J Knee Surg
DOI: 10.1055/s-0039-3400951

Original Article

Thieme Medical Publishers 333 Seventh Avenue, New York, NY 10001, USA.

Micronized Dehydrated Human Amnion Chorion Membrane Injection in the Treatment of Knee Osteoarthritis—A Large Retrospective Case Series

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Abstract

Osteoarthritis (OA) of the knee is a leading cause of chronic pain and disability in the United States. Current treatment options primarily target OA symptoms reserving surgical intervention and knee replacement for those who fail conservative measures. With average age of patients with knee OA decreasing, regenerative treatment approaches to reduce symptoms, increase quality of life, and delay the need for surgical intervention are increasingly sought. Human amniotic membrane contains growth factors and cytokines, which promote epithelial cell migration and proliferation, stimulate metabolic processes leading to collagen synthesis, and attract fibroblasts, while also reducing pain and inflammation. Micronization of the tissue allows for suspension in normal saline and injection. We conducted a retrospective review of 100 knees treated for symptomatic OA with micronized dehydrated human amnion/chorion membrane (mdHACM) and followed for 6 months. Our purpose is to present our experience and patient outcomes. Data were abstracted from electronic medical records of 82 consecutive OA patients (100 knees) injected with 100 mg mdHACM. Patient age, gender, adverse events and routinely collected Knee Injury and Osteoarthritis Outcome Score (KOOS) were evaluated. Effectiveness of mdHACM treatment was measured by serial KOOS at baseline, and posttreatment at 6 weeks, 3, and 6 months. Overall mean KOOS for the cohort was 40 at baseline, improving to 52, 62, and 65 at 6 weeks, 3 months, and 6 months post-mdHACM injection. Percent increases were 32, 56, and 65%, respectively. Quality of life and sports/recreation domains improved by 111 and 118%, respectively, at 6 months. Pain scores improved by 67% at 6 months. All scores improved throughout the observation period. The most common adverse event was pain after injection lasting 2 to 7 days, observed in 68% of cases. This represents the largest single-physician experience with mdHACM for treatment of knee OA reported to date. Injectable mdHACM appears to be a potentially useful treatment option for knee OA patients. Controlled studies are underway to confirm these observations.

Keywords

amniotic membrane - dehydrated human amnion/chorion membrane - osteoarthritis

Worldwide, osteoarthritis (OA), a degenerative joint disease, is a leading cause of chronic disability, pain, and loss of quality of life.[1] OA is a chronic, progressive degeneration of the articular cartilage accompanied by cartilage loss, joint deformity, pain, and instability. As it progresses to end-stage disease, exposure of bone surfaces leads to progressive pain, loss of function of the affected joint, and disability. Patients with OA experience a diminished quality of life, manifested as limitations in physical function and their ability to perform normal daily tasks, along with substantial pain when active.[2]

The impact of OA on individuals and society in general is severe and expected to grow. Between 2013 and 2015, it has been determined that approximately 22.7% of adults (54.4 million people) in the United States had doctor-diagnosed arthritis, and over 43% of those diagnosed had arthritis-attributed activity limitations.[3] OA has been reported to be the single most expensive condition among Medicare patients.[4] Hip and knee OA is one of the leading causes of global disability.[5] Symptomatic knee OA is believed to be particularly problematic and impactful on overall health and mobility. [2] [5]

Current treatment modalities target the symptomatic management of OA, which may ultimately include surgical procedures such as joint replacement for severely symptomatic patients or patients who fail conservative measures. Patients and clinicians are increasingly seeking disease-modifying and regenerative approaches to decrease symptoms, increase quality of life, and delay the need for surgical intervention.[6] [7] Effective, injectable, intra-articular therapies that can be utilized in lieu of, or prolong the need for joint replacement are desirable. Research and development on the use of injectable intra-articular therapies as sources of growth factors, anti-inflammatory mediators, and medicinal signaling cells for treatment of OA is rapidly evolving.

