석 사 학 위 논 문

High Tibial Osteotomy Versus High Tibial Osteotomy with Cartilage Regeneration Surgery Using Human Umbilical Cord Blood Derived-mesenchymal Stem Cells

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이 논문을 석사학위 논문으로 제출함

2021년 8월

계명대학교 대학원

의학과 정형외과학 전공

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최병찬의 석사학위 논문을 인준함

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2021년 8월

최 병 찬

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1. Introduction

High tibial osteotomy (HTO) is an established procedure for treatment of young and active patients with medial compartment osteoarthritis (OA) by changing alignment of the lower limb (1,2). Many surgeons have reported that HTO was effective in pain relief and caused significant change of radiologic parameters and showed good long-term results. In addition, several studies have reported remodeling of the articular cartilage after HTO and attributed improvement to reduced contact stress (3-5). However, HTO alone can induce only partial remodeling of the articular cartilage (5). HTO is joint preserving procedure, thus healthy articular cartilage is critical for good results. As a result, medial femoral condylar cartilage wear is a challenging issue when performing an HTO procedure.

Orthopaedic surgeons can treat cartilage lesions conventionally using micro fracture, micro drilling, osteochondral autograft transfer, and autologous chondrocyte implantation. However, there are many limitations with these options, such as partial repair, autologous and invasive harvesting procedure.

Many surgeons have reported that HTO with cartilage regeneration surgery shows significant pain relief and functional restoration and there are many additional treatment options concomitant HTO for medial femoral condylar cartilage lesions for regeneration of cartilage such as injection or implantation of platelet rich plasma (PRP) (6), bone marrow aspirate concentrate (BMAC), and human umbilical cord blood derived-mesenchymal stem cells (hUCB-MSCs) (6-8). hUCB-MSCs are allogenic mesenchymal stem cells and progenitor cells attained from human umbilical cord blood. hUCB-MSCs have an additional advantage

because of their high expansion capacity, non-invasive harvesting, and hypo-immunogenicity. In addition, because they are allogenic stem cells, surgeons can supply a sufficient amount of stem cells.

However, there are few studies of the effect of additional cartilage regeneration surgery after HTO on radiologic parameters and clinical outcomes compared with a control group. The purpose of this study is to compare clinical outcomes and radiologic parameters in HTO only versus HTO with cartilage regeneration surgery using hUCB-MSCs. Hypothesis of this study was that cartilage regeneration surgery can cause differences in radiologic parameters and significant improvement of clinical outcome compared to the control group.

2. Materials and Methods

2.1. Patient Enrollment:

A review of patients who underwent medial open wedge high tibial osteotomy from January 2015 to November 2019 was conducted. Patients 1) with medial compartment OA 2) who underwent HTO alone (group H) or HTO with cartilage regeneration surgery using hUCB-MSCs (group HS) were included. Patients 1) who underwent surgery because of other disease not primary OA and patients 2) with follow up less than 12 months were excluded (Figure 1). This study was approved by the institutional review board (DSMC IRB No. 2021-04-075).

2.2. Surgical Methods:

Before the surgical procedure, correction angle and correction height were measured using the Miniaci technique to correct the mechanical axis to pass the Fujisawa point (9,10). For the surgical procedure, arthroscopy was performed for the first time in all patients who underwent HTO. During arthroscopy, medial femoral condylar cartilage defect size was checked. Medial open wedge HTO was then performed. A proximal anteromedial incision was made and pes anserinus was identified. Preserving pes anserinus, biplanar medial open wedge osteotomy was performed. After widening of the osteotomy site, the gap was measured and, using a prepared hydroxyapatite block (Otho biowedge®, Ohtomedical Co. Ltd., Goyang-si, South Korea), the gap of the open wedge osteotomy site was filled. Finally, the plate (Ohtofix®,

논문 여러군데 형광펜으로 표시를 왜 해놓으신건지?

