Temporomandibular Joint Arthrocentesis and Microfragmented Adipose Tissue Injection for the Treatment of Internal Derangement and Osteoarthritis: A Randomized Clinical Trial

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Purpose: Internal derangement and osteoarthritis are the most common degenerative temporomandibular joint diseases and initial treatment for such conditions relies on arthrocentesis. Microfragmentation of adipose tissue has been proven in orthopedic literature to represent a more effective method to preserve stem cells, but no application has ever been reported in the temporomandibular joint. The purpose of this randomized clinical trial is to compare standard treatment conducted by injecting hyaluronic acid after the procedure to the new treatment relying upon microfragmented adipose tissue injection using the Lipogems technology.

Materials and Methods: A randomized clinical trial was designed enrolling 20 patients in the control group receiving the standard treatment and 20 patients in the experimental group receiving microfragmented adipose tissue obtained through the Lipogems technology after arthrocentesis. Two main outcomes were defined, pain (visual analogic scale) and function (maximum interincisal opening). Both were measured in the immediate preoperative time, and 10 days, 1 month, and 6 months after the procedure.

Results: In both groups, pain reduction and mouth opening significantly improved compared with preoperative situation ($P = .001$). At 6-month follow-up, there was an almost statistically significant reduction of pain compared with preoperative visual analogic scale ($P = .0546$) and a statistically significant improvement of mouth opening ($P = .0327$). Overall, statistical analyses showed that the experimental group had a statistically significant superiority in the success rate of the procedure compared with the control group ($P = .018$).

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Conflict of Interest Disclosures: Carlo Tremolada is founder of Lipogems S.p.A. and inventor of the technology. Carlo Tremolada is consultant for Lipogems and he does not own any stock of the society. All the other authors declare no conflicts of interest.

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Conclusions: Preliminary results of this clinical trial show that the injection of microfragmented adipose tissue can significantly improve outcomes of pain and function compared with the standard treatment and encourage to pursue research on this topic. Further studies with a longer follow-up time are needed to evaluate the clinical stability of the achieved improvement in pain and function.

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Internal derangement and osteoarthritis are the most common degenerative temporomandibular joint (TMJ) diseases and can lead to pain and functional impairment affecting quality of life. Initial management for such conditions includes oral appliances, NSAID drugs, physical therapy and behavioral adaptations. Q6

Arthrocentesis first described by Nitzan et al.[1,2] is the simplest intervention on the TMJ with the aim to decrease joint pain and improve the range of motion in patients not responding to initial conservative treatment.

Arthrocentesis consists of an intraarticular lavage using 2 needles placed in the upper joint space. It is a versatile technique which can be performed under local anesthesia in an outpatient setting as well. The rationale of this procedure is to remove inflammatory mediators, reduce friction, stimulate the production of new synovial fluid, eliminate suction-cup effect.

Arthrocentesis has been demonstrated to be a very effective procedure with a high success rate and a favorable benefit-cost ratio.

In addition to arthrocentesis, the injection of hyaluronic acid (HA), local anesthetics such as bupivacaine and mepivacaine, morphine and steroids has been reported in literature.

Most of studies describing these procedures are conflicting in terms of superiority respect to the base technique represented by arthrocentesis alone, demonstrating a lack of evidence on which technique offers the best outcomes. For instance, Bouloux et al.[3] in 2016 showed that the additional instillation of corticosteroids or hyaluronic acid provided no additional benefits in decreasing pain and jaw function. On the other hands the results reported by Dolwick et al.[4] in 2020 support steroid supplementation after arthrocentesis.

In recent years research has been directed towards biological fields as the injection of platelet-rich plasma (PRP) that is a concentrate of platelets and associated growth factors achieved by centrifugating the patient's blood. A systematic review on this topic showed a slight evidence on the benefits of intraarticular injection of PRP.[5]

New horizons are represented by biological therapies and tissue engineering, which led to the development of techniques to inject stem cells derived from bone marrow in the field of orthopedics. Based on these studies, De Riu et al.[6] reported their promising results comparing the efficacy of intraarticular TMJ injection of bone marrow nucleated cells with hyaluronic acid.

Recent research and clinical application in knee osteoarthritis increased interest in the potential of autologous microfragmented adipose tissue demonstrating the benefits related to the injection of adipose derived mesenchymal stem cells in improving pain and function.[7]

The purpose of this study was to evaluate the hypothesis that TMJ arthrocentesis with intraarticular injection of autologous microfragmented adipose tissue leads to better clinical outcomes in terms of reducing pain and improving function compared with arthrocentesis and intraarticular injection of hyaluronic acid (HA) in patients with TMJ internal derangement and osteoarthritis. The trial has been reported according to the CONSORT statement (http://www.consort-statement.org) for improving the quality of reporting of parallel-group, randomized, controlled trials.