Human amniotic membrane synthesizes a variety of growth factors, cytokines, and vasoactive peptides that modulate inflammation.[8] [9] [10] In addition, these tissues contain amniotic epithelial cells and amniotic mononuclear undifferentiated stromal cells, which have chondrogenic and osteogenic differentiation capacity.[8] [9] [10] Amniotic membranes are also rich sources of hyaluronic acid and proteoglycans, which could play a role in the potential therapeutic relief of OA.[8] [9] [10] Preclinical and clinical studies have shown promising results on the use of placental tissues as a treatment for OA and other orthopedic conditions.[8] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22]

A contemporary tissue processing technique (PURION process) which cleans, and dehydrates human amniotic membrane, allows for the material to be micronized for suspension in normal saline and injection. Human cells, tissues, and cellular and tissue-based products (HCT/Ps) fall under Section 361 of the Public Health Service Act and are currently regulated by the United States Food and Drug Agency (FDA) under 21 C.F.R. 1271. Presently, FDA approvals are not granted for products with this classification, but FDA has begun an initiative necessitating that certain human tissue products meet additional requirements in the future. The purpose of this report is to present our clinical experience with using micronized dehydrated human amnion chorion membrane (mdHACM) injection (AmnioFix Injectable, MiMedx Group Inc., Marietta, GA) as a treatment for symptomatic knee OA.

Methods

In a retrospective study design, clinical and administrative data were abstracted from the medical records of 82 OA patients and 100 knees injected with 100 mg mdHACM by a single physician, over a 14-month period. During this period, the treating physician routinely offered treatment with mdHACM injection to patients presenting with knee OA pain recalcitrant to conservative treatment, in an attempt to prolong the need for knee replacement surgery. Prior to mdHACM injection, patients were informed of the limited evidence related to mdHACM for treatment of knee OA, and the potential risks and benefits of the injection therapy. As insurance reimbursement for this type of treatment is not widespread, patients were informed of expected out-of-pocket costs related to the mdHACM product.

Treatment consisted of an injection of 100 mg of mdHACM, suspended in 3 mL of 0.9% sterile normal saline performed by the primary author. Prior to mdHACM administration, local anesthesia was achieved by injection of 2 mL of 0.5% Marcaine in the subcutaneous tissue. The mdHACM allograft was injected with ultrasound guidance through a 22-gauge needle. Patients were instructed to stop all nonsteroidal anti-inflammatory drugs (NSAIDs) postinjection. Routine follow-up was scheduled to occur in the physician's office at 6 weeks, 3months, and 6 months after the mdHACM injection. Reported level of pain associated with their knee OA diagnosis, adverse events to treatment, and Knee Injury and Osteoarthritis Outcome Score (KOOS)[23] were recorded in the patients' clinical record at each office visit.

Institutional Review Board (ADVARRA IRB) exemption was obtained for data collection and presentation. Only minimally necessary data were abstracted and deidentified for analysis. Data collected from the investigators' electronic medical record included age, gender, adverse events after treatment with mdHACM, and KOOS routinely recorded at baseline and 6 weeks, and 3 and 6 months, posttreatment. The KOOS was determined using a patient-reported outcome measurement instrument, developed to assess the patient's opinion about their knee and associated problems. In the KOOS scale used in this evaluation, 0 represents the worst situation (extreme problems with item assessed), while 100 is an ideal situation (no problems with item assessed). Effectiveness of mdHACM treatment was measured by serial KOOS collected at 6 weeks, and 3 and 6 months postinjection. Data were summarized using descriptive statistics to evaluate changes in KOOS over time. An improvement in KOOS of at least 10 points was considered to represent meaningful positive clinical change.

Results

Data from 82 patients with100 treated knees were included for analysis. Of these 82 patients, the majority were female (51/82, 62%). Mean age at treatment was 61.6 ± 10.6 years, median age of 58.0 years with an age range of 36 to 89 years.

