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Matrix-associated stem cell transplantation is successful in treating talar osteochondral lesions

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Abstract

Purpose Osteochondral lesions (OCLs) of the talus are a challenging and increasingly recognized problem in chronic ankle pain. Many novel techniques exist to try and treat this challenging entity. Difficulties associated with treating OCLs include lesion location, size, chronicity, and problems associated with potential graft harvest sites. Matrix-associated stem cell transplantation (MAST) is one such treatment described for larger lesions > 15 mm^2 or failed alternative therapies. This cohort study describes a 3 year review of the outcomes of talar lesions treated with MAST.

Methods A review of all patients treated with MAST by a single surgeon was conducted. Pre-operative radiographs, MRIs, and FAOS outcome questionnaire scores were reviewed. Intraoperative classification was undertaken to correlate with imaging. Post-operative outcomes included FAOS scores, return to sport, revision surgery/failure of treatment, and progression to ankle fusion.

Results In this study, 38 OCLs in 32 patients were identified. Median patient age was 35 years of which (68.8%) were male. Median length of follow-up was 36.7 months (range 12–64 months). (83%) returned to playing sport. Twenty-three patients underwent MAST in the setting of a failed previous operative attempt, with just nine having MAST as a first option. Nine patients out of 32 had a further procedure. Improvements were seen in all domains of the FAOS ($p < 0.05$).

Conclusion MAST has demonstrated encouraging results in lesions which prove challenging to treat, even in a "failed microfracture" cohort.

Level of evidence IV.

Keywords Talus · OCL · Matrix-assisted stem cell transplantation · AMIC · Microfracture · Bone marrow aspirate concentrate

Introduction

The long-term sequelae of OCLs of the talus can lead to chronic pain and secondary arthritis [18, 33]. The proposed treatment strategies are based on the symptoms associated with the lesion, the chronicity of the lesion, the size, and location of the lesion [6, 17]. Lesions less than 15 mm^2 are associated with more favorable outcomes versus lesions larger than 15 mm^2 [3, 4]. Non-operative treatments include non-weight bearing, protected weight bearing, and analgesia, and can include joint injections [7, 14, 39]. For lesions less than 15mm^2, the operative treatments can include bone marrow stimulation. This can be in the form of microfracture or drilling, the aim of which is to breach the subchondral plate [20]. The subchondral plate is thinned and damaged in OCLs [26]. Microfracture generates a fibrin clot via the influx of cytokines, growth factors, and mesenchymal stem cells which creates a super clot which then infill and forms fibrocartilage. This is distinct from the normal hyaline articular cartilage [22].

For lesions greater than 15mm^2, operative treatments include osteochondral grafting techniques [17, 22]. The goal of grafting is to implant a material which has similar

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biological and mechanical properties to the native articular cartilage. The delivery of the graft can be as a single unit or multiple plugs (mosaicplasty) or osteochondral autograft transfer system (OATS). The concern with utilizing grafts is the morbidity from the donor site [13, 29]. Autologous grafts are often harvested from the ipsilateral knee [33]. Other methods of treatment include cellular-based reparative treatments, such as autologous chondrocyte implantation (ACI) or matrix-associated chondrocyte implantation (MACI).

MACI is a two-step procedure which avoids the need for a covering layer [8, 10]. ACI commonly utilizes a collagen I/III membrane [12].

Newer techniques use a one-step procedure, combining microfracture with a collagen matrix scaffold [1, 34]. Chondro-Gide® is the most commonly used scaffold in autologous matrix-induced chondrogenesis (AMIC). It is a porcine-based membrane which has a bilayer structure made of type I/III collagen. Matrix-associated stem cell transplantation (MAST) is a technique which utilizes bone marrow aspirate as an adjunct to AMIC [10, 30].

Materials and methods

A prospective cohort study from a single specialized foot and ankle clinic using 5 year follow-up data was conducted. The aim of the study was to conduct a review of patients treated with MAST treatment to assess for functional outcomes, return to sport, and associated complications.

Patients' selection

The study was conducted over a 5 year period. The inclusion criteria were patients with an OCL of the medial or lateral talar dome of 15 mm^2 or greater as well as patients with previous failed attempts at microfracture. Exclusion criteria included patients with inflammatory joint disease, generalized degenerative changes throughout the joint, or patients with less than 12 month follow-up. A chart review and telephone survey were also conducted. This was to ensure that no additional complications had occurred outside of the follow-up period. The FAOS questionnaire was used to assess functional outcome. It is a validated questionnaire which has five domains and is scored from 1 to 100. A score of 100 score equals excellent functionality. Two patients were lost to follow up as they could not be contacted.

