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Viable cartilage allograft outperforms existing treatments for focal knee cartilage defects

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Abstract

Purpose: Viable cartilage allograft (VCA) is a cartilage tissue matrix that contains cryopreserved viable allogeneic cartilage fibres. This study aimed to assess safety and benefits in treating focal knee cartilage defects with VCA. We hypothesized that VCA is a safe single-stage procedure in isolated chondral defects.

Method: In vitro analysis, in vivo studies and a prospective case series were performed. VCA was evaluated in a goat cartilage repair model. Symptomatic International Cartilage Repair Society grade 3/4A lesions of the femoral condyle or patella were implanted with VCA. International Knee Documentation Committee (IKDC), Knee injury and Osteoarthritis Outcome (KOOS) subscales, Lysholm, Short Form-12, Visual Analog Scale and pain frequency levels were assessed. Radiographic and magnetic resonance imaging (MRI) was performed at regular intervals postoperatively. Data were analysed by statisticians to determine the power and significance of the results.

Results: The goat study confirmed that VCA is effective for cartilage repair. Twenty patients were implanted; the mean age was 28.1 (16–56), the mean body mass index (BMI) was 27.9 ± 5.6 and the mean follow-up was 24.1 months (range = 12.0–36.0 months). Lesions were in either the femoral condyle (7) or patella (13). Lesion sizes ranged from 1.5 to 6.0 cm^2 (mean = 4.58 cm^2). Outcome scores improved from preoperative baseline (POB): IKDC (78.2), Lysholm (89.0), KOOS: Pain (95.8), Symptoms (86.3), ADL (87.8), Sports (85.0) and QOL (75.0). MRI imaging demonstrated excellent osteochondral allograft assimilation. Second-look arthroscopy (two patients) demonstrated complete fill and incorporation (Brittberg scores 11/12). Functional scores were maintained at 24 (M): IKDC (86.24 ± 17.2), Lysholm

Abbreviations: ACI, autologous chondrocyte implantation; ADL, activities of daily living; BMI, body mass index; CPM, continuous passive motion; DMSO, dimethyl sulfoxide; ECM, extracellular matrix; FDA, Food and Drug Administration; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; IRB, Institutional Review Board; KL, Kellgren-Lawrence; KOOS, Knee injury and Osteoarthritis Outcome subscales; MACI, matrix associated autologous chondrocyte implantation; MCID, Minimal Clinically Important Difference; MOCART, magnetic resonance observation of cartilage repair tissue; MRI, magnetic resonance imaging; MSF-12, Mental Short Form-12 (component of Short Form-12); *N*, sample size; NC, North Carolina; N.S., nonsignificant; OATS, osteochondral autograft transfer system; OCA, osteochondral allograft transplantation; P, calculated probability; POB, preoperative baseline; PSF-12, Physical Short Form-12 (Component of Short Form-12); PWB, partial weight-bearing; QOL, quality of life; ROM, range of motion; SAS, statistical analysis software; SF-12, short form-12; *T* (in *T2*), transverse relaxation time; VAS, visual analog scale; VCA, viable cartilage allograft; YRS, years.

(87.23 ± 15.0), KOOS: Pain (91.72 ± 17.3), Symptoms (84.92 ± 16.1), ADLs (93.80 ± 16.1), Sports (84.45 ± 27.7), QOL (81.30 ± 20.8).
Conclusion: VCA is an off-the-shelf, single-stage, conformable allogeneic graft that treats chondral defects with no additional fixation. Preclinical and short-term prospective clinical studies show that VCA can safely treat chondral defects with potential advantages to existing options.

Level of Evidence: Level IV study.

KEYWORDS
allograft, articular, biology, cartilage, knee, regeneration

INTRODUCTION

Hyaline cartilage is composed of dense extracellular matrix (ECM) proteins which surround the chondrocytes and provide structural support; once disrupted, it has a limited capacity to heal [1, 17, 18, 25, 28]. Subchondral bone marrow lesions have been associated with disorganized hyaline cartilage [13]. This disruption can lead to pain, mechanical symptoms and associated synovitis [13]. Synergistic interactions of the ECM proteins and chondrocytes are needed to help integrate and remodel the microenvironment and provide biomechanical stability [5, 9, 27]. Algorithms for operative management of International Cartilage Repair Society (ICRS) grade 3 or 4A/B lesions are based on several factors [2]. There are limitations of standard approaches; the optimal treatment would restore hyaline cartilage through a single-stage, minimally invasive procedure with long-term stability [24].