Materials and Methods

STUDY DESIGN

A prospective randomized clinical trial was designed and conducted at the Oral and Maxillofacial Surgery Department, Academic Hospital, University of Udine.

The investigation was performed in compliance with the principles of Helsinki Declaration (1975) for medical research on human subjects. This study was approved by Regional Ethical Committee with the approval number (CEUR-2019-Sper-073).

Patients were enrolled in a period between July 2019 and February 2020. Both unilateral and bilateral cases were included.

Inclusion criteria were determined as follows: *1)* TMJ internal derangement and osteoarthritis assessed by clinical examination and MR imaging; *2)* presence of TMJ-related symptoms including at least limited mouth opening and joint pain; *3)* previously failed conservative treatment; *4)* age superior to 16 years; *5)* no previous TMJ surgical procedures; *6)* acquisition of informed consent; *7)* complete availability of the data acquired preoperatively and during each follow-up.

Patients were excluded from the study for: *1)* previously diagnosed hematological and neurological conditions; *2)* previous malignant head and neck neoplasms; *3)* contraindication to fat harvesting.

According to the study design patients were randomized (1:1 ratio): the control group consisting of 20 patients (5 bilateral, 15 unilateral) who underwent traditional arthrocentesis with intraarticular instillation of HA (group 1) and the experimental group including 20 patients (6 bilateral, 14 unilateral) who underwent arthrocentesis with intraarticular injection of microfragmented adipose tissue (group 2).

PROCEDURES

In group 1, arthrocentesis of the superior joint compartment was performed in all patients under local anesthesia using the technique described by Nitzan et al. For anesthesia, the auricolotemporal nerve block and periarticular local infiltration were performed with 2-4 mL of carbocaine and adrenaline; anesthetic solution was injected into the upper joint compartment if required during the joint lavage. The skin was then penetrated with a 19-gauge needle at the articular fossa followed by the injection of 3 mL saline solution to distend the joint space, pumping it in and out repeatedly. Another 19-gauge needle was inserted into the distended compartment in the area of the articular eminence, and the superior joint space was irrigated with 200 mL saline solution, allowing a free flow through the first needle. On termination of procedure, 2 mL commercially available sodium hyaluronate was injected into the superior compartment.

In group 2 harvesting and processing of adipose tissue was performed using the Lipogems system in local anesthesia. The patient was evaluated in supine position to determine and mark the abdominal area for harvesting procedure. A local anesthesia was made at the skin point identified for cannulas entrance and small incisions were made using the tip of an 18-gauge needle at these points (Fig 1A). A blunt tip anesthesia cannula was used with a 60 mL syringe to infiltrate a 120/150 mL of tumescent solution composed of saline (1,000 mL), lidocaine 1% (100 mL), epinephrine 1:1,000 (1 mL), and sodium bicarbonate 8.4% (10 mL), as shown in Figure 1B. Waiting few minutes, lipoaspiration was then conducted with a cannula