Ohtomedical Co. Ltd., Goyang-si, South Korea) was fixed using cortical and locking screw. In group HS, arthrotomy was performed and the medial condyle of the femur was exposed after HTO. The cartilage defect was checked and defect size was measured again. After debridement and multiple drilling, implantation of hUCB-MSCs (CARTISTEM®, Medipost, Seongnam-si, Gyeonggi-do South Korea) with hyaluronic acid was performed (Figure 2).

2.3. Radiologic Parameters:

Pre-operative, post-operative 6-month, 1-year and the latest radiologic parameters such as hip-knee-ankle (HKA) angle, tibia plateau inclination (TPI), knee joint line orientation (G-KJLO), ankle joint line orientation (G-AJLO), medial and lateral joint width (MJW and LJW), and joint line convergence angle (JLCA) in a standing telegram were evaluated. Correction height and correction angle in tibia simple radiography were also evaluated.

Hip-knee-ankle angle was evaluated as the angle between the mechanical axis of the femur and the mechanical axis of the tibia (Figure 3a) (3). TPI was defined as (the angle between the mechanical axis of the tibia and the tangent to the subchondral plate of the tibia) - 90 º ; TPI shows negative values in varus alignment (Figure 3b) (3). G-AJLO was defined as the angle between the tangent to the subchondral plate of the talus and the horizontal grid line on radiographs; a negative value was given when the tangent of the talus surface tilted medially relative to the horizontal grid line. Lateral tilting was defined as positive value and medial tilting as negative value (Figure 3c) (3).

On the knee standing anteroposterior radiograph, medial and lateral

joint width was measured as follows: 1) the medial and lateral edges of the proximal tibia, as well as the midpoint of the intercondylar eminences and the distal shaft of the tibia, were identified and designated. These points were connected, forming the long axis of the tibia. 2) Two separate lines representing each compartment of the knee. 3) Next, two lines bisecting the midpoints of each compartment of the knee were drawn parallel to the long axis of the tibia. 4) Finally, the points at which the midpoint lines met the lowest point of the femoral cortex and the highest point of the tibial cortex were specified by the investigator. 5) The length of the line connecting these points was defined as the joint space width in each compartment (Figure 4a) (1). G-KJLO was defined as the angle between the line connecting the mid-points of the medial and lateral knee joint space, and a horizontal grid line on radiographs that was parallel to the floor; a negative value was given when the mid-joint space line tilted medially relative to the horizontal grid line (Figure 4b) (3). JLCA was defined as the angle formed between a line tangential to the distal femoral condyle and the tibial plateau (Figure 4c) (11).

Correction angle was defined as the angle between upper border of osteotomy site and lower border of osteotomy site. Correction height was defined as the distance between the upper and lower edges of the opened posteromedial osteotomy site (Figure 5a&5b) (10).

2.4. Clinical Score:

In addition, the pre-operative and last follow up post-operative clinical scores were reviewed according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (12) and international Knee

Documentation Committee (IKDC) scores (13). WOMAC score includes three categories, consisting of pain (five questions), stiffness (two questions), and activity of daily life (17 questions). The maximum score is 96. The IKDC score also includes three categories, consisting of symptoms (seven questions), functions (two questions), and activity level (10 questions). The maximum score is 105.

2.5. Statistical Analysis:

Statistical analyses were performed using SPSS software version 26. A paired t-test was used for analysis of pre-operative and post-operative difference in group H. The Wilcoxon rank sum test was used for analysis of pre-operative and post-operative difference in group HS. The Mann-Whitney U test was used for analysis of difference between the two groups. Statistically significant difference was defined as $p < 0.05$.