Microfracture treats well-contained small- to medium-size (≤2–4 cm^2) lesions through marrow stimulation, removal of the calcified cartilage layer and placement of holes in the subchondral bone [14, 30]. Some studies show that the fibrocartilaginous repair site can deteriorate 1–2 years postsurgery [15], while others revealed deterioration of function during the intermediate (2–5 years) postoperative period with intra-lesional osteophytic formation and bone overgrowth [8, 15]. Revision rates of 2.5%–6% at 2 years postoperatively and 9%–31% at 5 years postoperatively have been reported [20].

Osteochondral autograft transfer system (OATS) or mosaicplasty procedure takes advantage of using the patient's own ECM of hyaline cartilage, providing immediate biomechanical stability; donor site morbidity can occur and increases with increasing lesion size [29]; fibrocartilage formation at the periphery of the plug creates a 'cobblestone' appearance when multiple grafts are used. Cystic formation, graft hypertrophy and calcifications have also been reported postoperatively, which are associated with poor long-term outcomes [21, 29].

Osteochondral allograft transplantation (OCA) is a single-stage procedure for larger lesions (>4 cm^2) providing allogeneic ECM of hyaline cartilage and viable chondrocytes to the defect site recreating the articular contour and delivering immediate biomechanical stability. Cellular viability in these allografts drops below 60% after storage of greater than 42 days at 4°C, placing time restrictions on transplantation [32]. Long-term studies have demonstrated an increased risk of graft failure in patients ≥30 years old and in patients with previous knee surgeries [10, 11, 23].

Autologous chondrocyte implantation (ACI) or matrix-associated ACI (MACI) can treat large lesions (>4 cm^2). ACI demonstrated good to excellent results in 89% of patients at 2–9 years after surgery [22]. The Summit study demonstrated the superiority of MACI over microfracture at two years and these results were maintained in a voluntary follow up extension of the study out to 5 years [26].

Considering the current approaches and their limitations, the optimal treatment would provide hyaline cartilage and viable cells to the defect in a single-stage procedure, remodelling over time, without violating the subchondral bone plate. Viable cartilage allograft (VCA, MTF Biologics, Edison, NJ/ConMed) is a novel allograft solution that offers these features. VCA contains hyaline cartilage fibres that are cryopreserved to maintain endogenous viable chondrocytes. Once thawed, these fibres are mixed with lyophilized cartilage allograft matrix processed to retain natural ECM proteins. The two components are mixed at the time of surgery, forming a putty-like material. VCA can be molded by the surgeon to easily fill cartilaginous defects of various shapes and defect sizes matching the articular surface contour. The procedure does not require violation of the subchondral bone plate, avoiding fibrocartilaginous fill and bone morbidity associated with microfracture, osteochondral transfer and transplantation procedures. The current study presents data supporting the potential for this procedure to restore small- to medium-sized cartilage defects and addresses some of the limitations of the other procedures.

The primary goal of this study was to evaluate the safety and performance of VCA through clinical studies. VCA was investigated clinically in a case series of 20 patients with symptomatic focal knee articular cartilage defects, evaluating improvements in outcome measures from preoperative baseline and greater than 2 years postoperatively. The study hypothesized that VCA offers improvements in functional outcome scores compared to preoperative baseline scores.

MATERIALS AND METHODS

The clinical case study review was approved by the institutional review board (IRB 2019.069; The University of Queensland Medical School).

Patients with isolated ICRS grade 3 or 4A chondral defects of the knee were treated between August 2018 and January 2020. Procedures using the VCA system were performed by one of two senior sports medicine fellowship-trained surgeons. Twenty patients (11 female and nine male) underwent procedures using VCA (Table 1). The mean clinical follow-up was 24.1 months (range = 12.0–36.0 months). The mean patient age at the time of surgery was 28.1 years (range = 16–56 years). The mean body mass index (BMI) was 27.9 ± 5.6 (21.5–41.5). The mean defect size was 4.58 cm^2 (range = 1.5–6.0 cm^2). Following an initial diagnostic arthroscopy, a mini-open medial or lateral arthrotomy was made based on lesion location. The lesion site was visualized, and a #15 blade was used to demarcate the junction between the normal and abnormal articular cartilage creating vertical borders. The fibrillated and calcified cartilage was removed, avoiding breakage through the subchondral bone plate and limiting bleeding at the defect base. The cryopreserved cartilage fibres were thawed at room temperature, and the sterile top was removed by the surgeon. A separate sterile straining top was applied, and the storage media was decanted. The fibres were mixed three times with normal saline at room temperature, and all excess saline was removed. The fibres were then mixed in the same container with the cartilage allograft matrix creating a putty-like material. The material was implanted into the defect flush with the normal articular cartilage margin (Figure 1a–c).