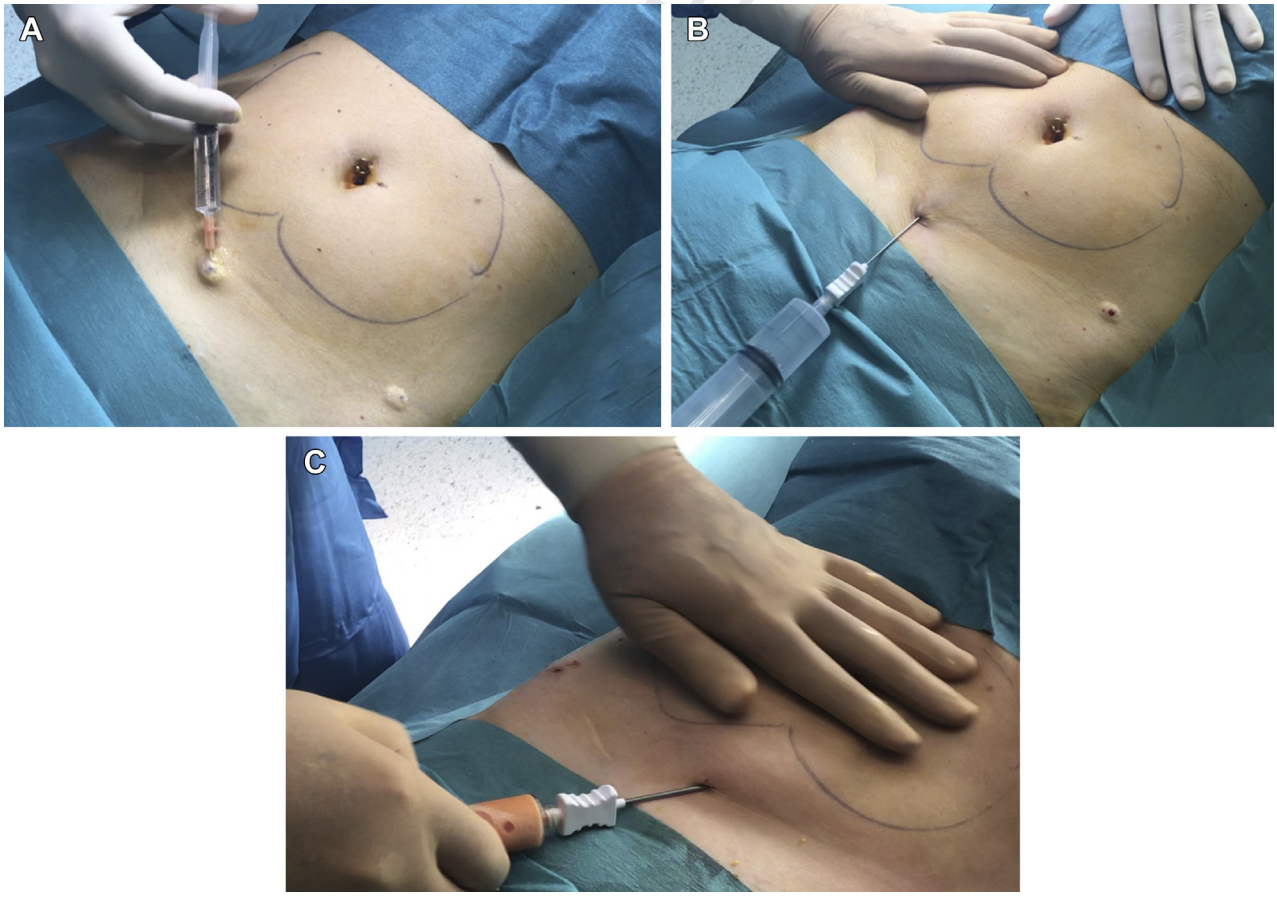

FIGURE 1. *A*, infiltration with local anesthetic in the site marked for the introduction of cannulas; *B*, infiltration with Klein's solution using blunt-tipped cannulas; *C*, lipoaspiration.

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placed through the incision site toward the umbilicus and posteriorly using a low-pressure vacuum syringe (Fig 1C). The average lipoaspirate volume to perform microfragmentation of adipose tissue was 30 mL.

MICROFRAGMENTATION OF ADIPOSE TISSUE

The Lipogems device consists of a completely closed system in which the lipoaspirate is processed using physical forces without the use of enzymatic additives. In a first phase, the lipoaspirate undergoes a first, gross-cluster reduction achieved by pushing the fatty aspirate through an inlet filter. Fat clusters enter the circuit and the corresponding quantity of saline exits to the wasting bag. Within the circuit, stainless steel marbles continue lipoaspirate microfragmentation while the device is shaken, and an emulsion of oil, blood, and saline is achieved, the latter being washed away thanks to the lower density of fat using a gravity counterflow mechanism (Fig 2A). The washing phase is complete and the saline flow is stopped when the solution inside the device appears clear and the lipoaspirate yellow. An additional cluster reduction is obtained by passing the floating adipose microclusters into an outlet second filter; subsequently, the final product is collected into a 10 ml syringe connected to the upper opening of the device, which was left to decant to eliminate the excess of liquid fraction. The final product is transferred to 1 mL syringes which are used to inject the appropriate volume of fat within the upper joint space (Fig 2B). The whole process permits a wash out of impurities and a breakdown of adipose tissue clusters. The product thus obtained is microfragmented, nonexpanded adipose tissue containing a concentrate of pericytes and mesenchymal stem cells suitable for injection.

As described for the control group, a standard arthrocentesis procedure was performed and once the lavage was completed, the processed adipose tissue was injected in the superior joint space through the inflow needle, carefully checking that the fat emulsion comes out from the second needle that is then removed leaving the articular upper space completely filled, avoiding the spreading of the injected fat in the surrounding periarticular soft tissue (Fig 2C). The average injected lipoaspirate volume was of 2 mL.

OUTCOME EVALUATION

As primary outcome measures, the following clinical parameters were evaluated at the preoperative examination (baseline) and reassessed at follow-up

