RESEARCH ARTICLE

Combination of High Tibial Osteotomy and Autologous Bone Marrow Derived Cell Implantation in Early Osteoarthritis of Knee: A Preliminary Study

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Abstract

Background: High tibial osteotomy (HTO) is a recommended treatment for medial compartment knee osteoarthritis. Newer cartilage regenerative procedures may add benefits to the results of HTO. In this prospective study we have investigated the safety and also results of HTO associated with autologous bone marrow derived cells (BMDC) implantation in relatively young and middle aged active individuals with early osteoarthritis of the knee.

Methods: A total of 24 patients (mean age of 47.9 years) with varus knee and symptomatic medial compartment osteoarthritis were treated with medial opening-wedge high tibial osteotomy in conjunction with implantation of bone marrow derived cells into the chondral lesions. The clinical outcomes were assessed by IKDC, KOOS, VAS, and Tegner scores. The radiographic studies were performed preoperatively and at follow-ups.

Results: No major complications were seen during the operations and postoperative follow-ups. All clinical scores were significantly improved for the IKDC score (from 32.7±15 to 64±21) (*P<0.005*), KOOS score (from30±11 to 68±19) (*P<0.005*), VAS (from 7.5 to 3) and Tegner score (from 1.2 to 2.1) (*P<0.004*).

Conclusion: HTO in conjunction with BMDC implantation is a safe and feasible treatment and is associated with good results in short term follow up for early medial compartment osteoarthritis in varus knees.

Level of evidence: IV

Keywords: Bone marrow derived cells implantation, Cartilage repair, High tibial osteotomy, Osteoarthritis, Stem cells

Introduction

Early osteoarthritis remains a big challenge for orthopedic surgeons (1). Patients with early osteoarthritis are predominantly young or middle aged active individuals who like to maintain their high level activity (2, 3). Non-operative treatments including weight loss, physical therapy, injections, use of analgesics and anti-inflammatory medications usually provide only short term benefits and may not prevent cartilage degeneration. Although unicompartmental or total knee replacement is a good option for advanced osteoarthritis, it has limited indications in this group of patients due to the high probability of revision surgery and low patient satisfaction (4).

High tibial osteotomy (HTO) has been proved to be a reliable solution in the treatment of early osteoarthritis with malalignment (5). Correction of weight bearing axis

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leads to better distribution of contact forces in the joint and to some degrees prevents more cartilage degeneration (6, 7). Also, some authors have reported cartilage remodeling after HTO (8, 9). However, even the positive results of HTO deteriorate overtime at long term follow-up (10). There are some evidences stating that addition of cartilage repair procedures such as microfracture or autologous chondrocyte implantation (ACI) to HTO may be effective in pain relief (11, 12).

Recently a single step procedure was successfully developed for cartilage repair, with the use of concentrated bone marrow derived cells (BMDC) (13-15). This technique may enhance and maintain good results of HTO and delay the need for arthroplasty, providing multiple years of high quality of life to middle-aged active people.

The purpose of this preliminary study was to evaluate the safety and feasibility of implantation of bone marrow derived cells (BMDC) in combination with HTO in early osteoarthritis of knee.

The hypothesis was that the combination of BMDC implantation and HTO may lead to the advantages of both the procedures without additional complications.

Materials and Methods

Patient selection

A total of 24 patients (15 males and 9 females, age: 47.9±12.3years) with varus knee and symptomatic medial compartment early osteoarthritis were enrolled in this study between 2009 and 2011. This study was approved by the institutional review board. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consents were obtained from all individual participants in the study.

The inclusion criteria were: age<60 years; varus knee with angle between 1 and 15 degrees; medial compartment osteoarthritis grade IV or less according to the Kellgren-Lawrence classification; cartilage lesion at the level of the medial femoral condyle; and failure in conservative treatment. Patients with tricompartmental osteoarthritis; cartilage lesions on opposing surfaces of femoral condyle and tibial plateau (kissing lesions); inflammatory arthritis; knee instability; previous total or subtotal lateral meniscectomy; and general hematologic and systemic disorders were excluded from the study.