Patients were examined physically and radiologically in a standard fashion. They completed a standard Foot and Ankle Outcome Score questionnaire (FAOS) [32] to gather subjective symptoms, while pain was further assessed through the visual analogue scale (VAS) [28]. MRI was used to characterize the lesions, and identify the location of the lesions and any concomitant pathology. The lesions were categorized according to the Hepple et al.'s classification [16]. Ethical approval for this study was granted by institutional review board through Merlin Park Clinical Research Ethics Committee, I.D. number C.A. 2091.

Surgical technique

Technique

Patients undergo an ankle arthroscopy initially. This is conducted with a standard set up, antibiotic prophylaxis according to local guidelines with a thigh tourniquet and side support with the ankle in a traction stirrup to provide joint distraction. This allows evaluation of the joint surface, characterization of the lesion, and whether any adjunctive procedures like synovectomy, cheilectomy, or ligament reconstruction are warranted.

The MAST procedure is performed according to lesion location. Medial-based lesions are accessed through a medial malleolar osteotomy. A ventrolateral approach is utilized for lateral-based lesions. The lesions are prepared in a standard fashion (Figs. 1, 2).

Bone marrow aspirate concentrate harvest and spongiosa graft harvest

The harvest technique is generally conducted before the microfracture, because the centrifuge process can take 15 min to complete. This process can be conducted simultaneously, while preparation of the OCL is being undertaken [24]. The iliac crest is utilized as the site of harvest in our clinical practice. The BMAC is then prepared using

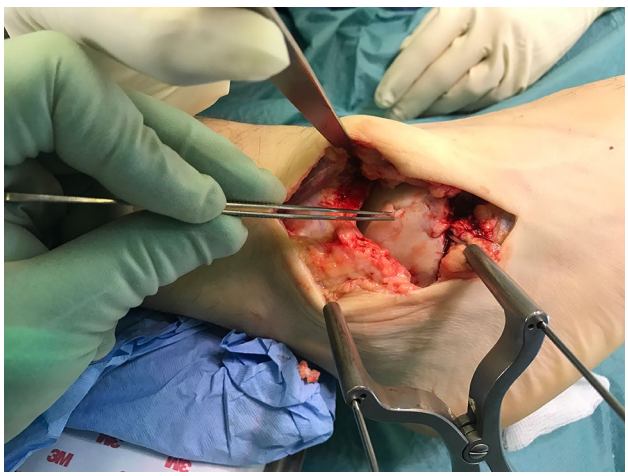

Fig. 1 Preparation of the lesion. Joint distraction with hintermann distractors

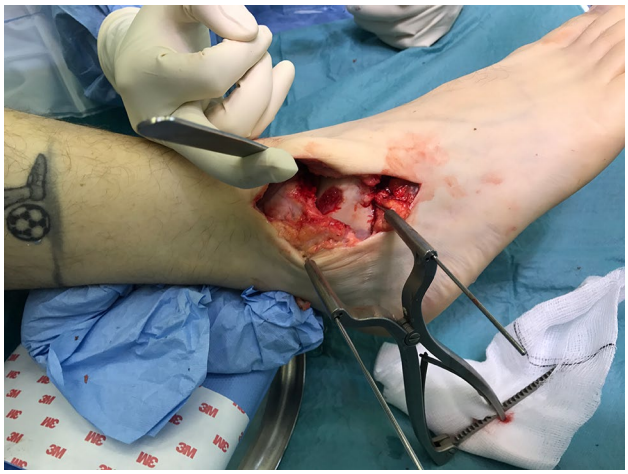

Fig. 2 Lesion curetted and drilled with k wire down to bleeding cancellous bone

the Harvest® BMAC Cellular Therapy System® by CelgenTek Limited, a commercially available system.

The procedure pack (BMAC 30-02) includes proprietary contents to collect the aspirate concentrate. The system includes a bedside workstation to produce the BMAC called the Harvest SmartPRep 3 system workstation®. A 15-gauge BMA needle with a depth stop is used to aspirate the bone marrow from the iliac crest. The iliac crest incision is centered over the middle one-third of the iliac crest, via a stab incision. The needle is introduced until the depth stop is employed. It is stabilized by hand. The plunger is depressed and the bone marrow is collected. The system collects 30 ml of bone marrow. The process produces 3–4 ml of mesenchymal stem cells. The iliac crest bone graft is harvested using an osteotome through careful dissection in the middle one-third of the iliac crest. Cancellous (spongiosa) bone is harvested.