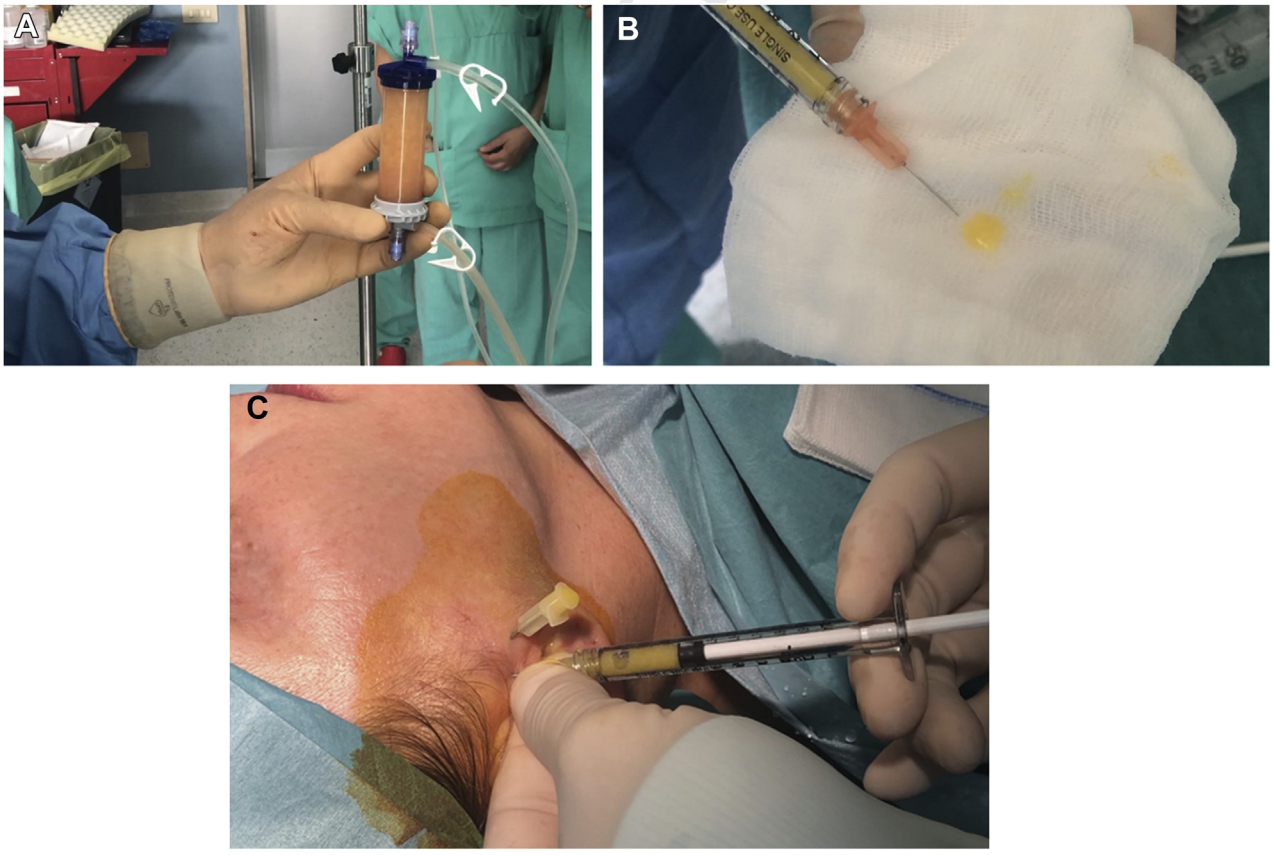

FIGURE 2. *A*, overview of the Lipogems kit for adipose tissue microfragmentation; *B*, the lipoaspirate, consisting of microfragmented fat clusters; *C*, TMJ arthrocentesis and instillation of microfractured adipose tissue.

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evaluation at 10 days, 1 month, and 6 months after the procedure:

1) Mandibular mouth opening, defined as MIO (maximum interincisal opening)
2) Pain measured through a 10 cm visual analogic Scale (VAS), where 0 represents absence of pain and 10 represents maximum pain the patient can experience. At the physical examination, the patient was asked to average pain perceived at TMJ during spontaneous mouth opening and pain evoked with articular palpation and forced opening. It was asked to the patient to sign with a crossmark on the scale the level of perceived pain.

Criteria of success of the procedure were defined: MIO $\geq$ 35 mm and VAS scale $\leq$ 2. If both criteria were satisfied the procedure was considered as success.

As secondary outcome measure, the incidence of adverse events related to the procedures was evaluated.

STATISTICAL ANALYSIS

This study considered procedures performed both unilaterally and bilaterally. In fact, not the single joint, but the entire patient was considered as statistical unit. Power sample size definition was determined based on the following assumption prior to the study: hypothesizing that 65% of patients undergoing basic procedure (arthrocentesis plus HA) meet success criteria, a sample size of 40 patients (20 in experimental group and 20 in the control group), would allow to assess an improvement of 30% of the primary outcome in the experimental group (95%) compared with the control group (65%), with 80% power and an alpha-type error of 5% using a one-tailed t-test.

The random allocation sequence was done by computerized algorithm which casually generated a number between 1 and 40; the patients were assigned to the experimental group with a number between 1 and 20; patients with a number from 21 to 40 were assigned to the control group.

Clinical success rate between both groups was calculated according to the aforementioned criteria, including a mouth opening > 35 mm and a VAS scale $\leq$ 2. Quantitative variables were summarized using mean and standard deviation, while qualitative variables were summarized by calculating relative and absolute frequencies.