All patients were treated with medial opening wedge high tibial osteotomy associated with arthroscopic (or with mini-open arthrotomic access, 9 cases) BMDC implantation.

Clinical evaluation

The patients were evaluated preoperatively including detailed medical history and physical examination. The knee was checked for ROM, alignment and stability. Subjective IKDC (International Knee Documentation Committee), KOOS (Knee Osteoarthritis and Outcome score), VAS (Visual Analogue Scale) for pain, and Tegner scores were recorded preoperatively (T_0) and after 2 (T_1) and 3 years (T_2) of follow up (T_1 mean=29.4 months SD=15.1; T_2 mean=44.4 months SD=17.7).

Radiographic evaluation

Radiographic assessment included standard weight bearing full leg X-ray as well as Rosenberg, lateral, and skyline views of patellofemoral joint. The control radiographies were taken 1, 2, 3, and 12 months after surgery and at the final follow up. Preoperative MRI was done for all patients to identify the location and size of cartilage lesions as well as bony and ligamentous elements of the knee. Postoperative MRI was not performed routinely due to hardware artifacts.

Surgical technique

Preoperative Planning

On the full leg (hip to ankle) radiograph, the varus angle was determined as the angle between the femoral and tibial mechanical axes [Figure 1]. The valuation of the correction was obtained as "Dugdale" method, with calculation of the tibio-femoral angle and the necessary degree of correction

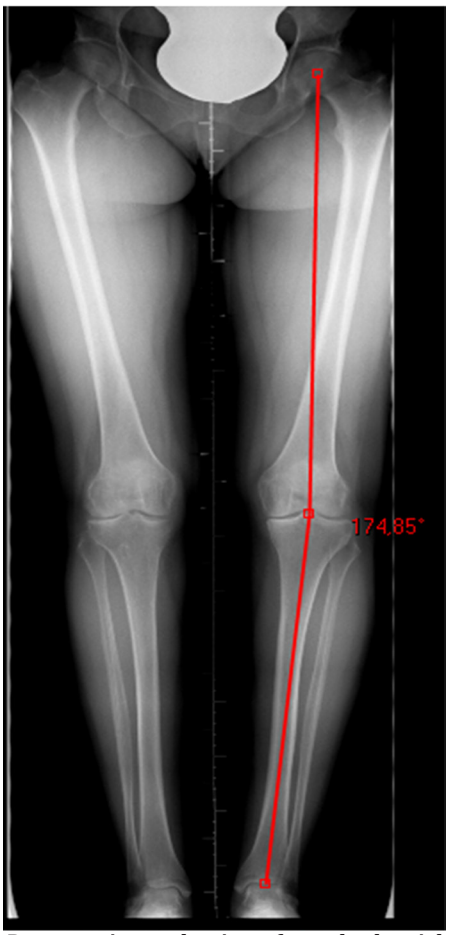

Figure 1. Preoperative evaluation of standard weight bearing full leg X-ray with identification of the mechanical axes of the femur and tibia and the angle of Varus.

to shift the axis to the point of Fujisawa (62.5% of the way across to the lateral tibial plateau) (16). The point of Fujisawa equates to 3° to 5° of valgus.

Harvesting Bone Marrow Derived Cells

After spinal or general anesthesia in the prone position, first we aspirated 60 ml of bone marrow from the posterior iliac crest with a marrow needle (size: 11G x 100 mm). Aspiration was done in small fractions from different points in bone but thorough the same skin puncture to maximize the cell harvesting and decrease blood dilution. The harvested material was processed in the operating room (IOR-G1, Novagenit, Mezzolombardo, TN, Italy) and after 15 minutes centrifugation cycles, 6 ml of bone marrow concentrate was obtained.