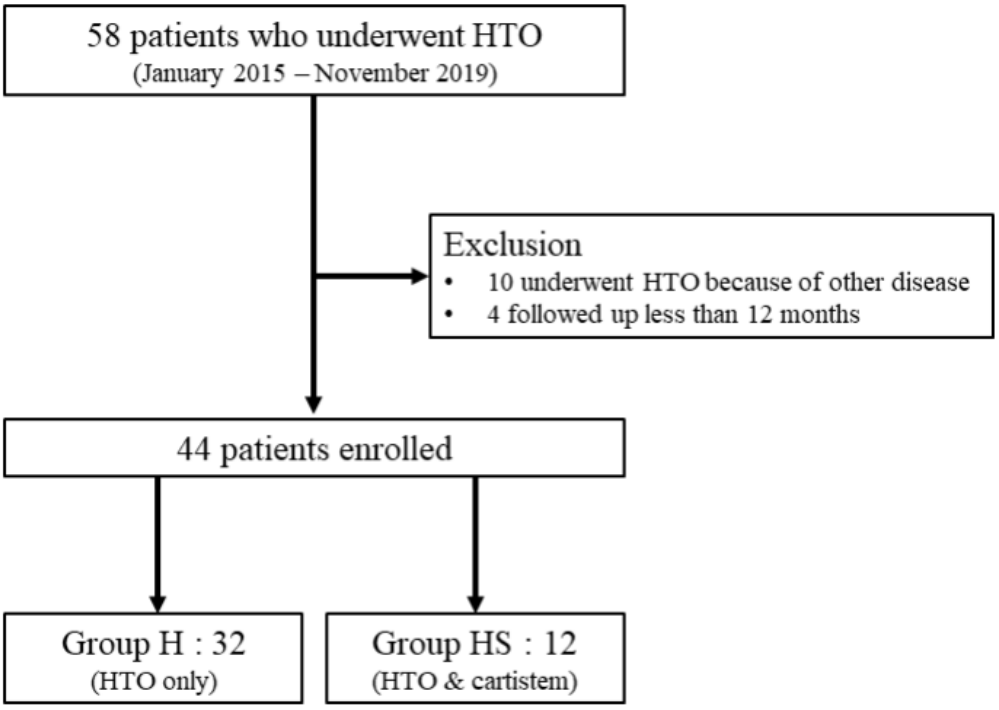

Figure 1. Patients enrollment flowchart. Patients with medial compartment OA who underwent HTO alone (group H) or HTO with cartilage regeneration surgery using hUCB-MSCs (group HS) were included. H: HTO only; Hs: HTO with cartilage regeneration surgery; HTO: High tibial osteotomy; hUCB-MSCs: human umbilical cord blood derived-mesenchymal stem cell; OA: osteoarthritis.

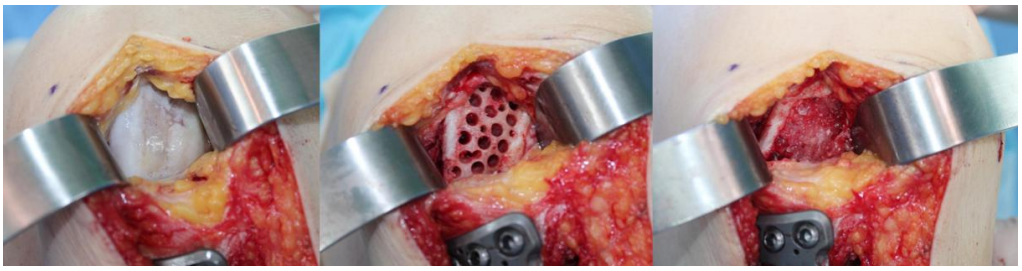

Figure 2. A case of cartilage regeneration surgery concomitant HTO. Arthrotomy was done and exposed medial condyle of femur after HTO. Debridement, multiple drilling, stem cell implantation was performed. HTO: High tibial osteotomy.