Quantitative variables between both groups were compared using t Student test or Mann-Whitney *U* test for independent samples, based on the distribution of values. Saphiro-Wilk W test was performed to verify Gaussian distribution of values. Chi-square (χ^2) test was used to compare qualitative values. Significance level was set to 5%. Analyses were conducted using Stata software (Stata Corporation, College Station, TX, USA).

Results

Sixty-three patients were initially evaluated for eligibility. Seventeen patients did not meet the inclusion criteria and were excluded for this study, while 6 patients declined to participate, resulting in the enrollment of 40 patients, consisting of 31 females and 9 males (Fig 3). The age of the patients was between 17 and 74 years for females with an average age of 35.7 years and between 22 and 68 years for males, with an average age of 51.3 years.

All patients enrolled successfully completed required follow-up.

The harvesting site was the abdominal wall in the majority of patients, with only one patient having the harvesting procedure performed in the medial thigh owing to deficiency of abdominal fat. No adverse events related to the joint procedures and to the lipoaspiration were reported in all patients. In 3 patients, mild hematoma formation was assessed in the abdominal wall 1 week after surgery that did not persist at later follow-up.

One week after the procedure all patients allocated to the experimental group receiving emulsified fat injection reported a mild malocclusion with ipsilateral open-bite, which was not further assessed at 1-month follow-up.

PAIN

There was a statistically significant decrease of perceived pain at 10 days ($P < .001$ for both groups), 1-month ($P < .001$ for both groups) and 6-month ($P < .001$ for both groups) follow-up compared to baseline VAS. Results of the intergroup comparison were the following:

- For preoperative VAS, Mann-Whitney *U* test did not show a statistically significant difference between groups ($P = .1102$). This is expected on the basis of the randomization process.
- For 10 days postprocedure VAS, 2-sample *t* test with equal variances showed a statistically significant difference between groups ($P = .0465$) with a greater reduction of pain in the experimental group.
- For 1-month postprocedure VAS, Mann-Whitney *U* test showed a statistically significant difference between groups ($P = .0184$) and a greater reduction of pain in the experimental group was confirmed.

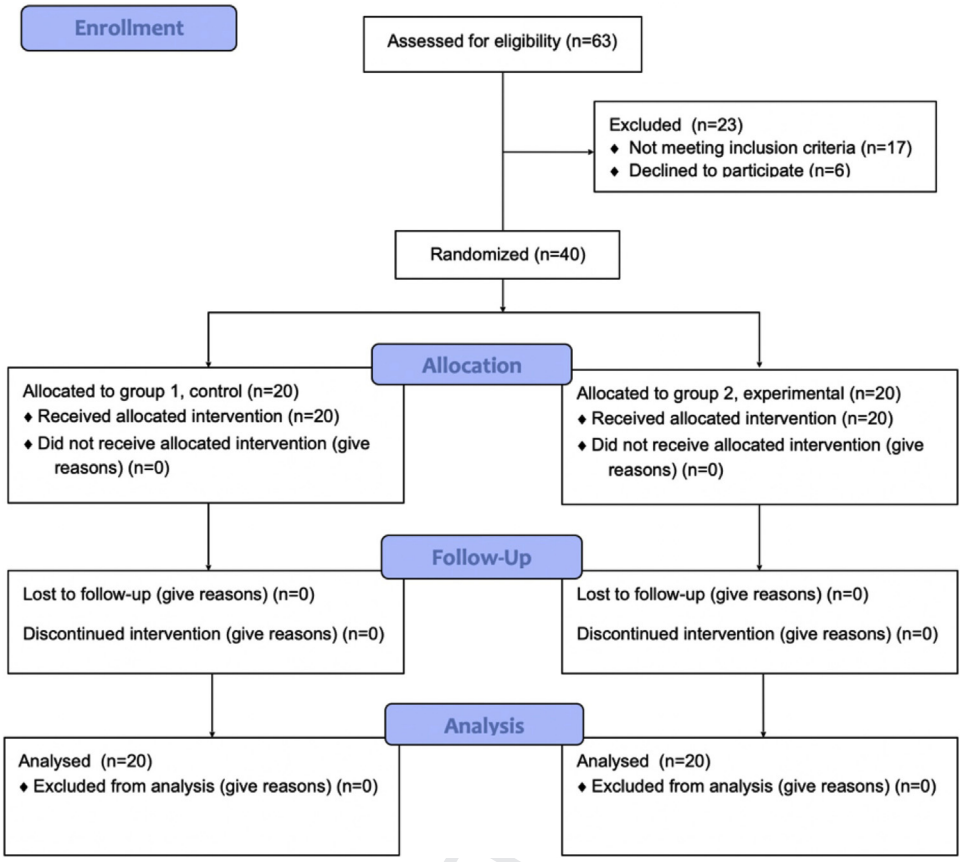

FIGURE 3. CONSORT flow diagram.

