

Intra-articular Injection of Autologous Fat Micro-graft for the Treatment of Knee Osteoarthritis: Preliminary Experience

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Abstract: Objectives: Main manifestations of osteoarthritis (OA) are pain and joint stiffness. This prospective observational study aims to evaluate the effect of intra-articular fat micrograft injection on Knee OA pain, stiffness and physical function After confirming the safety of the intra-articular injection of the fat micro graft in our previous animal model experiment. **Methods:** The study was conducted at King Abdulaziz University Hospital from May 2012 to Aug 2013. Ten adult patients with severe knee OA changes were enrolled. Liposuction was performed to collect fat micrograft. 20 ml of autologous fat micrograft were injected intra-articularly in the affected knee. **Results:** Visual Analogue Scale (VAS) values were significantly higher in pre versus post-injection both during rest (5.50 ± 1.65 vs 1.10 ± 0.57 , $P < 0.004$) and with activity (7.70 ± 1.89 vs 2.20 ± 0.63 , $P < 0.005$) which reflected a highly significant improvement in OA pain. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) before and after intra-articular fat micro-graft injection. The three domains of WOMAC index: pain, stiffness and physical function were significantly lower in the post intra-articular fat injection period compared to the pre-injection values. The total score of WOMAC test and its percentage was significantly lower in the post intra-articular fat injection period compared to the pre-injection values (22.30 ± 9.91 versus 73.40 ± 9.50 , $P < 0.005$; 23.23 ± 10.32 versus 76.46 ± 9.90 , $P < 0.005$). **Conclusion:** the preliminary findings support the injection of autologous fat micrograft as an effective and safe method for the treatment of knee osteoarthritis. Further studies are needed to determine the exact mechanism of action and the persistence of effect.

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Key words: Pain, Intra-articular injection, Osteoarthritis, Fat micro-graft, Knee

1. Introduction

Knee osteoarthritis (OA) is one of the major causes of morbidity, disability, and health care utilization, particularly in elderly patients.¹ The main clinical manifestations of OA are pain and joint stiffness.² Therapeutic interventions usually directed toward the improvement of physical function and relief of symptoms of OA.³ Unfortunately, pharmacological options often render limited effects and also carry the burden of potentially serious side effects.⁴ Hence, many patients try alternative therapy to relieve their pain. Intra-articular injection of corticosteroids, hyaluronic acid, and other less traditional compounds is a well-established treatment option.⁵ Recently, some investigators described the injection of preparation of platelet-rich plasma into osteoarthritic knee with an encouraging result.⁶ Other investigators demonstrated that in dogs autologous adipose-derived mesenchymal stem cell (MSC)

therapy involves harvesting fat from animals, isolating the stem cells and regenerative cells and administering the cells back to the chronic osteoarthritic joint improved the clinical signs.^{7, 8} In human, the efficacy of MSC as a therapeutic modality potentially applicable to a wide range of disorders was studied widely in various studies.⁹⁻¹¹ Previous studies have shown that MSC can be isolated from most adult tissues including the adipose tissues¹²⁻¹³. We conducted an animal experiment involving sheep where autologous fat micrograft was obtained from the animal and re-injected in hind knee joint intra-articular which confirmed the safety of the injected fat micro-graft to the joint cavity without any pathological changes of the articular surface of the joint or limitation of movement with normal activity of the animal in using the injected joint moreover histological study of the injected joint showed positive regenerative effect on injected joint cartilage

compared to the control contralateral joint of the same animal where significant proliferative effects on chondrocytes of cartilage in the treated joint and increased the thickness of the articular cartilage of the treated joints. The follow-up of the animal and final result were encouraging and showing that autologous fat micro graft is safe and has a healing power and lubricating effect of the joints with no clinical negative manifestations in the fat injected joints of the experimental animals.¹⁴

We aim in this prospective observational study to assess the effect of intra-articular knee joint injection of autologous fat micro-graft on the OA knee pain, stiffness and function. Searching the database (Pub Med, Cochrane Library, and manual search of published literatures) did not reveal any similar study.