Mean KOOS at baseline and at 6 weeks, 3 months, and 6 months postinjection are presented in [Table 1]. Baseline scores reflected patients reporting most difficulty with sports/recreation (mean score 24.7 ± 21.2) and quality of life issues (mean score 27.0 ± 18.8). Within 6 weeks of mdHACM injection, all areas of assessment in the KOOS subscale had an improvement of mean score by greater than 10 points signifying meaningful positive clinical change. By 6 months, differences of 24.8 to 30 points were observed in all subcategories. Mean percent change in score is reported in [Table 2]. Greatest change was noted in those subscale categories where patients had reported the most difficulty at baseline.

Table 1
Mean KOOS over time

KOOS subscale	Preinjection	6 wk	3 mo	6 mo
Daily living	48.6 ± 18.0	65.8 ± 18.0	73.3 ± 18.4	77.3 ± 18.5
Pain	43.5 ± 15.6	60.5 ± 17.5	68.4 ± 19.0	72.8 ± 18.3
Quality of life	27.0 ± 18.8	43.3 ± 19.8	51.7 ± 22.1	57.0 ± 22.5
Sports/Recreation	24.7 ± 21.2	41.3 ± 25.5	50.9 ± 26.7	53.8 ± 28.8
Symptoms	44.7 ± 18.3	61.7 ± 17.7	67.8 ± 19.3	69.5 ± 19.5
Overall KOOS	39.6 ± 14.2	52.2 ± 17.9	61.9 ± 19.4	65.4 ± 21.0

Abbreviation: KOOS, Knee Injury and Osteoarthritis Outcome Score.

Note: Data presented as mean ± standard deviation.

Table 2
Mean percent increase over preinjection time point

KOOS subscale	Preinjection	6 wk	3 mo	6 mo
Daily living	0%	35%	51%	59%
Pain	0%	39%	57%	67%
Quality of life	0%	60%	91%	111%
Sports/Recreation	0%	67%	106%	118%
Symptoms	0%	38%	51%	55%
Overall KOOS	0%	32%	56%	65%

Abbreviation: KOOS, Knee Injury and Osteoarthritis Outcome Score.

Note: Data presented as percentage.

Overall, at 6 weeks postinjection 36/100, 36% of treated knees had a minimum of a 10-point improvement in KOOS in all subcategories, while 47/100, 47% had at least a 10-point improvement in the overall KOOS. At 3 and 6 months postinjection, 55 and 63% of patients, respectively, had reported clinically meaningful improvement in all subcategories, while 65 and 76% had meaningful improvement overall.

Clinical records were examined to identify adverse events associated with mdHACM injections in the knee within 6 months of injection. No serious or ongoing, unresolved adverse events were observed in this cohort. Pain, postinjection was commonly observed. Postinjection patients were instructed to stop all NSAIDs which had been the mainstay of treatment for their knee symptoms prior to the injection. Discomfort postinjection was managed with rest, ice, compression, and elevation as needed. Although patients were instructed not to take NSAIDS postinjection, acetaminophen was allowed if needed. Following mdHACM injection, knee pain was reported as mild in 21/100 (21%) of knees. Moderate pain and soreness were reported in 68/100 (68%) of treated knees, which typically resolved within 5 to 7 days of the injection. A small number, 5/100 (5%), rated their knee pain as severe and required the use of assistive devices (i.e., single crutch or cane) for ambulation in the 3 to 4 days following the injection. Six of 100 knees (6%) had no pain or soreness following the injection. Additional reactions around the injection site included swelling, redness, and soreness which typically resolved within 4 to 6 days following the injection.

Discussion

OA is a leading cause of pain and disability among adults with a current prevalence of around 15% and a predicted prevalence of 35% in 2030 for symptomatic OA.[6] With an aging population, these numbers will only continue to rise. Symptomatic and advanced knee OA is particularly impactful on overall health and mobility. The impact of this highly prevalent disease on both individuals and society is quite formidable, and the costs associated with knee OA are significant. [4] [24] [25] To our knowledge, these data represent the largest single-physician experience with injectable amniotic tissue for treatment of knee OA reported to date. In our experience, injectable mdHACM is easy to obtain and use and appears to be a potentially useful treatment option for knee OA patients. Pain associated with treatment was transient and inconsequential to observed patient outcomes.