Patellar and trochlear lesions required either concomitant medial patella-femoral ligament reconstruction or anterior tibial tubercleplasty to stabilize patellar tracking. Lesions of the medial or lateral femoral condyle required no concomitant realignment procedures but did have concomitant meniscal repair or meniscectomy. Range of motion (ROM) was restricted after surgery in a hinged knee immobilizer locked at 10° of hyperextension. Continuous passive motion (CPM) was initiated on

TABLE 1 Demographic data ($n = 20$).

Mean age (years)	28.1 (16–56)	Chondral lesion site	
Mean BMI	27.9 (21.5–41.5)	Patella	60%
		Lateral femoral condyle	10%
Gender		Medial femoral condyle	15%
Female	55%	Multiple sites	10%
Male	45%	Trochlea	5%
Affected joint		ICRS lesion grade	
Knee	100%	Grade 3	20%
		Grade 4A	70%
		Grade 4B	10%

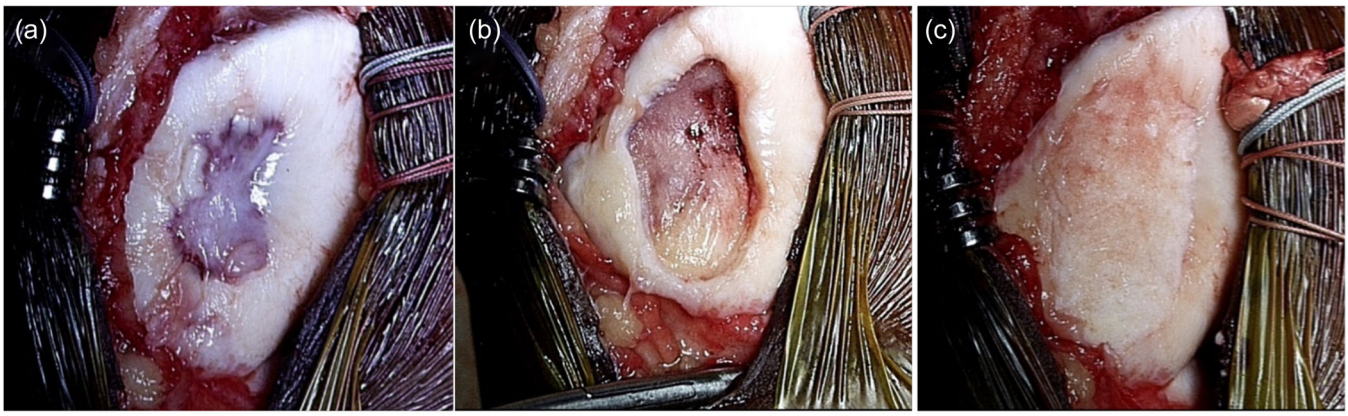

FIGURE 1 (a) Intra-operative photographs of International Cartilage Repair Society 4A patellar defect, (b) Site preparation, (c) viable cartilage allograft implantation.