Bone Marrow Derived Cells implantation

The patient was positioned supine after bone marrow puncture and a standard knee arthroscopy was performed. The status of menisci was checked and meniscal tears were treated. The chondral lesion was identified and debrided to obtain a stable healthy edge around the defect [Figure 2]. A collagen scaffold (IOR-G1, Novagenit, Mezzolombardo, TN, Italy) fashioned according to the defect shape and immersed into the bone marrow concentrate was implanted into the defect, PRF (platelet rich fibrin) that prepared the day before operation was injected into the joint and on the implanted defect [Figure 3]. Finally, the stability of stamp was evaluated by flexion and extension of the knee, and the accesses were sutured.

Osteotomy

A periosteal flap at the pes anserinus insertion was elevated through an incision on medial proximal tibia. Under fluoroscopic control, a K-wire was placed from the medial tibial cortex 3-4 cm below the joint line to the tip of the fibular head. With the K-wire guide, an oblique osteotomy, proximal to the tibial tuberosity was performed and the osteotomy was opened with a graduated wedge to obtain a progressive correction of the varus until reaching the calculated angle in preoperative plan. A cryopreserved homologous bone wedge (Rizzoli Bone Bank) was used to fill the gap and enhance the union rate. Then, the osteotomy was fixed with plate and screws (Titan plate, Citieffe, Calderara di Reno, Bologna, Italy). A control X-ray was performed at the end of the procedure to check the osteotomy.

Post-operative care and Rehabilitation

The patients mobilized with brace and two crouches in non-weight bearing manner the day after the surgery. Passive and active ROM and isometric exercises as well as soft tissue and patellar mobilization were started gradually after one week and increased as tolerated. Straight leg exercises, trunk strengthening, and hip adduction and abduction were begun after 4 weeks. Partial weight bearing was permitted at six weeks after surgery. Full weight bearing with brace was allowed after obtaining control radiography and evaluation of bone consolidation at eight weeks. After a further two weeks the brace was removed. Proprioceptive and balance activities, walking and cycling were introduced at 3 months. The patients were returned to usual life activities at six months and high impact sports were permitted after one year of surgery [Figure 4].

Statistical analysis

All continuous data were expressed as mean ± SD. The categorical data was expressed as frequency and percentages. The Kolmogorov-Smirnov test was performed to test normality of continuous variables.

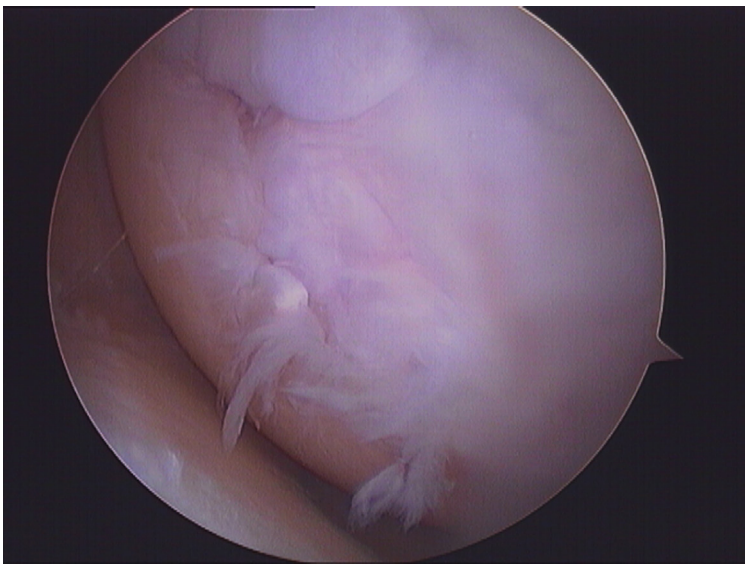

Figure 2. Arthroscopic view showing the condylar cartilage lesion.