Nonsurgical alternatives to joint replacement are desirable. For a variety of reasons including patient preference and/or medical comorbidities and costs, health care providers need to be prepared to care for and counsel all patients suffering from knee OA who are looking for nonsurgical effective treatments that can delay or eliminate the need for surgical intervention. Evidence-based, nonsurgical approaches to the treatment of knee OA include nonpharmacologic and pharmacologic modalities targeted at relieving pain, improving joint function, and modifying risk factors for disease progression. Exercise and weight loss are effective for long-term treatment of knee OA and recommended for most patients.[26] In addition to these lifestyle modifications, oral analgesics and intra-articular injections of cortisone, hyaluronic acids, platelet-rich plasma, and autologous stem cells are often utilized for symptom relief, with varying levels of clinical acceptance and reported short- and long-term success rates.[26] [27]

Preclinical studies have shown that micronized placental tissue can attenuate OA development and cartilage destruction. [11] [12] [13] Despite these promising results, there are limited clinical data currently available regarding the use of amniotic membrane-derived products for the treatment of OA. Vines et al[14] reported on 6 patients with knee OA receiving a single intra-articular injection containing cryopreserved particulated human amnion and amniotic fluid cells. Patients were followed for 12 months after treatment without any significant injection reactions observed. In 2017, Gellhorn and Han[21] reported on the use of mdHACM allograft injection for the treatment of tendinopathy or arthritis. In that report, there were 20 patients with arthritis (including 8 knees) treated with an ultrasound-guided injection of 40 mg mdHACM reconstituted in 1 mL normal saline. As observed in the current report, localized pain at the injection site was common, but no other adverse events or side effects were identified. Gellhorn and Han concluded that mdHACM injection was clinically effective in reducing pain and improving function in the setting of tendinosis or arthropathy.[21] Data such as those reported by Vines et al[14] and Gellhorn and Han,[21] and those within this article are very encouraging. Many prospective randomized trials are currently underway to examine the efficacy of amniotic membrane products to treat specific musculoskeletal indications[8] and address FDA's upcoming Investigational New Drug regulatory changes relative to this type of tissue and to support Biologic License Application approval.

Limitations with interpreting data from this case series include those characteristic to any retrospective review. This was not a randomized trial and patients were not blinded to treatment. Indeed, patients chose to receive mdHACM injection in lieu of other treatment or surgical options, thus their choice may have influenced their perception of symptom improvement. As the goal of the review was to report our experience with using mdHACM, we did not compare with a control group of patients that did not receive mdHACM, or other injectable treatments. The ability to report KOOS that were prospectively collected as a course of standard practice over a 6-month period of patient encounters is a strength of this report, although our conclusions as to treatment effectiveness could be supported with the addition of objective data and longer-term follow-up. As only one treatment was performed, we do not know if additional mdHACM injections would improve our results.

In summary, preclinical data support the use of treatments derived from placental tissue as a treatment for OA. Clinical data are emerging which support the use of products such as mdHACM as a treatment for OA of the knee. The material appears to be safe with injection site pain and flare similar to other injectable treatments. Large prospective studies are

currently underway to prove the efficacy of injectable mdHACM for treatment of knee OA and other orthopedic conditions. Further studies will be needed as to how these types of injectable treatments may reduce or prolong the need for surgical joint replacement.

Conflict of Interest

K.J.A. reports research support from Mimedx; none outside the submitted work.

S.H. was an employee of MiMedx; and reports stock options and stock grants received from MiMedx.

B.H. was an employee of MiMedx; and reports personal fees from MiMedx outside the submitted work.

K.K. is an employee of MiMedx; and reports stock options and stock grants received from MiMedx.

N.B.I. reports personal fees from MiMedx outside the submitted work; and reports stock options and stock grants received from MiMedx.

D.M. is an employee of MiMedx; and reports stock options and stock grants received from MiMedx.

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