postoperative day 6–10 based on lesion location, starting at 10° hyperextension to 45° flexion as tolerated for 6–8 h/day. CPM was continued for 3–4 weeks, increasing to 90° at 4 weeks and 120° at 6 weeks. Full flexion was allowed after 6 weeks. Weight-bearing was toe-touch weight-bearing to 25% partial weight-bearing (PWB) immediately in femoral chondral lesions, and patients advanced to 25%–50% PWB at 2–4 weeks and full weight-bearing as tolerated at 4–6 weeks. Patello-femoral cases were maintained locked in extension with gait for 6 weeks but allowed immediate weight-bearing as tolerated while in extension. Open-chain exercises were not allowed until 3 months, followed by limited open-chain exercises at 3–4 months in patello-femoral patients. Running was initiated at 3–4 months once single leg balance ability was obtained; sport-specific training was allowed at 4–6 months and based on balance and cutting abilities. Patients had functional scores taken and filed in a prospective registry dedicated to storage of patient outcome scores confidentially implemented for the use of systematic data collection. Two patients required arthroscopic lysis of adhesions allowing gross visualization of the implantation site. Post-operative MRI studies with T2 mapping and cartilage-specific sequences were obtained in 13 of 20 cases. All cases were assessed with a radiographic series preoperatively, and 19/20 cases were assessed postoperatively consisting of bilateral anterior standing, posterior-anterior 45° flexion weight-bearing, lateral and merchant's (30° patella-femoral) views.

Outcome measures

Patient-reported outcome measures were collected preoperatively, at 6 weeks, at 3, 6, 12, 18 and 24 months and at 6–12-month intervals thereafter. The primary outcome measure was defined as a clinically minimal significant improvement of ≥12 points on KOOS subscales. Additional characterization of the functional status of the patients was performed using the International Knee Documentation Committee (IKDC) Questionnaire, Lysholm score and the 12-Item Short Form Health Survey (SF-12). The change in VAS and pain frequency from baseline was evaluated as well.

Statistical analysis

Descriptive statistics were reported as the mean with standard deviations. Data analysis of functional scores was conducted using a student's *t* test. Statistical analysis was performed using SAS v9.4 (SAS Institute). The *p* value was set at 0.05 for significance.

RESULTS

Outcome scores

Preoperative and postoperative functional score data were collected for all 20 patients. Each of the 20 patients had a minimum 2-year postoperative follow-up. Progressive increases in functional scores were noted, and trends were maintained at the most recent follow-up with significant increases compared to the preoperative state. The most recent follow-up mean functional scores are presented in Table 2. Absolute improvements in mean score were noted for every functional score modality recorded, and 9 of 10 functional score modalities exhibited a statistically significant improvement (Table 2). Subset analysis of outcome scores stratified by postoperative follow-up period is shown in Figure 2 (IKDC, Lysholm), Figure 3 (subjectively reported knee pain frequency), Figure 4 (KOOS) and Figure 5 (MSF-12, PSF-12).

Radiology

Nineteen of 20 patients had postoperative radiographs. The mean KL grade at the final postoperative radiograph was 0.3 (KL grade 0 [$n = 13$]; KL grade 1 [$n = 6$]). Thirteen of 20 patients had follow-up MRI analysis which showed an improved

TABLE 2 Mean functional score difference between preoperative and at final follow-up.

	Mean pre-op score	Mean final score	*p* Value
MSF-12	48.77 ± 14.0	55.64 ± 11.7	N.S.
PSF-12	37.30 ± 9.0	51.28 ± 8.8	0.0002*
KOOS	49.51 ± 15.2	72.51 ± 24.4	0.0013*
KOOS Symptom	56.43 ± 17.5	84.92 ± 16.1	<0.0001*
KOOS Pain	62.59 ± 16.3	91.72 ± 17.3	<0.0001*
KOOS ADL	66.27 ± 18.6	93.80 ± 16.1	<0.0001*
KOOS Sports	30.33 ± 28.7	84.45 ± 27.7	<0.0001*
KOOS QOL	31.70 ± 24.8	81.30 ± 20.8	<0.0001*
Lysholm	50.47 ± 21.5	87.23 ± 15.0	<0.0001*
IKDC	42.14 ± 14.9	86.24 ± 17.2	<0.00001*

*Statistical significance $p \leq 0.05$.