Medial malleolar osteotomy and microfracture

The medial malleolar osteotomy is performed through a chevron osteotomy technique. It is first pre-marked with wires, and a saw is used to start the cut and then completed with an osteotome.

The defect is prepared by elevating the cartilage cap off the lesion. A curette is used to clear all damaged bone or cystic materials until bleeding bone is encountered.

Microfracture is conducted using a low-speed drill with a 1.1 mm k wire. It is important that the subchondral plate is breached.

The iliac crest bone graft is then impacted into the defect.

MAST technique

The bilayer matrix is pressed against the filled defect. The foil is then cut to shape with the help of the template. The bilayer has a rough side and a smooth side. The smooth side consists of a cell-occlusive surface. The purpose of this is to prevent the blood coagulate and graft from diffusing into the joint surface. The smooth side faces the joint. The rough or porous side has collagen fibres which allow the ingrowth of new cells. The bilayer matrix is cut to size roughly before and definitively after.

The BMAC is used to impregnate the collagen I/III bilayer matrix and the graft. The Chondro-Gide is soaked in the BMAC. The matrix with the BMAC is fixed into the lesion and sealed with fibrin glue (Tisseel®). The matrix expands by 10–15% when wet, and this is incorporated into the planning of the size of the lesion. The ankle is then cycled to ensure that the structure is stable. The osteotomy site is reduced and fixed using the wires as markers and two 4.5 mm screws to hold the reduction. The joint is then closed in a layerwise fashion.

Post-operative care

Patients were placed in a non-weight-bearing backslab cast for 10 days with an office check for suture removal. They were then changed to an aircast boot and kept non-weight bearing for 4 weeks to allow the osteotomy to heal. At 6 week post-operative, progressive weight bearing in an aircast boot was then allowed for a further 6 weeks.

Statistical analysis

The data were analysed using SPSS version 24 (IBM SPSS statistics, IBM, Armonk, NY, USA). An unpaired *t* test was used to compare the visual analogue scores pre- and post-intervention and the FAOS questionnaire scores, as well. The significance level was set at a p value of <0.05. A power analysis was calculated per test and justified sufficient power with a sufficient power of (>0.8).

Results

Demographic data

Thirty-two patients were included in the study, with total of 38 lesions. Table 1 delineates the age and demographic details. The mechanism for the development of an OCL was a preceding ankle fracture (6), sprain (8), and repetitive injury from sports (11), while, in four cases, the mechanism was unknown (Table 2). Twenty-three patients had a previous failed procedure for OCL, twenty-one patients had

Table 1 Patient and lesion characteristics

	Number	%
Male	22	68.8
Female	10	31.2
Mean age at surgery (SD)	35	(SD 9.6)
Age range	18–54	
Smoker	2	6.25
OCL location		
Medial talar dome	19	
Lateral talar dome	7	
Medial and lateral talar dome	6	
Mean size of OCL < 15 mm^2	1.7 mm^2	
MAST as first operation	9	
MAST as salvage operation	23	

Table 2 Mechanism of injury of OCL

Mechanism of injury	Number	%
Ankle fracture	6	18.7
Single sprain	6	18.7
Multiple sprains	2	6.2
Sports injury	11	34.3
Unknown mechanism	4	12.5

Table 3 Previous Surgery prior to MAST treatment

Previous surgery	Number	%
Ankle fracture ORIF	4	12.5
Microfracture for OCL	21	65.6
OATS	1	3.1
AMIC	1	3.1

failed microfracture surgery, one patient had OATS, and one patient had attempted AMIC (Table 3). Nine patients had MAST as a first-line treatment.

Pre-operative MRI

Table 1 delineates the location of the lesions and size. All thirty-two patients had at least one lesion greater than or equal to 15mm^2. The mean lesion size in the cohort was 1.7 cm^2 (SD 0.19).

Additional procedures

An important part of treating OCLs is recognizing underlying contributing pathology. Table 4 shows the stabilization or corrective alignment procedures which patients underwent. This included lateral ligament stabilization or calcaneal osteotomies. These procedures were uncomplicated and all went on to heal.