2.Method:

According to principles of the Helsinki Declaration, a prospective observational study was conducted at King Abdulaziz University Hospital, Jeddah, Saudi Arabia from May, 2012 to Aug, 2013. After approval from the Research and Ethics Committee of the Faculty of Medicine, King Abdulaziz University Hospital (approval number 822-12, dated May 15th, 2012), 13 adult patients of both genders were screened for eligibility to participate in the study. Written informed consent was obtained from 10 patients. All patients with severe osteoarthritic changes confirmed by standing radiographs involving one or both knees were included in the study. Exclusion criteria were patients' refusal, patients with congenital or traumatic deformity of knee joint, malignant disease, history of recent knee surgery, chronic intake of opioids and bleeding disorders. During the preoperative visit visual analogue scale (VAS) for pain assessment on 10-cm line (0= no pain and 10= worst imaginable pain) was explained to patients and VAS at rest and during activity was obtained. Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index is a widely used questionnaire to assess the symptoms and physical disability associated with OA.¹⁵

In our study we used 5 points Likert type WOMAC index to collect information regarding the 3 subscales of WOMAC:

- Pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing.
- Stiffness (2 items): after first waking and later in the day.
- Physical Function (17 items): stair use, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath,

sitting, getting on / off toilet, heavy household duties, light household duties.¹⁵

Anesthesia and surgical interventions were also explained to the patients. A list of adverse effects was introduced to the patient to report any adverse effect post procedure.

In the operating room patients were monitored by non-invasive blood pressure (NIBP), heart rate (HR), pulseoximetry and temperature; surgical site of liposuction was selected according to patients' wishes and fat availability; and monitored anesthesia care was initiated. Dexmedetomidine 0.7 µg /kg/ hr was administered intravenously as a sedative and pain relieving agent. Under complete aseptic technique the surgical site was prepared. 100 ml of tumescent solution was injected in the surgical site. Solution was prepared by mixing 50 ml of 1% lidocaine, 0.5 mg (0.5 ml) of epinephrine in 449.5 ml of lactated ringers. Fat harvesting was obtained using ten-holes, Oliveira blunt cannula (Pouret Medical, Clichy, France) with 1 mm tip attached to a 10-ml Luer-Lok syringe (Terumo®, Auburn, WA, USA). 30 ml of fat was collected then it was left for 20 min to settle and separate into various layers. Impurities were removed and the middle layer was kept for intra-articular injection. In the mean while the osteoarthritic knee joint was cleaned and prepared. 20 ml of the fat were divided into seven syringes. Each syringe of 3 ml capacity. We injected autologous fat micro-graft intra-articular up to 20 ml was achieved or the patient complained of severe pressure inside the joint.

Post procedure all patients were followed up in the pain clinic on regular bases every three months to check for incidence of side effects, complications, assessment of pain, stiffness and knee functions, and recurrence of pain.

Statistical Analysis:

Statistical Science for Social Package (SPSS Inc, USA) software computer program version 20 was used for data analysis. Data were presented as mean \pm SD and minimum - maximum or number and percentage (n, %) as appropriate. Wilcoxon test for non-parametric variables was used to compare pre injection to post injection values. A probability ($P < 0.05$) was considered statistically significant.

3.Result:

Table 1 showed the demographic data and the clinical characteristics of the patients. The associated co morbidities were: hypertension in 4 patients, diabetes mellitus in 4 patients, 3 patients suffered of chronic low back pain, one patient of rheumatoid arthritis and one of lower limbs lymphedema. The duration of OA the symptoms of disease ranged from 3 to 7 years.

VAS values were significantly higher in pre versus post-injection both during rest (5.50 ± 1.65 vs 1.10 ± 0.57 , $P < 0.004$) and with activity (7.70 ± 1.89 vs 2.20 ± 0.63 , $P < 0.005$ table 2) which reflected a highly significant improvement in OA pain (Figure 1).

Table 3 presented The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) before and after intra-articular fat micro-graft injection. The three domains of WOMAC index:

pain, stiffness and physical function were significantly lower in the post intra-articular fat injection period compared to the pre-injection values. The total score of WOMAC test and its percentage were significantly lower in the post intra-articular fat injection period compared to the pre-injection values (22.30 ± 9.91 versus 73.40 ± 9.50 , $P < 0.005$; 23.23 ± 10.32 versus 76.46 ± 9.90 , $P < 0.005$).

Table 1: Demographic and clinical characteristics of patients.