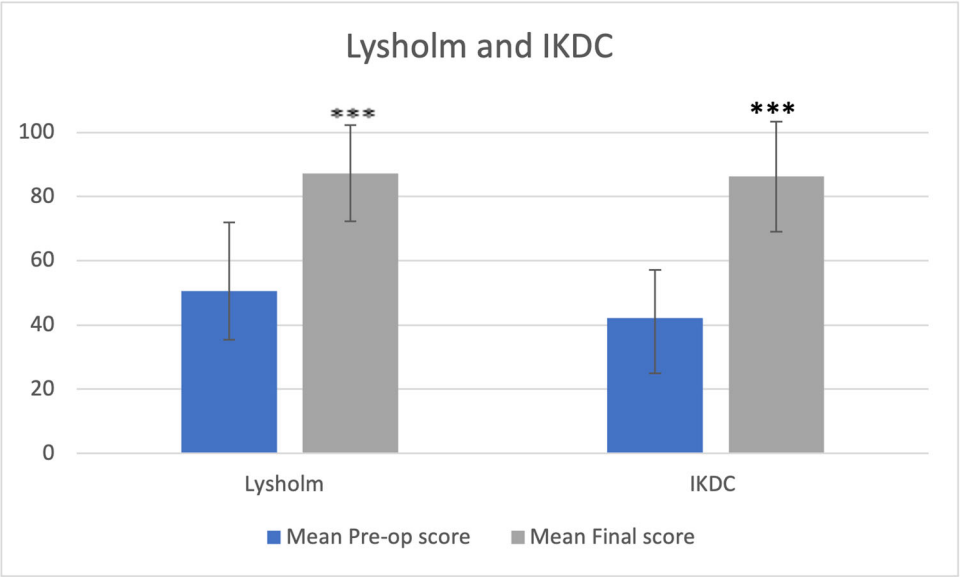

FIGURE 2 Viable cartilage allograft (VCA) series International Knee Documentation Committee (IKDC) and Lysholm outcome scores.

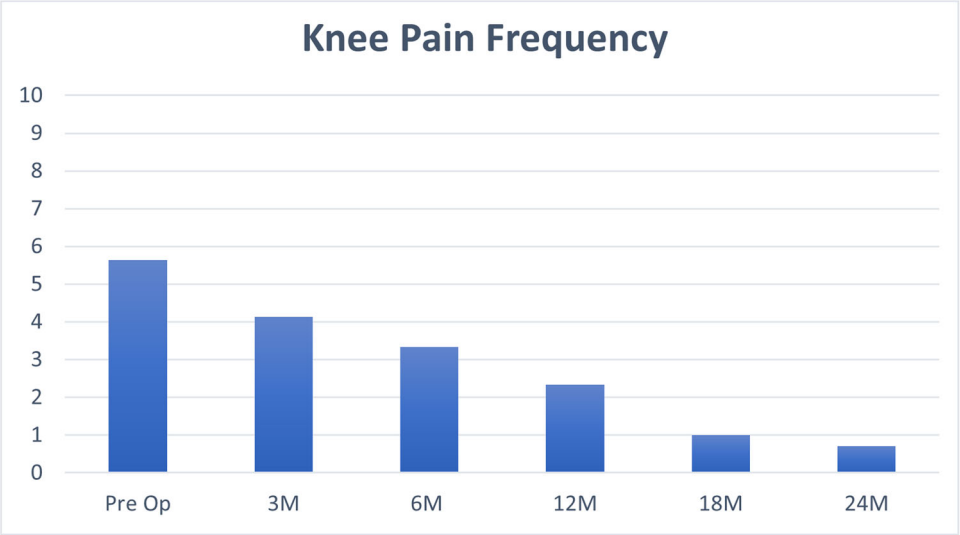

FIGURE 3 Viable cartilage allograft series subjectively reported knee pain frequency scores.

degree of intrasubstance signal heterogeneity with minimal to mild underlying bone marrow edema. All 13 patients with postoperative MRIs had evidence of cartilage allograft incorporation. The mean MRI follow-up was 11.2 months, with an average MOCART 2.0 score of 63.3.

Two second-look arthroscopic evaluations were performed at ~2.5 months postoperatively for lysis of adhesions allowing visualization of the repair sites (Figure 6a,b). The average Brittberg scores were 11/12, with excellent early incorporation into the native cartilage demonstrated.

DISCUSSION

The most important finding of the present study was that a single-stage procedure can outperform other forms of allograft transplantation, underscoring an innovative approach to address knee cartilage defects. VCA contains cartilage matrix with viable cells that conform to the defect site, remodelling over time to hyaline cartilage while offering immediate biomechanical support in a single-step procedure. VCA provides cryopreserved cartilage tissue preserving endogenous viable chondrocytes in an off-the-shelf option.