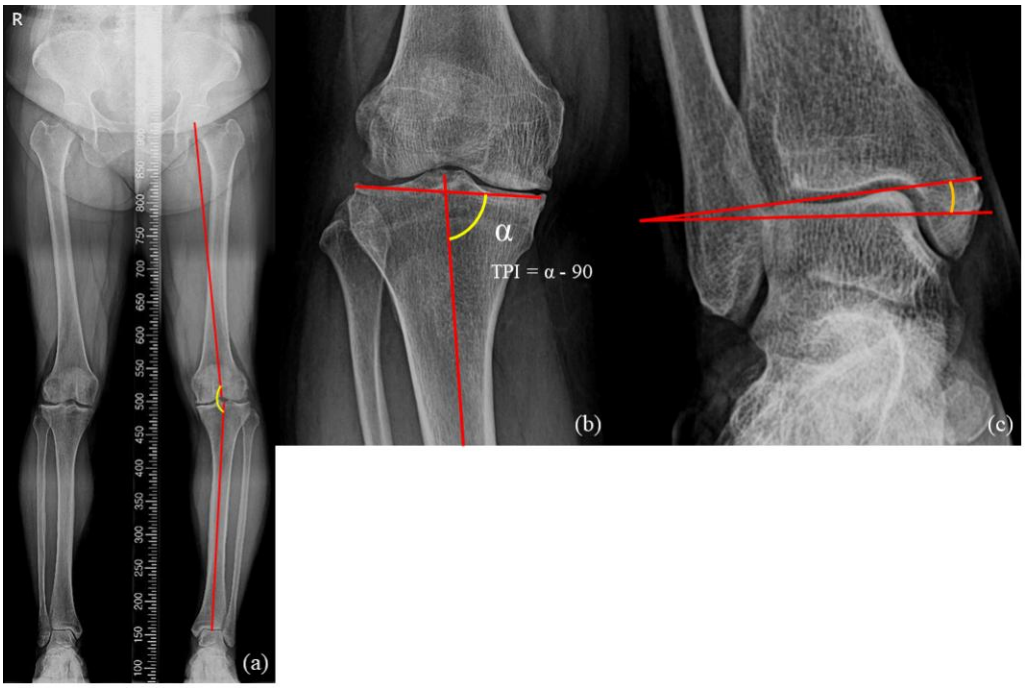

Figure 3. Radiologic parameters in standing radiograph. (a) Hip-knee-ankle angle, (b) TPI, (c) G-AJLO. G-AJLO: ankle joint line orientation; TPI: tibia plateau inclination.

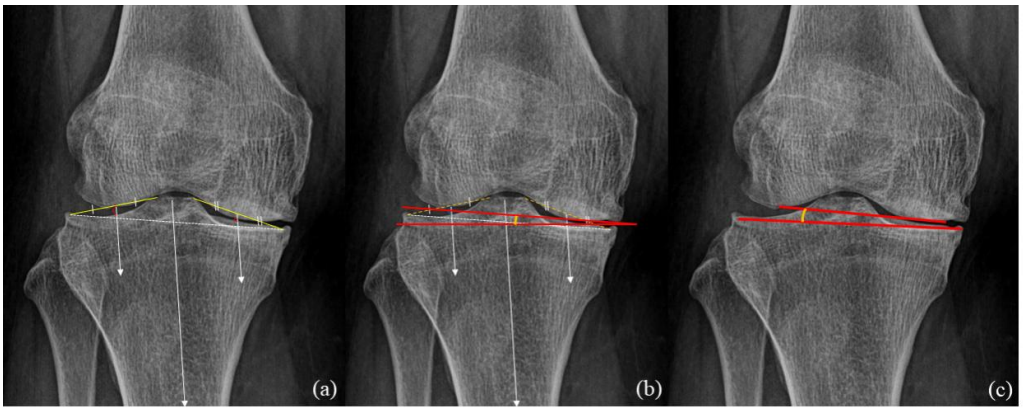

Figure 4. Knee joint standing radiograph. (a) MJW & LJW, (b) G-KJLO, (c) JLCA. G-KJLO: knee joint line oritentation; JLCA: joint line congruency angle; LJW: lateral joint width; MJW: medial joint width.