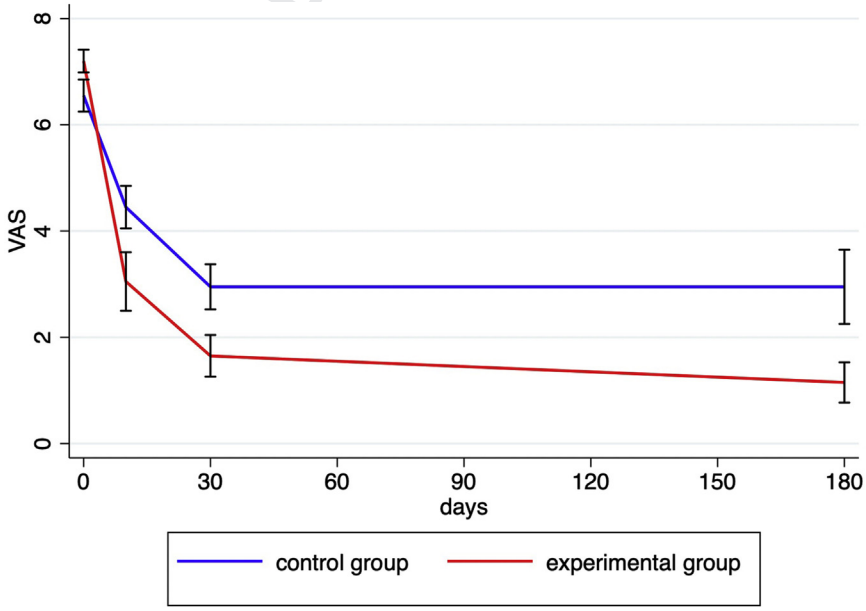

FIGURE 4. Plot showing modification of VAS over follow-up time.

- For 6-month post-procedure VAS, Mann-Whitney *U* test showed an almost statistically significant difference between groups (P = .0546), due to the greater standard deviation registered in the control group. However, in the experimental group VAS score was stably under 2, while in the control group it remained above 2.

The plot showing VAS modification over time is shown in Figure 4.

MOUTH OPENING

There was a statistically significant improvement of TMJ function at 10 days (P = .022 for group 1; P = .002 for group 2), 1-month (P < .001 for both groups) and 6-month (P < .001 for both groups) follow-up compared to baseline MIO. Results of the intergroup comparison were the following:

- For preoperative mouth opening, 2-sample *t* test with equal variances did not show a statistically significant difference between groups (P = .4344). This is expected on the basis of the randomization process.
- For 10 days postprocedure mouth opening, 2-sample *t* test with equal variances did not show a statistically significant difference between groups (P = .7419); therefore, injection of lipoaspirate did not significantly improve TMJ function in the immediate postoperative period.
- For 1-month postprocedure mouth opening, 2-sample *t* test with equal variances did not show a statistically significant difference between groups (P = .1103) confirming the superiority, but not the statistical significance, of the lipoaspirate injection after 1 month.
- 6-month postprocedure mouth opening, 2-sample *t* test with equal variances showed a statistically significant difference between groups (P = .0327), showing that differences in TMJ function become statistically significant after 6 months.

The plot showing MIO modification over time is shown in Figure 5.

SUCCESS OF THE PROCEDURES

Procedures met success criteria in 10 patients of the control group (50%) and in 17 patients of the experimental group (85%). Using χ^2 test, it was thus possible to state that the number of successful procedures was significantly superior (P = .018) in the experimental group. Therefore, our results confirm that at 6-month follow-up the group undergoing arthrocentesis plus injection of lipoaspirate has a success rate superior than the group treated with arthrocentesis plus HA, meeting the assumption of a 30% difference in the primary outcome.

Characteristics of patients and results for the considered variables are summarized in Table 1.

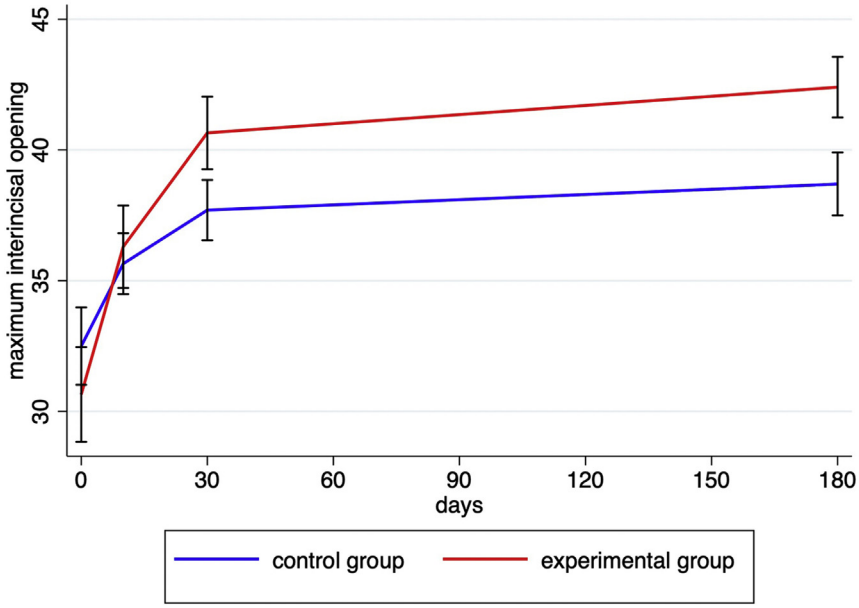

FIGURE 5. Plot showing MIO modification over follow-up time.