Table 4 Additional surgical procedures performed

Additional procedure	*N*	%
Synovectomy	6	18.7
Tibial plafondplasty	5	15.6
Lateral ligament reconstruction	4	12.5
Varus osteotomy	2	6.2
Calcaneal osteotomy	2	6.2
Valgus osteotomy	1	3.1

Subjective outcomes

There was a 95% response rate to the questionnaires. Table 5 delineates the pre-operative and post-operative scores. The mean pre-operative score for pain on the VAS was 8.7 (±1.2 SE) and mean post-operative pain VAS score was 3.8 (±2.3 SE). The mean improvement score for burden of symptoms was 32.1 (±22.1 SE). The mean improvement score for ADLs was 23.9 (±23.8 SE). The mean improvement score for QOL was 33.8 (±25.1 SE). The mean improvement score for pain on the FAOS questionnaire was 31.2 (±22.9 SE). These improvements were statistically significant with a p value of <0.05 based on an independent samples t test.

Long-term outcomes

Twenty-three patients (71.9%) of the cohort participated in sport prior to their injury and 83% of these patients returned to sport after their treatment. Table 6 demonstrates the complications in the cohort.

Nine patients underwent further procedures. Two patients had a further operation in relation to their OCL. The MRI for these two patients demonstrated a problem with the operation site, showing failure of matrix layer in the form of oedema and fissuring around the site. The intraoperative findings in both demonstrated a corner of the graft to be loose and this was revised. At final follow-up, these patients were doing well. Two patients from this cohort underwent future ankle fusion. Their radiographs and MRI showed subtalar and ankle arthritis. The time from MAST treatment to fusion was 3 and 4 years, respectively. Another patient had tenosynovitis of their posterior tibial tendon on MRI. Of note, this patient had had a calcaneal osteotomy. The patients who had a cheilectomy and arthrofibrosis did not have any concerning features with relation to their talar lesion sites. Both of these patients had two initial failed microfracture treatment procedures. The remainder of the patients had a further cheilectomy or arthrofibrosis debridement. Table 6

Table 5 Subjective outcome VAS scores and FAOS scores with the SE mean recorded

	Pre-op mean	SE mean	Post-op mean	SE mean	Mean improvement	SE mean	*p* value
Pain VAS	8.7	(1.1)	3.8	(2.3)	4.8	2.5	< 0.005
FAOS pain	42.1	(20.8)	73.4	(18.2)	31.2	22.9	< 0.005
FAOS ADL	50.3	(22.7)	79.1	(18.4)	23.8	23.8	< 0.005
FAOS symptoms	38.6	(18.4)	70.7	(19.1)	32.1	22.1	< 0.005
FAOS sports	22.2	(21.0)	58.9	(27.1)	36.7	27.9	< 0.005
FAOS QOL	16.1	(18.4)	49.9	(29.2)	33.8	25.1	< 0.005

Table 6 Further surgeries/complications

Complication	Number	%
Stiffness	1	3.1
Infection	1	3.1
Neuropraxia	1	3.1
Revision of OCL	2	6.2
Ankle fusion	2	6.2
Other procedure	5	15.6

demonstrates the complications or further surgeries incurred by this patient cohort.

Discussion

The most important finding in this study is that MAST for treatment of OCL is successful, even in patients who have undergone prior failed microfracture treatment. One patient in the study had five previous attempts at microfracture before ultimately having MAST technique. A recent review by Lambers et al. [19] demonstrated the need for ongoing research into this secondary cohort.

The concern with microfracture is that the repair generates type I cartilage or fibrocartilage [21, 27]. Non-operative treatment was observed in a systematic review by Verhagen et al. to be successful in 45% of cases [39].

Grafting techniques can provide intact cartilage, but the challenges are in achieving integration of the graft, matching anatomic congruence and problems with failure of junctional areas, or healing of the graft [38]. In this cohort, two patients required revision of the graft due to a corner of the graft becoming loose.

Lesion size is one of the key prognostic factors for the successful treatment of OCLs. Choi et al. [5] originally showed that bone marrow stimulation should be reserved for lesions with a size < 15 mm^2 and lesions greater than this faired poorly. However, more recently, a systematic review by Ramponi et al. suggested that a size of 107 mm^2 be utilized instead [28]. Scaffolds are commonly utilized for lesions greater than 150 mm^2. Ramponi et al. demonstrated that the mean size of lesions being treated with scaffolds was 215 mm^2 [28]. However, the level of evidence in these studies is acknowledged to be of low quality.