Parameters	Data (number =10)
Age (years)	63.60 ± 10.23 (55.00-82.00)
Weight (kg)	89.60 ± 16.73 (70.00-120.00)
Height (meter)	1.64 ± 0.11 (1.52-1.82)
Body mass index (kg/m^2)	33.39 ± 6.21 (25.71-46.88)
Gender	
Male	4 (40%)
Female	6 (60%)
Comorbidity	
Hypertension	4 (40.00%)
Diabetes mellitus	4 (40.00%)
Chronic low back pain	3 (30.00%)
Lower limbs lymphedema	1 (10.00%)
Low back pain	1 (10.00%)
Disease duration (years)	4.10 ± 1.29 (3.00-7.00)

Data are expressed as mean \pm SD (minimum- maximum) or number (%) as appropriate.

Table 2: Visual analogue scale (VAS) values at rest & with activity before and after intra-articular fat micro-graft injection.

VAS	Pre- injection	Post- injection	Significance (P -value)
Rest	5.50 ± 1.65 (3.00-8.00)	1.10 ± 0.57 (5.00-10.00)	0.004
Exercise	7.70 ± 1.89 (5.00-10.00)	2.20 ± 0.63 (0.00-2.00)	0.005

Wilcoxon test for non-parametric variables was used to compare pre injection to post injection values

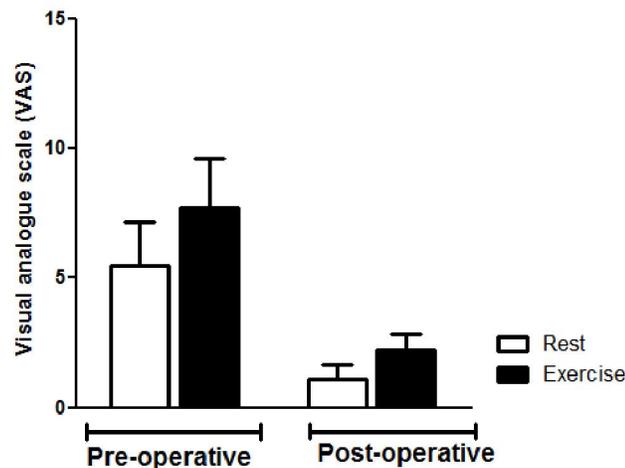


Figure 1: Visual analogue scale (VAS) values at rest & with activity before and after intra-articular fat micro-graft injection.

Table 3: The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) before and after intra-articular fat micro-graft injection

WOMAC Index		Pre- injection	Post- injection	Significance (P-value)
Pain	1. Walking	3.70±0.48 (3.00-4.00)	1.00±0.47(0.00-2.00)	0.004
	2. Stair Climbing	3.70±0.95 (1.00-4.00)	1.60±0.52 (1.00-2.00)	0.006
	3. Nocturnal	2.70±0.95 (1.00-4.00)	0.60±0.52 (0.00-1.00)	0.004
	4. Rest	2.20±0.79 (1.00-3.00)	0.20±0.42 (0.00-1.00)	0.005
	5. Weight bearing	4.00±0.00 (4.00-4.00)	1.40±0.70 (0.00-2.00)	0.004
Stiffness	1. Morning stiffness	3.40±0.70 (2.00-4.00)	0.90±0.57 (0.00-2.00)	0.005
	2. Stiffness occurring later in the day	3.20±0.92 (2.00-4.00)	0.70±0.48 (0.00-1.00)	0.005
Physical Function	1. Descending stairs	3.50±0.53 (3.00-4.00)	1.30±0.67 (0.00-2.00)	0.004
	2. Ascending stairs	3.90±0.32 (3.00-4.00)	1.50±0.53 (1.00-2.00)	0.004
	3. Rising from sitting	3.10±0.88 (2.00-4.00)	0.80±0.42 (0.00-1.00)	0.004
	4. Standing	2.90±0.57 (2.00-4.00)	0.60±0.52 (0.00-1.00)	0.004
	5. Bending to floor	3.50±0.53 (3.00-4.00)	1.20±0.63 (0.00-2.00)	0.004
	6. Walking on flat surface	2.70±0.67 (2.00-4.00)	0.40±0.52 (0.00-1.00)	0.003
	7. Getting in / out of car	3.30±0.82 (2.00-4.00)	1.10±0.74 (0.00-2.00)	0.004
	8. Going shopping	3.60±0.52 (3.00-4.00)	1.30±0.67 (0.00-2.00)	0.004
	9. Putting on socks	2.90±0.74 (2.00-4.00)	1.00±0.94 (0.00-3.00)	0.004
	10. Lying in bed	2.20±1.03 (1.00-4.00)	0.40±0.52 (0.00-1.00)	0.004
	11. Taking off socks	2.80±0.42 (2.00-3.00)	1.10±0.58 (0.00-3.00)	0.006
	12. Rising from bed	2.40±0.97 (1.00-4.00)	1.00±0.67 (0.00-2.00)	0.010
	13. Getting in/out of bath	2.60±0.84 (1.00-4.00)	0.60±0.70 (0.00-2.00)	0.004
	14. Sitting	2.10±1.10 (0.00-4.00)	0.60±0.52 (0.00-1.00)	0.006
	15. Getting on/off toilet	2.80±0.92 (1.00-4.00)	1.10±0.57 (0.00-2.00)	0.007
	16. Heavy domestic duties	4.00±0.00 (4.00-4.00)	1.50±0.53 (1.00-2.00)	0.004
	17. Light domestic duties	2.20±0.79 (1.00-3.00)	0.40±0.52 (0.00-1.00)	0.007
Total score	Out of 96	73.40±9.50 (56.00-88.00)	22.30±9.91 (9.00-38.00)	0.005
	Percentage (%)	76.46±9.90 (58.33-91.67)	23.23±10.32 (9.38-39.58)	0.005