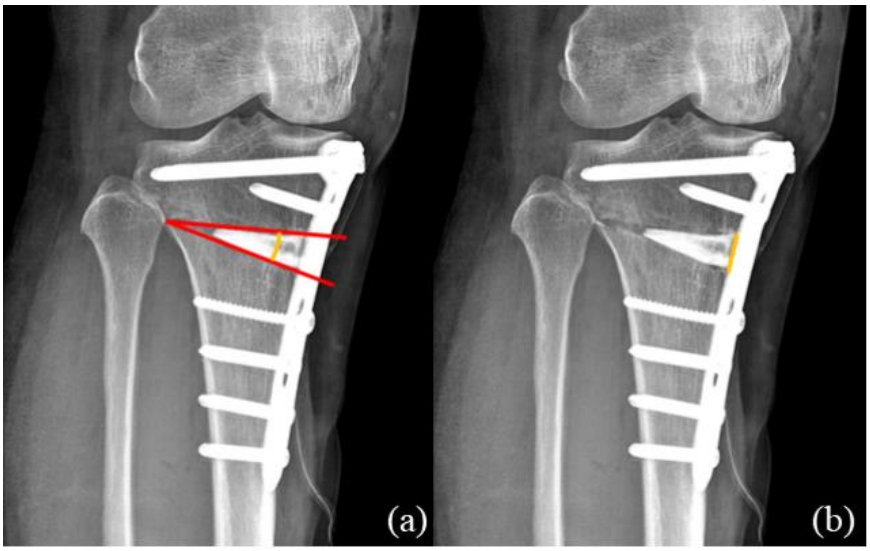

Figure 5. Tibia simple radiograph. (a) correction angle, (b) correction height.

3. Results

3.1. Demographics:

A total of 58 patients were reviewed and 14 patients were excluded. Ten patients were excluded because they underwent HTO because of other disease, not OA. Four patients were excluded because they had a follow up period less than 12 months. A total of 44 knees (group H: 32, group HS: 12) were enrolled. Thirty five females and nine males were enrolled and average age was 56.7 ± 5.0 years old. The mean follow-up period was 27.5 ± 11.4 months. The average age was 57.3 ± 4.9 years in group H and 55.1 ± 5.2 years in group HS. No significant difference in sex and age was observed between the two groups (Table 1).

3.2. Radiologic Parameters:

In group H, the pre-operative average HKA angle was 8.28 º varus alignment and the last follow up post-operative average HKA was 3.21 º valgus alignment. The pre-operative average MJW was 4.17 mm and the last follow up post-operative average MJW was 3.97 mm. The pre-operative average LJW was 6.55 mm and the last follow up post-operative average LJW was 5.44 mm.

In group HS, the pre-operative average HKA was 7.79 º varus alignment and the last follow up post-operative average HKA was 2.69 º valgus alignment. The pre-operative average MJW was 4.62 mm and the last follow up post-operative average MJW was 4.32 mm. The pre-operative average LJW was 6.11 mm and the post-operative average

LJW was 4.87 mm.

No significant difference in all pre-operative radiologic parameters was observed between the two groups (all $p > 0.05$) (Table 2). In addition, there were significant changes in radiologic parameters after surgery, except for medial joint width, in both groups (MJW; group H: $p > 0.05$, group HS: $p > 0.05$).

There was no statistically significant difference between six months post-operative radiologic parameter and last follow up radiologic parameter except for G-KJLO in the two groups ($p < 0.01$) (Table 3). In group HS, average G-KJLO increased 1.18 º.

However, these differences between last follow up post-operative radiologic parameter and pre-operative radiologic parameter in two groups were not statistically significant (all $p > 0.05$) (Table 4).

3.3. Clinical Scores:

No significant difference in pre-operative WOMAC score and IKDC score was observed between the two groups ($p > 0.05$).