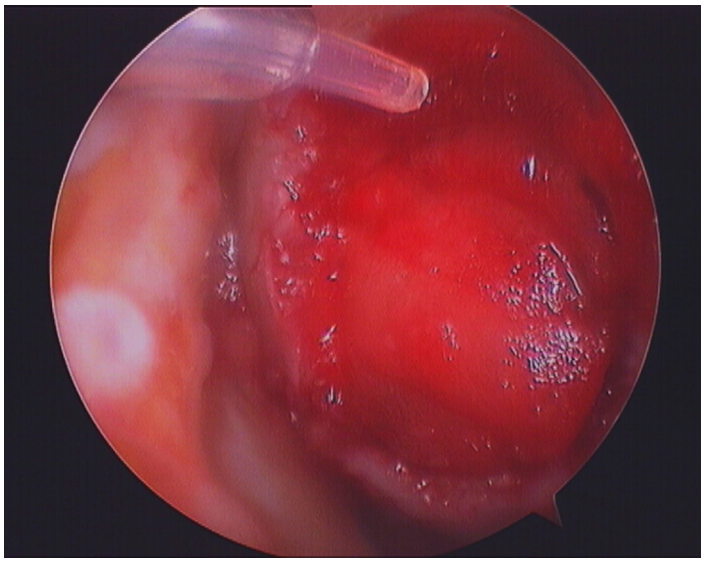

Figure 3. Arthroscopic view showing the Bone Marrow Derived Cells implantation and PRF injection.

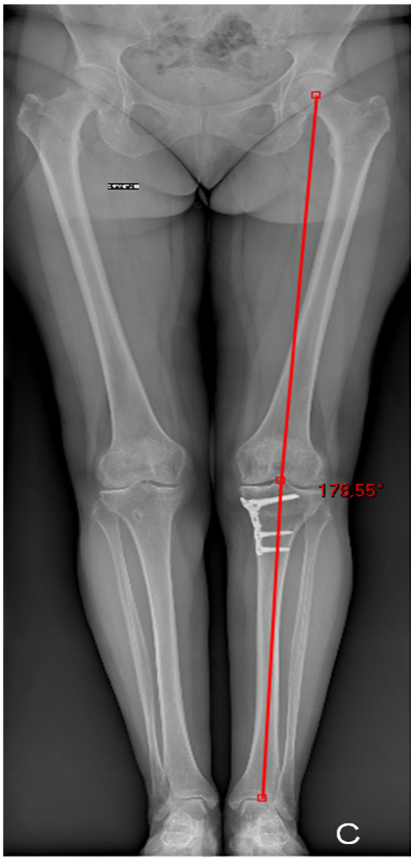

Figure 4. Representative X-ray control after 3 years of follow up: weight bearing full leg X-ray with identification of the new corrected mechanical axes.

The Repeated Measures General Linear Model (GLM) with Sidak test for multiple comparisons was performed to assess the differences at various follow-up times. The Spearman rank correlation was used to assess the correlation between the continuous data. The Kendall Tau correlation was used to assess the correlation between the ordinal data. The ANOVA test was performed to assess the between groups differences of continuous, normally distributed, and homoscedastic data. The Mann Whitney test was used otherwise. For all tests *P<0.05* was considered as statistically significant. All statistical analyses were performed using SPSS v.19.0 (IBM Corp., Armonk, NY, USA).

Results

No major complications were observed during treatment and follow-up periods. Knee swelling due to hemarthrosis in three cases were treated with a temporary suspension of the rehabilitation protocol and one week rest. No case with fever above 38° C was reported. Two cases of infrapatellar nerve injury were observed, with partial recovery at final follow up. One case of delayed union of the osteotomy occurred, with dilation of the recovery time up to three months. No failure of the procedure requiring a revision surgery has been reported to date.

A statistically significant improvement was obtained in all the scores. The mean preoperative IKDC score (T_0) was 32.7±15.8; at 2 years of follow-up (T_1) was 58.7±23.4 (T_0 vs. T_1 *P<0.0005*); while at 3 years of follow up (T_2) scored 64.6±21.8 (T_0 vs T_2 *P<0.0005*; T_1 vs. T_2 *P= 0.044*) [Figure 5; Graph 1].

The KOOS score (general) also showed significant improvement from 30.46±11.67 (T_0) to 68.9±19.2 (T_0 vs. T_1 *P<0.0005*) at 2 years (T_1) and 72.38±20.1 at 3

years (T_2) (T_0 vs. T_2 *P<0.0005*). This improvement was reported for all KOOS sub-scores [Figure 5; Graph 2-3].

