (23.8)	72.3 (23.8)	0.014	78.2 (26.6)	0.003
SF36 Mental Function	47.7 (7.5)	77.3 (13.7)	< 0.001	84.1 (16.9)	< 0.001
Total IKDC Score	58.0 (11.6)	73.5 (7.6)	0.001	80.6 (7.5)	< 0.001
Symptoms	17.7 (5.9)	24.9 (5.1)	0.024	28.5 (6.7)	0.001
Sports activities	30.2 (4.9)	33.4 (3.2)	0.161	34.8 (2.7)	0.019
Functional ADLs	2.6 (0.8)	5.6 (0.9)	< 0.001	6.8 (1.9)	< 0.001
VAS	6.8 (2.5)	3.6 (1.7)	0.004	2.4 (2.0)	< 0.001

Table 4
Clinical outcomes: CartiFill™ (C) vs Microfracture (M).

Microfracture vs CartiFill™						
	Pre-operative Mean Difference (C- M)	Significance	6 Month Post-operative Mean Difference (C-M)	Significance	24 Month Post-operative Mean Difference (C-M)	Significance
SF36 Physical Function	−2.27	0.816	2.90	0.760	4.54	0.673
SF36 Mental Function	0.91	0.800	18.64	0.019	22.73	0.017
Total IKDC Score	2.30	0.592	4.49	0.201	12.02	0.001
Symptoms	0.52	0.103	1.0	0.614	5.81	0.026
Sports activities	0.82	0.683	2.55	0.150	3.73	0.026
Functional ADLs	0.36	0.326	0.36	0.332	0.91	0.263
VAS	0.55	0.554	−0.46	0.574	−2.09	0.010

repair.²² A systematic analysis showed short-term effectiveness of microfracture with significant improvement in knee function in all studies at 24 months. Various previous studies however have illustrated issues with its durability.^{7–9,23} In our microfracture-alone group, all patients demonstrated statistically significant improvement of all scores except the sports activities (subcategory of the IKDC) at 24 months follow-up. Two patients had to undergo total knee replacements within 24 months and another patient required a repeat arthroscopic debridement. Recent evidence has suggested that clinical improvement after microfracture is not sustained after 5 years.^{24–28} Gobbi et al. reported deterioration of scores in athletes 2–5 years after surgery, with the older ones with multiple and large lesions having the worse prognosis.²⁵ This might be explained in a meta-analysis by DiBartola et al., where majority of the reparative tissue after microfracture was fibrocartilage and only 8.2% of patients yielded histological evidence of hyaline cartilage repair.²⁹

ACI was first developed by Brittberg et al., in 1994¹⁰ which involved a two-stage open surgical procedure. Chondrocytes are harvested from a non-weight bearing portion of the patient's knee during arthroscopic surgery and cultured in the laboratory over a 4–8 week period.³⁴ After a sufficient number of chondrocytes have been cultured, they are injected back into the defect of the knee, where a periosteal flap or more recently, a biocompatible scaffold is surgically affixed to cover the defect. Despite it being staged, having higher cost and longer protected weight bearing time, Knutsen et al. showed no clear advantage in clinical outcomes and prevention of osteoarthritic changes of ACI over microfracture in a randomised multicentre trial at 15 years.³⁵

ACIC of the knee is a single-stage, low morbidity, joint-preserving surgery that potentiates return to a healthy lifestyle. This would be advantageous in reducing time and expense of the procedure as well as reducing risk to the patient.^{36–38} This technique combines microfracture with an exogenous scaffold to confine mesenchymal stem cells to the chondral defect, preventing them from dispersing into the intra-articular space.⁷ The advantage of CartiFill™ over patch scaffolds is that when it is combined with fibrin glue, the injectate can easily fill up defects of any size, depth or shape. Shetty et al. were the first to describe the use of Atelocollagen in chondral defects in 2013. At 2 years after surgery, all patients had significant and sustained improvement in Lysholm score. Post-operative MRI performed showed good cartilage defect filling with good MOCART scores.³⁹ Similarly, atelocollagen has been used for treatment of chondral lesions of the talus and results showed significant improvement in VAS scores and AOFAS scores at 6 months follow up.⁴⁰

To our knowledge, this is one of the first case control studies comparing the use of Atelocollagen and microfracture with microfracture alone. In our study, patients who underwent CartiFill™ augmentation showed statistically superior outcomes in SF-36 MCS and IKDC scores compared to the microfracture-alone group. Even though not statistically significant, SF-36 PCS scores showed superior improvements compared to the Microfracture group. An animal study reported that at

12 weeks after CartiFill™ injection, lesions had complete cartilage and subchondral bone repair. Moreover, histological analysis of revealed hyaline cartilage regeneration as compared to fibrocartilage in the control groups. This result implies that atelocollagen has a critical role for the early cartilage repair.⁴¹ The biological resemblance of the regenerated cartilage to hyaline cartilage could be the reason for none of our patients in the CartiFill™ group required a second invasive procedure during the follow up period compared to the microfracture group.

The limitations of our study include a small sample size and a midterm follow-up of 2 years. Further studies with post-operative MRI and biopsy of the regenerated cartilage and a longer follow-up would be needed to prove the effectiveness of CartiFill™ in regenerating hyaline cartilage.

5. Conclusion

In our study, we demonstrated that CartiFill™ with microfracture was an excellent and effective treatment modality in osteochondral defects compared to microfracture alone. Chondrogenesis with CartiFill™ is an effective, single-stage, joint-preserving procedure which is comparable, if not better, in treating chondral defects.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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