The last follow up post-operative WOMAC score was average 80.56 and IKDC was average 76.16 in group H and last follow up post-operative WOMAC score was average 84.33 and IKDC was average 82.75 in group HS. Significant improvement in WOMAC ($p < 0.005$) and IKDC score ($p < 0.005$) compared to preoperative score was observed in both groups. (all $p > 0.05$) (Table 5).

Table 1. Demographics

	Group H (n = 32)	Group HS (n = 12)	p-value
Age (year)	57.2	55.09	> 0.05
Sex (male/female)	6 / 26	3 / 9	> 0.05
Height (cm)	157.3	159.4	> 0.05
Weight (kg)	67.3	65.4	> 0.05
BMI (kg/m)	27.22	25.67	> 0.05

BMI: body mass index; H; HTO only; HS: HTO with cartilage regeneration surgery; HTO: High tibial osteotomy.

Table 2. Pre-operative Radiologic Parameters Comparision between Both Group

	Group H (n = 32)	Group HS (n = 12)	p-value
HKA (°)	-8.28	-7.79	> 0.05
TPI (°)	-4.94	-5.34	> 0.05
G-KJLO (°)	-1.86	-2.76	> 0.05
G-AJLO (°)	8.31	6.67	> 0.05
MJW (mm)	4.17	4.62	> 0.05
LJW (mm)	6.55	6.11	> 0.05
JLCA (°)	-3.72	-3.14	> 0.05

G-AJLO: ankle joint line orientation; G-KJLO: knee joint line orientation; H; HTO only; HKA: hip knee ankle angle; HS: HTO with cartilage regeneration surgery; HTO: High tibial osteotomy; JLCA: joint line congruency angle; LJW: lateral joint width; MJW: medial joint width; TPI: tibia plateau inclination.

Table 3. Difference between Last Follow Up Post-operative Radiologic Parameter and 6 Months Post-operative Radiologic Parameter in Two Groups

	Group H (n = 32)	Group HS (n = 12)	p-value
HKA (°)	0.14	0.78	> 0.05
TPI (°)	-0.2	0.40	> 0.05
G-KJLO (°)	-0.49	1.18	< 0.005 *
G-AJLO (°)	-0.25	1.61	> 0.05
MJW (mm)	0.35	0.36	> 0.05
LJW (mm)	0.25	0.13	> 0.05
JLCA (°)	0.59	0.02	> 0.05

G-AJLO: ankle joint line orientation; G-KJLO: knee joint line orientation; H: HTO only; HKA: hip knee ankle angle; HS: HTO with cartilage regeneration surgery; HTO: High tibial osteotomy; JLCA: joint line congruency angle; LJW: lateral joint width; MJW: medial joint width; TPI: tibia plateau inclination; *: Statistically significant.

Table 4. Difference between Last Follow Up Post-operative Radiologic Parameter and Pre-operative Radiologic Parameter in Two Groups

	Group H (n = 32)	Group HS (n = 12)	p-value
HKA (°)	11.49	10.48	> 0.05
TPI (°)	8.15	8.88	> 0.05
G-KJLO (°)	3.64	4.95	> 0.05
G-AJLO (°)	-8.28	-7.44	> 0.05
MJW (mm)	-0.20	-0.30	> 0.05
LJW (mm)	-1.11	-1.24	> 0.05
JLCA (°)	2.61	2.06	> 0.05

G-AJLO: ankle joint line orientation; G-KJLO: knee joint line orientation; H; HTO only; HKA: hip knee ankle angle; HS: HTO with cartilage regeneration surgery; HTO: High tibial osteotomy; JLCA: joint line congruency angle; LJW: lateral joint width; MJW: medial joint width; TPI: tibia plateau inclination.