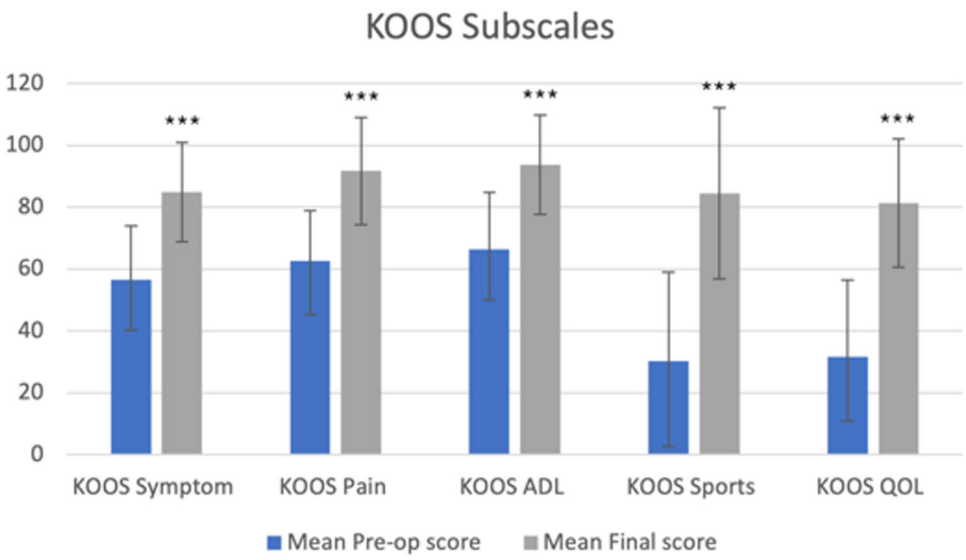

FIGURE 4 Viable cartilage allograft series Knee injury and Osteoarthritis Outcome (KOOS) subscales. ADL, activities of daily living; QOL, quality of life.

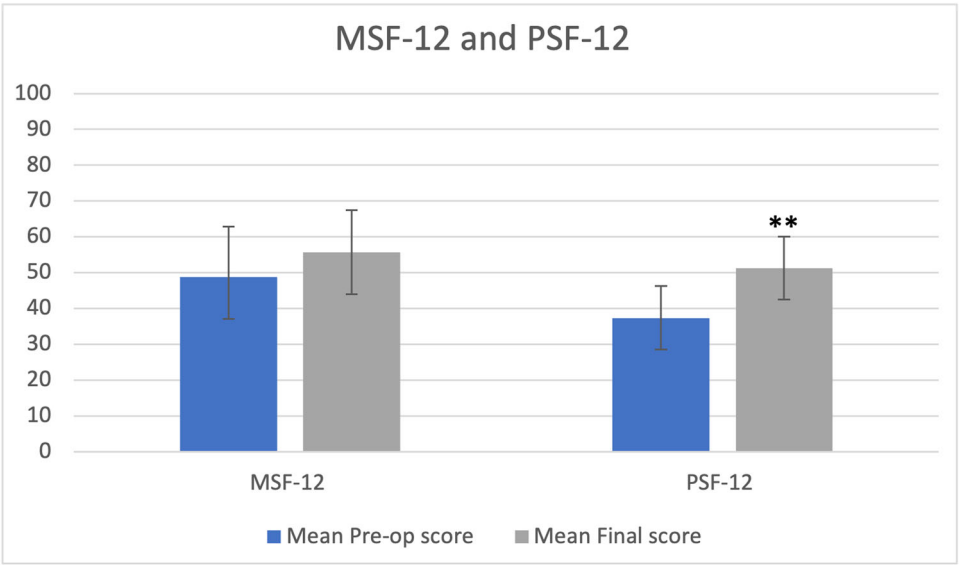

FIGURE 5 VCA series patients Mental Short Form-12 (MSF-12) and Physical Short Form-12 (PSF-12) outcome scores.

There have been numerous attempts to cryopreserve viable articular chondrocytes [1]. Curran and Gibson, using radioactive uptake of chondroitin sulphate, demonstrated that chondrocytes cooled to −25°C did not maintain viability [6]. Trypsinized cartilage slowly frozen to −79°C in 15% glycerol-maintained cell viability [12]. These isolated frozen-thawed cells, when transplanted into cancellous bone, were able to produce a new cartilage matrix [4]. Optimal cooling rates and toxicity limits of cryoprotective agents such as DMSO were further delineated by Tomford and others using chondrocytes from several sources [26, 28, 31]. Using sheep osteochondral dowels, Muldrew et al. demonstrated depth dependency, with the middle zone demonstrating the greatest cell death [16]. The pattern of cell preservation was clearly delineated by Ohlendorf et al. demonstrating cell preservation in the superficial zone but no other layers [19].