Table 1. OVERVIEW OF DATA—DEMOGRAPHIC CHARACTERISTICS OF PATIENTS ENROLLED AND SERIATE MEASUREMENTS OF PAIN AND JAW FUNCTION

	HA Group	Lipogems Group	*P*-value
Demographic data			
Number of patients	20	20	N/A
Age, mean, ± SE (years)	50.7 ± 17.4	43.3 ± 21.4	0.238
Pain assessment (VAS, cm)			
Preoperative pain ± SE	6.55 ± 1.36	7.2 ± 0.93	.1102
10 days postoperative pain ± SE	4.45 ± 1.79	3.05 ± 2.4	.0465
1-month postoperative pain ± SE	2.95 ± 1.90	1.65 ± 1.71	.0184
6-month postoperative pain ± SE	2.95 ± 3.12	1.15 ± 1.65	.0546
TMJ function (mm)			
Preoperative MIO	32.5 ± 6.62	30.7 ± 8.1	.4344
10 days postoperative MIO	35.7 ± 5.2	36.3 ± 6.9	.7419
1-month postoperative MIO	37.7 ± 5.16	40.7 ± 6.04	.1103
6-month postoperative MIO	38.7 ± 5.38	42.4 ± 5.04	.0327
Success rate (total)			
# cases meeting success criteria	10	17	.018

Abbreviations: MIO, maximum interincisal opening; VAS, visual analogic scale.

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Discussion

Mesenchymal stem cells (MSCs) are progenitor cells that can differentiate into several cell lineages derived, including chondroblasts, osteoblasts, myocytes, adipocytes and, in human, are generally derived from bone marrow, dental pulp, fetal membrane, and term placenta.[8]

Although bone marrow aspirate concentrate was the main focus of research,[6] recently, interest has risen towards adipose tissue as an ideal source of mesenchymal cells due to their abundance. MSCs were commonly isolated by enzymatic dissociation into single-cell suspensions, subsequent elimination of adipocytes by centrifugation and collection of the remaining stromal vascular fraction which can be used immediately or following in vitro cell expansion.

Biological bases lie on the concept that the scaffold provided by adipose tissue containing activated-cellular components including adipocytes, pericytes/pericyte-derived MSCs and potentially angiogenic endothelial cells are able to moderate tissue repair.

In particular, pericytes, which are fittingly perivascular cells and enclose capillaries and microvessels, were identified as progenitors of mesenchymal cells, since they express the same markers of MSCs and exhibit a gene expression profile similar to mesenchymal cells.

The mechanism of action of these cells is due to their secretion, containing immunosuppressive and antinflammatory cytokines, and growth factors, including iNOS, IDO, PGE2,TSG6,HO1,TBG-ß, Galectin, with an antinflammatory and regenerative effect.[9]

Overall, how these molecules contribute to the final therapeutic effect is unknown, due to the fact that many of such mediators may have multiple modalities of action.

Unfortunately, the enzymatic method yielding the stromal vascular fraction may cause a decline in multipotency due to prolonged ex vivo expansion and senescence.

In the last years the use of a new method was proposed to process adipose consisting of mechanical microfragmentation, able to preserve cells and tissue microarchitecture of adipose tissue, eliminate impurities including oil and blood, thus providing a minimally manipulated product in accordance with FDA recommendations.[7]

Lipogems is a full-immersion closed system used to treat lipoaspirate and microfragment adipose tissue. A sequence of sieves and steel spheres enclosed in a cylinder yield a mild-mechanical size reduction of the lipoaspirate. Differently from the enzymatic treatment, mechanical microfragmentation maintains the microanatomy of the adipose tissue intact, preserving microvessels architecture together with adipocytes and pericyte, which are normally wrapped around endothelial cells. The pericyte-rich microenvironment allowed by mechanical microfragmentation of adipose

tissue is responsible for the strong regenerative capabilities, due to higher amounts of growth factors and cytokines compared with enzymatic methods. It has been shown that MSCs derived from adipose tissue secrete a number of molecules that are able to initiate and maintain angiogenic, antifibrotic, antiapoptotic, antimicrobial and immunomodulatory activities.

Lipogems technology, according to literature evidences, ensures the preservation of an intact vascular niche, including pericytes, which play a major role in the release of regenerative factors during the transition from pericyte to MSCs. In fact, after injection, MSCs exhibit a paracrine secretion though the release of exosomes, whose presence has been shown to be superior in microfractured adipose tissue than in enzymatically treated lipoaspirate.