Table 5. Comparison of Clinical Outcome Improvement between Both Groups

	Group H (n = 32)	Group HS (n = 12)	p-value
IKDC			
Pre-operative	41.81	46.67	> 0.05
Last follw up	76.16	82.75	> 0.05
WOMAC			
Pre-operative	46.63	52.75	> 0.05
Last follow up	80.56	84.33	> 0.05

H; HTO only; HS: HTO with cartilage regeneration surgery; HTO: High tibial osteotomy; IKDC: international Knee Documentation Committee; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

4. Discussion

Currently, orthopaedic surgeons are particularly interested in stem cells. Many surgeons have presented good clinical outcome of cartilage repair or regeneration procedure using autogenous or allogenous stem cells such as BMAC, hUCB-MSCs (6-8). Themistocleous et al. (14) reported good results of single intra-articular injection of BMAC in patients with knee OA in terms of clinical outcome. This research showed meaningful pain relief and functional restoration after a single intra-articular injection of BMAC in 121 knee OA patients. Ryu et al. (7) suggested that cartilage regeneration surgery using BMAC or hUCB-MSCs with concomitant surgery such as HTO, anterior cruciate ligament reconstruction, meniscus allograft transplantation was effective in both pain relief and functional restoration in 52 patients. In that research, there were no significant differences in the BMAC group and hUCB-MSCs groups.

Many surgeons have attempted an additional cartilage remodeling or regeneration procedure after reducing pressure on the medial compartment of the knee by HTO. Kahlenberg CA et al. (15) reviewed 827 patients who underwent HTO with a cartilage restoration technique such as micro-fracture, PRP, osteochondral autograft transfer, autologous chondrocyte implantation and concluded that HTO with cartilage restoration procedures provides reliable improvement in functional status in the medium to long term period. Wong KL et al. (16) suggested that HTO with bone marrow-derived mesenchymal stem cell injection is effective in improving clinical outcome. In this research, significantly better Tegner, Lysholm, and IKDC scores were observed in the HTO with mesenchymal stem cell injection group compared with the HTO alone

group.

In addition, several researchers have reported magnetic resonance imaging (MRI) outcome and second look arthroscopy after cartilage regeneration surgery. Many studies reported satisfactory MRI outcomes based on modified magnetic resonance observation of cartilage repair tissue (M-MOCART) after cartilage regeneration surgery (7,16-19). Although MRI outcomes showed good results, some studies mentioned that MRI cannot accurately determine the status of cartilage regeneration (20). In this study it was determined that second look arthroscopy should be performed to check the condition of repaired cartilage. Ryu et al. (7) reported significant improvement of international cartilage repair society (ICRS) repair score in patients who underwent HTO with cartilage regeneration surgery using hUCB-MSC or BMAC. In addition, Song et al. reported that cartilage was regenerated to ICRS grade 3 or better in all patients who underwent HTO with hUCB-MSC implantation (8). MRI was not performed in all patients so that MRI outcomes was not analyze in this study. Some patients have conducted MRI follow up after removal of internal fixation device and have showed improvement of cartilage status, so additional study about MRI outcome after HTO and cartilage regeneration surgery will be performed.

However, some studies claimed that although cartilage regeneration improved ICRS repair score, repaired cartilage was composed of mixed repair (hyaline cartilage and fibrocartilage) (21). Others have reported that repaired cartilage was composed of hyaline like cartilage (22,23). Despite controversy in cartilage status, it is certain that HTO with cartilage regeneration surgery showed significant improvement of clinical outcome and M-MOCART. Song et al. followed up 128 patients at least 2 years after HTO with cartilage regeneration surgery and claimed that

clinical score visual analogue scale (VAS) score, WOMAC score, IKDC score and M-MOCART was significantly improved after HTO with cartilage regeneration surgery. (19)

There are several limitations in this study. First, this is a retrospective study. As a result, there is a risk of bias in this study. Second, this study was based on relatively short term follow up results and a small number of subjects. In particular, group HS included a small number of patients. In addition, there was significant difference in follow up period between group H and group HS. This difference can cause bias in terms of radiologic parameters. Third, second look arthroscopy and post-operative MRI study were not performed because of the short term follow up period. post-operative MRI are being performed in patients who underwent removal of an internal fixation device. Nevertheless, the strength of this study is comparison of comprehensive simple radiologic parameters between the HTO only group and the HTO with cartilage regeneration surgery group.