The VAS score decreased significantly at various follow-ups (preoperatively (T_0) mean 7.50 ± 1.24; 3.87± 1.82 (T_1) at 2 years; 3.00 ± 2.08 (T_2) at final follow up).

The Tegner score also increased significantly from 1.21 +/-1.02 (T0) to 2.12 ± 1.39 (T_2) at final follow up (*P<0.004*). Although all of the scores increased between 2 years and the final follow up but this improvement was not statistically significant.

At multivariate analysis it was noticed that age, BMI, pre-operative Kellgren-Lawrence osteoarthritis grade and preoperative degree of axis deviation did not affect the clinical outcome and scores at short term follow up and so was the history of previous trauma and previous knee surgery. The correction angle ranged from 0.5˚ to 5.1˚ of valgus (measured on X-ray, one year after the procedure) with an average overcorrection of 2.73˚±1.25˚. The angle remained substantially unchanged at last follow-up (its variations were ±1˚, falling within the measurement error). Also, the postoperative degree of correction showed no significant correlation with the clinical outcomes.

Partial or subtotal meniscectomy of the medial meniscus was carried out in 12 cases during the arthroscopy among whom, partial meniscectomy of both medial and lateral meniscus was performed in 5 cases. A significant relationship was not found between the clinical results and the intraoperative meniscectomy.

The degree of cartilage damage according to ICRS scale significantly correlated with the outcome (T_0 vs. T_2: IKDC *P=0.031*; Tau=-0.364; KOOS *P=0.019* Tau =-0.400; VAS *P=0.028* Tau =0.390) [Figure 5; Graph 4].

The preoperative degree of A/P slope was significantly related with the results: a reduction in the scores was reported with higher values of the A/P slope degree (at 3 years of follow up: IKDC *P= 0.011* Tau=-0.413; KOOS *P=0.003* Tau=-0.483). The postoperative A/P slope was measured again on the X Ray: in agreement with the literature the A/P slope was on average 1.11±1.77 degrees higher than the preoperative (31, 32). Also, a significant correlation was found with respect to the clinical score (at 3 years of follow up: IKDC *P=0.025* Tau=-0.370; KOOS *P=0.004* Tau=-0.475) [Figure 5; Graph 5].