These attempts at cryopreservation techniques used osteochondral grafts and dowels and with controlled rate freezing and use of cryoprotectants still had difficulty entering the dense cartilage tissue structure and maintaining cell viability. VCA is composed of viable cartilage in a fibre configuration allowing penetration of the cryoprotectant due to increased surface area and more uniform temperature profiles within the graft. VCA fibres may allow for effective cell viability maintenance after cryopreservation compared to other types of graft

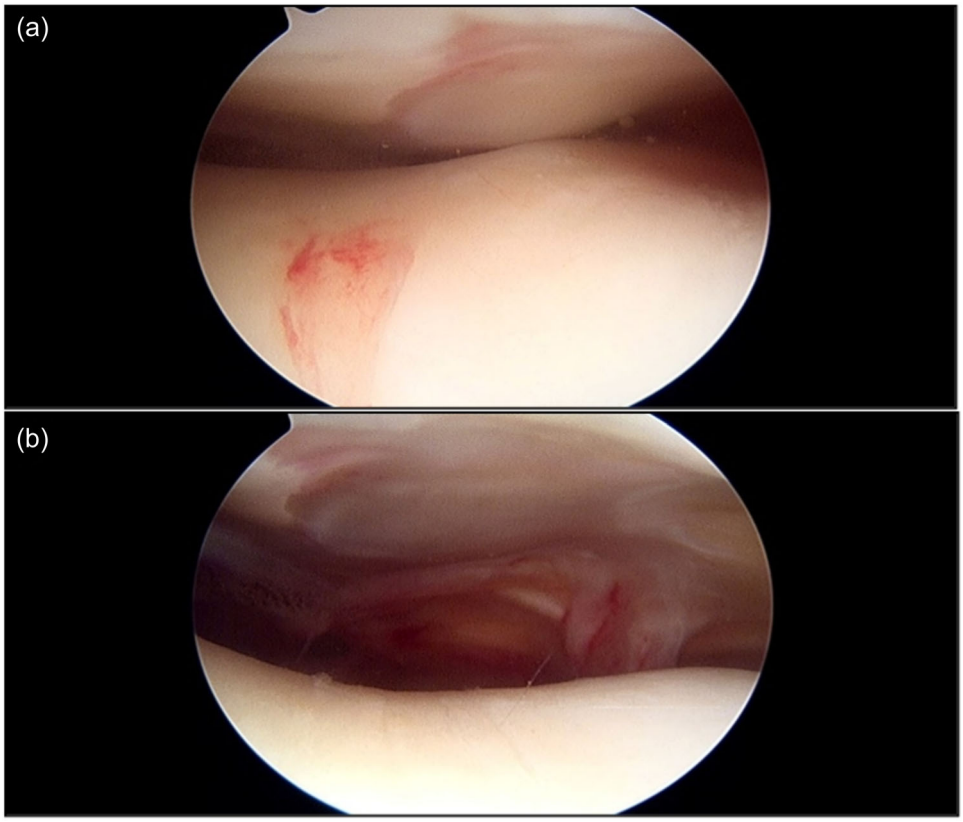

FIGURE 6 (a, b) Second-look arthroscopic pictures of patellar lesion 2.5 months after implantation of viable cartilage allograft incorporation to native articular cartilage, no delamination and retained contour.

geometries. The in vitro VCA characterization in this study confirmed that viable endogenous, functional chondrocytes originally present in the allograft tissue source are preserved in the cryopreserved cartilage tissue. The thawed viable chondrocytes produce proteoglycans and collagen type II, which are critical components of hyaline cartilage. The fibres, when mixed with the cartilage allograft matrix, create a conformable putty with ideal handling properties allowing treatment of articular cartilage defects of various shapes and sizes in multiple joints. The moldable nature of the graft creates a tight seal that may help integration with the surrounding host tissue by reducing void space while contributing to more complete fill and potentially providing immediate biomechanical support.