5. Summary

This study shows that patients were satisfied with the HTO procedure in terms of clinical score and significant change in several radiologic parameters such as alignment, TPI, G-KLJO, G-AJLO, LJW and JLCA was achieved. Statistically significant difference between 6-months post-operative G-KJLO and last follow up G-KJLO was observed between group H and group HS. This means that valgus alignment of the knee joint was well maintained in group HS compared with group H. However, there was no significant difference in other radiologic parameters in the HTO only group and HTO with cartilage regeneration surgery group. This study measured and compared clinical outcome and comprehensive radiologic parameters for evaluation of the knee joint after the cartilage regeneration surgery and control group. Group HS showed slightly higher IKDC and WOMAC scores. Although group HS showed greater improvement in clinical score, there was no statistically significant difference between two groups.

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High Tibial Osteotomy Versus High Tibial Osteotomy with Cartilage Regeneration Surgery Using Human Umbilical Cord Blood Derived-mesenchymal Stem Cells

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(Abstract)

When performing a high tibial osteotomy (HTO) procedure, femoral condylar cartilage wear is a catastrophic and challenging issue. The purpose of this study is to compare clinical and radiologic outcomes in HTO with or without cartilage regeneration surgery using hUCB-MSCs. Patients who underwent HTO alone (group H) or HTO with cartilage regeneration surgery using hUCB-MSCs (group HS) was included. Kellgren-Lawrence grade, hip-knee-ankle angle, tibia plateau inclination, knee joint line orientation, ankle joint line orientation, medial and lateral joint width, and joint line congruency angle were evaluated. clinical score was evaluated according to Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and international Knee

Documentation Committee (IKDC) scores. A total of 44 knees were enrolled. No significant difference was observed in pre-operative clinical outcomes and radiologic parameters. Significant improvements were observed between pre-operative and post-operative radiologic parameters in both groups, except for medial joint width. However, these parameters did not differ significantly in both groups. Significant improvement in WOMAC and IKDC score compared to preoperative score was observed in both groups at the last follow-up. However, there were no differences between the two groups. Both groups showed satisfactory clinical and radiological outcomes. However, no difference was observed between the two groups.

근위 경골 절골술 대 근위 경골 절골술과 인체 제대혈 유래 중간엽 줄기세포를 이용한 관절연골 재생술

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(초록)

근위 경골 절골술을 시행함에 있어, 대퇴골 관절연골의 마모는 해결하기 어려운 문제이다. 이번 연구의 목적은 근위 경골 절골술과 함께 인체 제대혈 유래 중간엽 줄기세포를 통한 관절연골의 재생술의 방사선학적, 임상적 결과에 대해 연구하는 것이다. 본 연구는 근위 경골 절골술만 시행한 집단과 근위경골 절골술과 함께 관절연골 재생술을 시행한 집단의 여러 방사선학적 지표를 비교하였고 임상결과를 평가하기 위해 WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) 점수, IKDC (international Knee Documentation Committee) 점수를 비교하였다. 총 44례가 등록되었고 두 집단 간 수술 전 방사선학적 지표와 WOMAC 점수, IKDC 점수는 통계학적으로 유의한 차이를 보이지 않았다. 두 집단 각각 수술 전의 방사선학적 지표와 WOMAC 점수, IKDC 점수를 수술 후와 비교했을 때 두 집단 모두 내측 관절 간격을 제외한 나머지 항목에서 유의한

차이를 나타내었다. 그러나 두 집단 간의 수술 후 방사선학적 지표와 WOMAC 점수, IKDC 점수는 유의한 차이를 보이지 않았다. 두 집단 모두 방사선학적, 임상적 결과에서 단기간 추시 상 만족할만한 결과를 보였지만 두 집단 간의 유의한 차이는 관찰되지 않았고 장기 추시 결과 등 추가 연구가 필요할 것으로 보인다.