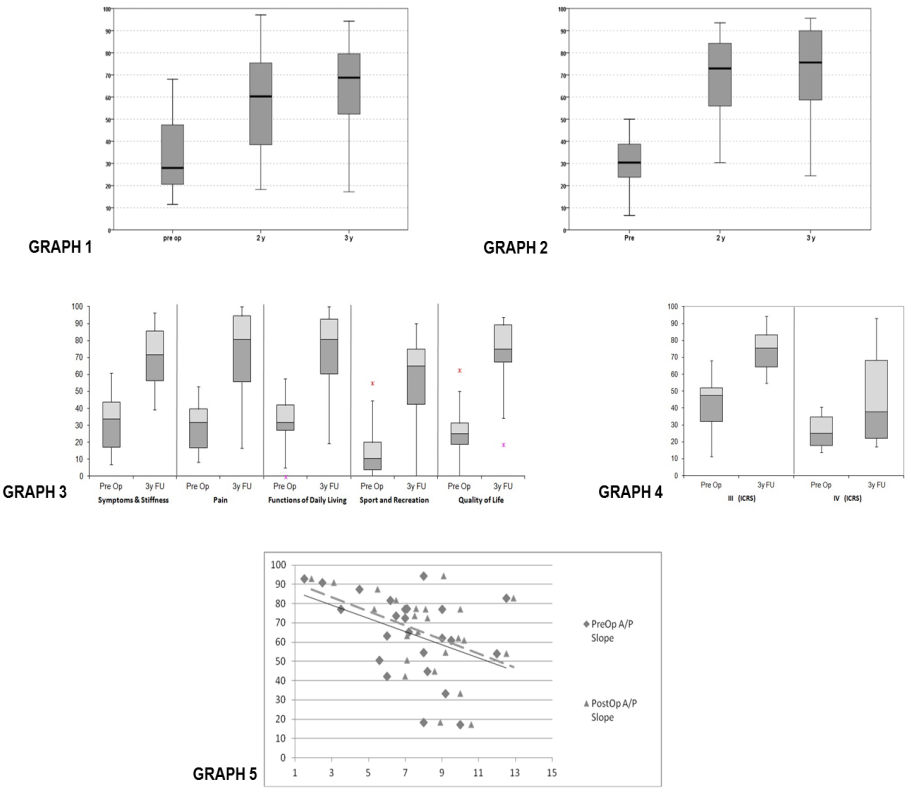

Figure 5. Graph 1) The IKDC subjective score before and two and three years after surgery. Graph 2) The KOOS score before and two and three years after surgery. Graph 3) The KOOS sub-scores before and three years after surgery. Graph 4) The relationship between IKDC score and degree (ICRS) of preoperative cartilage lesion. Graph 5) Preoperative and Postoperative A/P Slope was related with IKDC Score at three years of follow up: better clinical results were reported in cases of lower tibial A/P slope.

Discussion

High tibial osteotomy is an acceptable and reliable procedure in treatment of early osteoarthritis of varus knees, since in addition to medial compartment decompression it can produce fibrocartilage repair in chondral defects (4, 5, 9, 10).

The fibrocartilage repair produced by HTO and conventional cartilage regenerative procedures (i.e: microfracture, multiple drilling, abrasion chondroplasty) is reported to be mechanically inferior to the hyaline cartilage and cannot withstand the mechanical stresses overtime (13, 16). Newer cartilage regenerative procedures have been developed to produce hyaline like cartilage, with good results (10). It has been shown that ACI has reliable and durable clinical results but it needs two surgical procedures and the tissue expansion procedure is complex and expensive (17, 18). Recently, good and comparable clinical results have been reported with mesenchymal stem cell implantation in the management of osteochondral lesions (19, 20). BMDC implantation technique allows the use of not only mesenchymal stem cells, but the entire bone marrow cellular pool including multipotent cells in the site of cartilage repair in a one-step technique. This topic has recently been debated in literature, with a general consensus in the last years that thanks to all the supporting stromal cells and all the native microenvironment present in the bone marrow and maintained in the regeneration site, the cellular pool has more regenerative potential than the isolated mesenchymal stem cells (21, 22). Various authors have obtained good clinical results with this technique showing good quality cartilage regeneration in the osteochondral defects (13-15, 23).

This preliminary study was set up to investigate the safety and feasibility of the combination of the two procedures, in order to provide the patients a possible addition of the beneficial effects.

The current study showed good results in short term follow up. All the clinical and functional scores showed statistically significant increase at two years and these results improved more at three years follow up.

No major complication during operation procedure and follow ups were reported, providing preliminary data that the combination of the two well established procedures was not contraindicated. These data indicate that the whole procedure is safe and can be performed without any major additional risk compared to that of simple HTO.

A further analysis was also performed to determine the factors influencing the outcomes, highlighting that ICRS grade is a valuable factor in predicting the outcomes. Lesions scored with higher grades reported worst results. Conversely, age, BMI, and grade of osteoarthritis did not affect the clinical outcomes in this period of follow up. This finding probably indicates that the combination of the two procedures has to be strongly considered in patients with lower grades of chondral damages, while it lightens its beneficial effects with the increase of cartilage lesion grade.

K-L patients rated grade 4 were included in the study even if the OA was not properly early: this is because the patients were active and middle aged with high functional activity of the knee, therefore the combination of the procedures was considered to have a positive effect on these patients as well.

Limitations of this preliminary study are the lack of control group, short term follow up, absence of second look arthroscopy and histological assessment of the regenerated cartilage. According to our results, further randomized controlled studies are required to confirm the clinical advantage of this procedure in early osteoarthritic patients.

In conclusion, combination of HTO and one step BMDC implantation is safe, feasible, and associated with good results in short term follow up without major additional complications compared to HTO alone.

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