A systematic review by Hannon et al. addressed the inconsistencies between outcome measures [15]. Currently, a variety of treatment options for larger (> 15 mm^2) lesions exist including fixation, OATS, ACI, MACI, AMIC, or MAST [5, 23, 25]. OATS has been shown to have a positive outcome in several studies [17]. However, it is also known to be associated with donor site morbidity [20].

Follow-up in the form of MRIs has been described by Giannini et al. [9]. Valderobanno et al. [37] described a one-step technique, whereby talar OCLs were debrided, autologous grafted, and sealed with a collagen scaffold. AOFAS scores improved by a mean of 30 points, VAS scores improved and MOCART scores improved, as well [36]. Richter et al. in 2017 described promising outcomes in a large cohort of 100 patients with 5 year follow-up [31]. There were improved VAS outcome scores, but there was lack of a control group.

Cost has previously been cited as a concern for the newer biologic treatments. A review of insurance company databases by Zhang et al. demonstrated that ACI had the highest associated costs ($16,016.70), while the cost for microfracture was the lowest ($7,258.51) [41]. This procedure which we describe is one step and lower cost. Repeated procedures (knee stiffness or cartilage hypertrophy) were reported for ACI with a cost associated with this of ($710.00), while microfracture patients had no repeated procedures.

Some of the limitations quoted with autologous chondrocyte implantation (ACI) include cellular dedifferentiation and donor site morbidity. The cells are cultured in vitro and transferred into the defect [2, 35]. Mesenchymal stem cells are pluripotent and will continue to act as a progenitor in the new environment.

This study describes a modified AMIC technique with MAST treatment for difficult to treat OCLs of the talus. A proposed advantage of this method of treatment includes the potential to deliver higher quantities of mesenchymal stem cells directly to the defect in question [11, 23, 30, 40]. It is

estimated that the concentration of stem cells on peripheral blood is 0.1% versus 3% in the bone marrow aspirate from the pelvis of young adults [23]. The advantage of MAST over AMIC alone is the potential higher local concentration of mesenchymal stem cells [34]. The Chondro-Gide matrix is thought to be more physiological in content and structure [30]. The most commonly utilized scaffold was Chondro-Gide in this systematic review, and favorable outcomes were achieved with it.

This patient cohort includes a large number of lesions of > 150 mm^2 ($n = 34$). This cohort also contains a sizeable portion (71.8%) of previously unsuccessfully treated lesions. The 'failed microfracture' cohort is an under-reported phenomenon in the literature. Pestka et al. [26] reported on ACI in failed microfracture patients and compared the success versus ACI as first-line treatment in OCLs of the knee. The group found a higher success rate in the ACI as the first-line treatment. This has not been addressed to the same degree in the talus. A lack of clear guidelines persists despite the large number of low evidence small volume studies. This cohort demonstrates good survival outcomes with MAST treatment for this challenging cohort. The addition of bone marrow aspirate to the scaffold has little in the way of morbidity. There were no adverse events reported in this group with the collection and impregnation of bone marrow aspirate concentrate.

This study demonstrates the efficacy of MAST in a difficult cohort of patients. Twenty three (71%) of the cohort had a failed attempt at treating their OCL prior to the MAST intervention. The lack of a control group is somewhat mitigated by the fact that a high proportion of these patients already had a failed attempt at treatment. The authors postulate that this forms an internal control. Other strengths of this study include its robust methodology, single surgeon series, and 95% follow-up of patients.

The limitations of this study include the lack of MRI follow-up. It is not possible from a cost point of view to obtain MRIs if patients are asymptomatic in the climate which the study was conducted in. It must also be noted that six patients underwent an additional procedure and it is acknowledged that there was no control group.

Conclusion

MAST has demonstrated encouraging results with a good safety profile. Functional outcomes improved in all domains of the FAOS questionnaire, while 83% returned to a similar level of sport. Two patients (6.2%) underwent future ankle fusion with the same number undergoing revision of their OCL. MAST is an efficacious treatment for larger OCLs and can reliably be utilized even in the "failed microfracture" cohort. This helps to guide the treatment of the 'failed microfracture' cohort.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing conflicts of interest.

Ethical approval Ethical approval for this study was granted by institutional review board through Merlin Park Clinical Research Ethics Committee, I.D. number C.A. 2091.

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