The activities in each category according to the following: Scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Data are expressed as mean ±SD (minimum- maximum).

Wilcoxon test for non-parametric variables was used to compare pre injection to post injection values

4. Discussion:

Cell-based therapy which involves the transplantation of stem or progenitor cells to patients through local or systemic delivery is now widely adopted as a therapeutic modality for various diseases.¹⁶ Stem cells have an advantage over current treatment in that they can differentiate along multiple tissues lineages and proliferate to provide a continuous source of new cells.¹⁷⁻¹⁹ Recent studies show that MSC can be isolated from most adult tissues including fat.^{20, 21} These adipose-derived precursor cells were first identified in the stromal vascular fraction of adipose tissue more than three decade ago.²² There is strong evidence that MSC migrate to injured tissue or site of inflammation, support proliferation and differentiation to replace lost cells, increase tissue angiogenesis, and promote

recovery of injured tissue via growth factors secretion and matrix remodeling.²³⁻²⁵ Adipose tissue is widely distributed throughout the body but the panniculus adiposus the fatty layer of the subcutaneous tissue is the main source of fat grafts and adipose stem cells .plastic surgeons have been using fat as soft tissue filler for more than a century, Hence the born of our new idea of treating the OA joints by intra-articular injection of fat micro graft as lubricating and regenerative agent . The first step of our study was to test the safety and any other resulting effects of the intra-articularinjection of fat into the cavityof normal hind knee joint of sheep,this animal experiment confirm the safety and regenerative effects of the fat micro graft in injected joint of the animal compared to the control contra lateral joint of the same animal.¹⁴

In the current prospective observational human study we inject fat micro-graft intra-articular utilizing the contained stem cells to replace the injured knee tissues and lubricating fat micro-graft for the rough osteoarthritic knee surfaces. Our clinical experience in 10 patients with OA treated with intra-articular injection of fat micro-graft was encouraging with statistical significant improvement in pain, stiffness and physical functions of osteoarthritic joints indicated by reduction in VAS and the improvement in all subscales of WOMAC index following the injection of autologous fat micro-graft. This encouraging outcome creates a new hope for patients with osteoarthritis, but more studies are needed to compare this method to other therapeutic interventions, to assess the direct effect of such treatment on the injured tissues, and to evaluate the exact mechanism behind the beneficial effect of intra-articular fat micro-graft injection among patients with variable degree of OA changes.

Literature review did not reveal any previous attempt of injecting fat micro-graft in a similar way to our study. Other studies were dealing with stem cells, where isolation and processing of the stem cells was needed.⁸⁻¹² We injected the fat micro-graft directly into the joint without the use of any processing technique, depending on the high availability of stem cells in adipose tissue.^{14,22} Further studies are needed to compare our technique to other stem cells obtaining interventions and to estimate both clinical and economical beneficial effect of both techniques.

In conclusion, the use of autologous fat micro-graft for the treatment of severe knee osteoarthritic changes is an effective new treatment modality that requires further future assessment to evaluate its use in various body joints with different osteoarthritic changes, and determine its persistence and mechanism of action.

Short Title: Intra-articular Fat for Osteoarthritis

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