Each KOOS subscale met MCID with improvements in IDKC, Lysholm and KOOS pain, sports and quality of life scores. These findings correlated directly with improved pain scores. These functional improvements are comparable to those reported in the Summit study used to obtain FDA approval for the MACI procedure in the United States [29]. VCA has the benefit of being a single-staged procedure unlike the MACI procedure; furthermore, there is no requirement for additional fixation or fibrin glue as in the MACI procedure and no penetration of the subchondral bone plate as in the microfracture procedure, limiting bone marrow lesions postoperatively. The long-term impacts on future procedures have been demonstrated with the microfracture technique [3, 8, 15].

The mean MRI follow-up at 11.2 months demonstrated excellent average MOCART scores with solid fill and integration and limited bone signal, suggesting a positive impact of the VCA properties. By contrast, Ebert et al. reported MRI findings of 40.4% complete graft fill in patients who had undergone MACI [7].

This study is the first cohort with greater than 24 months of postoperative follow-up of this novel VCA solution for cartilage repair. The preliminary data from our study shows that this cartilage repair technique can provide patients with improved clinical outcomes and good defect fill. Repairing a chondral defect with VCA is a simple, single-stage procedure providing a cartilage matrix and viable endogenous chondrocytes while recreating articular contour. If a known or unsuspected lesion is encountered, there is no need to harvest autologous chondrocytes or violate the subchondral bone plate lessening morbidity, fibrocartilaginous ingrowth or the need for an additional procedure. VCA can also be used in other sites where small well-contained lesions are located, such as the talar dome of the ankle or the capitellum of the elbow.

There are some limitations to this paper. Selection bias is inherent as we selected patients with well-contained lesions and acute injury patterns. This initial evaluation of the procedure is limited to short-term clinical follow-up, and results will have to be followed further to obtain intermediate and long-term outcomes. This study contains no patient control group, limiting our ability to directly compare VCA to other treatment modalities. Future studies should examine the long-term impact on functional outcomes in comparison to alternative treatment options for similar-sized defects in a matched patient population. Further studies may also provide qualitative and quantitative data to confirm the early observations related to complete integration and fill to surrounding cartilage. Future studies should focus on randomized controlled trials comparing functional outcomes of chondrocyte allograft implantation to the standard of care.

Given the substantial functional profiles of VCA grafts, they are an option for surgeons interested in the availability and ease of use of a single-staged graft. Further studies are warranted to quantify the economic consequences of improved graft viability for longer periods of time in VCA grafts. Extrapolating these concepts into daily practice results in a more successful, efficient, and economically sound surgical practice without compromising the quality of outcomes.

CONCLUSION

VCA is a single-stage, conformable allogeneic graft that treats chondral defects and requires no additional fixation. This short-term evaluation shows that VCA can safely treat chondral defects with potential advantages to existing options.

AUTHOR CONTRIBUTIONS

Bhumit Desai: Contribution to concept of design, data analysis, acquisition; drafting the manuscript. **Eric Assid**: Contribution to concept of design, data analysis, acquisition; drafting and editing the manuscript. **Graylin Jacobs**: Contribution to concept of design; data acquisition; editing the manuscript. **Anouska Dasgupta**: Contribution to concept of design; basic science contributor; editing the manuscript. **Gerard Williams**: Contribution to concept of design, data analysis, acquisition; drafting and editing the manuscript. **Walter Choate**: Contribution to concept of design; editing the manuscript; contributing surgeon. **Scott Montgomery**: Contribution to concept of design; editing the manuscript; contributing surgeon. **Brian Godshaw**: Contribution to concept of design; editing the manuscript; contributing surgeon. **Misti Suri**: Contribution to concept of design; editing the manuscript; contributing surgeon. **Deryk Jones**: Contribution to concept of design; editing the manuscript; primary surgeon; primary investigator.

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CONFLICTS OF INTEREST STATEMENT

Deryk Jones, MD: Musculoskeletal Transplant Foundation—Research Support: Academic affiliation; Speaker honorarium: Speaking engagements. Misty Suri, MD: Arthrex—royalties and hospitality payments. The other authors declare no conflicts of interest.

ETHICS STATEMENT

The ethical approval was provided by DHHS Federal Wide Assurance Identifier: FWA00002050, IRB ID: 2019.069.

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