MSCs derived from bone marrow have the same properties as those obtained by adipose tissue, as shown by Mautner et al.[10] Remarkably, MSCs derived from adipose tissue have a significant advantage over MSCs derived from bone marrow, owing to the obviously inferior invasiveness related to the harvesting phase, while lipoaspiration is a minimally invasive procedure.

Lipogems technology has been successfully applied in various clinical settings, including general surgery, plastic and reconstructive surgery, and orthopedics surgery. In particular, it has been demonstrated that degenerative joint disease may benefit from intraarticular injections of microfractured adipose tissue. Several trials are still ongoing to evaluate efficacy and superiority of this technology in respect with the standard approach to the pathology.[11]

For this reason, this protocol has been designed with the aim to investigate whether injection in the TMJ of microfragmented fat tissue can achieve the same improvements of pain and function, and to compare this technique with standard arthocentesis with HA injection. In study design phase, to choose the most appropriate criteria to define procedures as successful, we referred to the publication of Yilmaz et al.[12] The American Association of Oral and Maxillofacial Surgeons proposed the following criteria to evaluate the success of arthrocentesis procedure: presence of mild or no pain (VAS score $\leq$3) and an MMO $\geq$35 mm at 12 months 15 after treatment. Our criteria are similar to those proposed by the American Association of Oral and Maxillofacial Surgeons, but even more strict in relation to VAS evaluation, which we required to be equal or inferior to 2.

The standard arthrocentesis procedure has shown, according to available literature, a satisfactory success rate. Our study, on the basis of our success criteria, the control group, namely the patient undergoing arthrocentesis plus HA injection, showed a success rate of 50%, although the majority of patients reported an improvement of their symptoms. Regarding to the other supplementary substances injected in the joint, such as anestehtics, corticosteroids, PRP and the HA itself, available literature seems to be inconclusive as to the effectiveness of such methods compared with arthocentesis alone. In a recent systematic review of literature, the authors concluded that studies with a better methodological design are encouraged to shed light on this topic and to obtain relevant clinical suggestions on the most appropriate treatment.[13] This is the first study on therapeutic effect of injection of microfragmented adipose tissue for TMJ osteoarthritis. The goal of our study was to demonstrate the hypothesis that microfragmented adipose tissue injection can lead to better clinical results than arthrocentesis with HA. For this reason, we designed a randomized clinical trial in which 2 groups of patients were enrolled and treated with arthrocentesis with HA (control group) and with arthrocentesis plus microfractured adipose tissue injection (experimental group). It was decided to perform arthrocentesis in the experimental group as well to avoid blind injection of lipoaspirate around the joint by randomly puncturing the TMJ area, but to ensure that all the superior joint space be filled with the lipoaspirate. This choice lies upon 2 reasons: first, maximizing the biological action of injected MSCs in the correct site, secondly, to avoid any complications such as the accidental intravascular injection of fat. The filling of the upper joint space was further proven by the clinical finding of ipsilateral malocclusion with open bite that was assessed at 1-week follow-up. This finding was not anymore detectable a 1-month follow-up, due to the intrarticular resorption of the lipoaspirate.

Particular attention was paid to the choice of the primary outcome variables, made only on the basis of the articular symptomatology and the function allowed by articular motion. For this reason, we did not take into consideration variables such as joint sounds or muscle palpation. In particular, joint sounds may also have a positive meaning, accounting for improved joint mobility which may be present after the procedure. Therefore, our aim was not to affect in any way the final evaluation.

The results of our study show that in both groups procedures were effective in reducing pain and improving function. Considering the aforementioned success criteria, there was a higher success rate in the patients undergoing arthrocentesis plus injection of microfragmented adipose tissue (85%) compared with patients undergoing arthrocentesis plus HA.

At 6-month follow-up experimental treatment with arthrocentesis and microfragmented fat injection showed a statistically significant superiority in improving TMJ function. A similar outcome was found also for pain where the experimental group performed

better than the control group, with a level of statistical significance slightly above the threshold.

Therefore, we can state that the null hypothesis of equality between experimental and control groups was rejected confirming that the injection of microfragmented adipose tissue in temporomandibular joint enhances the benefits of arthrocentesis in patients with TMJ internal derangement and osteoarthritis.

In conclusion, results of this study are encouraging as they demonstrate the clinical superiority of the injection of microfragmented adipose tissue processed though Lipogems technology compared with arthrocentesis and HA injection in terms of pain and function improvement outcomes in a medium-term evaluation (6 months). This preliminary follow-up at 6 months should be extended to a longer follow-up time to evaluate the clinical stability of the achieved improvement in pain and function. Additionally, it would be interesting to evaluate regenerative potential with MRI findings to provide imaging evidence of tissue healing.

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