Intra-Articular Bone Marrow Aspirate Concentrate Injection in Patients with Knee Osteoarthritis

Gi Beom Kim,†, Jae-Do Kim,‡, Young Choi, Chang Hyun Choi, and Gun Woo Lee

1 Department of Orthopedic Surgery, Yeungnam University College of Medicine, Yeungnam University Medical Center, 170 Hyeonchung-ro, Namgu, Daegu 42415, Korea; donggamgb@hanmail.net (G.B.K.); starch87@naver.com (C.H.C.)
2 Department of Orthopedic Surgery, Kosin University College of Medicine, Kosin University Gospel Hospital, 34 Amnam-dong, Seogu, Busan 602-702, Korea; jaedokim207@gmail.com (J.-D.K.); yuzo0n@naver.com (Y.C.)

* Correspondence: gwlee1871@ynu.ac.kr; Tel.: +82-53-620-3642
† Gi Beom Kim and Jae-Do Kim equally contributed to this work as the first author.

Received: 19 July 2020; Accepted: 26 August 2020; Published: 27 August 2020

Abstract: We aimed to evaluate the 5-year follow-up outcomes of an intra-articular bone marrow aspirate concentrate (BMAC) injection in patients with knee osteoarthritis. This is the first study to report the outcomes following BMAC injections over a 5-year follow-up period. Seventy knees of 37 patients, including 33 bilateral knees, were investigated. The primary outcome was the visual analogue scale (VAS) score for pain in the knee joint, and the secondary outcomes were the International Knee Documentation Committee score, the 36-Item Short Form Health Survey score, the Knee injury Osteoarthritis Outcome Score, Lysholm Knee Questionnaire/Tegner activity scale, BMAC injection-induced complications, and 5-year treatment success rate. The 5-year post-injection VAS scores (4.7 ± 0.5) were significantly lower than the preoperative scores (8.3 ± 1.2) (p = 0.01). Improvement in VAS scores was significantly greater in patients with Kellgren–Lawrence (K-L) Grade I or II than those in those with K-L Grade III or IV. Improvement in other clinical parameters and success rates were significantly low and the rates of secondary operation and failure were significantly higher in patients with K-L Grades III or IV. Intra-articular BMAC injections could be useful for managing patients with K-L Grades I or II osteoarthritis.

Keywords: osteoarthritis; knee; bone marrow aspirate concentrate; clinical outcomes

1. Introduction

Extensive studies have been performed on regenerative therapies for osteoarthritis (OA) and cartilage defects in the knee joint [1–5]. A strong body of evidence shows that the human bone marrow (BM) is a source of mesenchymal stem cells (MSCs) and growth factors that aid cartilage regeneration [6–9]. Thus, the BM plays an important role in cartilage regeneration. Alternatives, such autologous BM cells, have been used in recent times to achieve maximal regeneration with minimal ethical and/or other issues [1,3,10,11].

A bone marrow aspirate concentrate (BMAC) injection is one such method of intra-articular delivery of growth factors, which is currently approved by the United States Food and Drug Administration (FDA) [12]. Experimental studies have revealed that BMAC serves as a rich source of important growth factors for cartilage regeneration, such as platelet-derived growth factor and transforming growth factor-beta, and anti-inflammatory molecules that prevent cartilage degeneration and its noxious cascade [13–15]. Hence, BMAC has emerged as a promising tool for modulating the biomechanical factors of OA. Additionally, a few clinical studies have demonstrated that intra-articular BMAC injections in patients with knee OA might produce favorable results in terms of clinical parameters and
Appl. Sci. 2020, 10, 5945 2 of 12
cartilage restoration [16–18]. However, previous clinical studies on this subject have been conducted with a short-term follow-up of 1 or 2 years [16–18].

Considering the aforementioned limitation (short-term follow-up) in all the previous studies investigating intra-articular BMAC injections for OA, the current study evaluated the 5-year outcomes of intra-articular BMAC injection in patients with knee OA. We hypothesized that an intra-articular BMAC injection is a beneficial modality for patients with early OA in the knee joints and that its effect persists during mid-term follow-up.

2. Materials and Methods

2.1. Patient Criteria

The concept and procedural design of this study were approved by the Institutional Review Board. This retrospective study evaluated the efficacy of intra-articular BMAC injection with regard to patient outcomes, particularly focusing on a comparison of patients’ clinical outcomes based on the Kellgren–Lawrence (K-L) classification of knee OA (Grades I-IV). Originally, the study was designed to investigate the 1-year outcomes of BMAC injections for knee OA from April 2011 [17]. However, during the 1-year study period, it was decided to further investigate the mid-term effects in patients with knee OA. Thus, the original study (comprising the initially enrolled patients) was extended to include a 5-year follow-up.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) obvious findings of OA on radiographs of the knee joint (standing anteroposterior and lateral views) on standard knee radiographs, lower-extremity scanography, and magnetic resonance imaging (MRI) of the knee joint, which definitively corresponded to the patients’ symptoms and signs; (2) a clear understanding of the concept and procedure of BMAC injection with voluntary agreement to participate in this study; and (3) a minimum 5-year follow-up after BMAC injection. The exclusion criteria were as follows: (1) a history of infection, trauma, or tumors of the knee joint; (2) concurrent knee instability requiring surgical treatments, such as ligament reconstruction; (3) concurrent knee malalignment requiring surgical treatments, such as corrective osteotomy (i.e., varus alignment of negative value and hip–knee–ankle angle ≤−5°); (4) range of motion (ROM) limitations, especially flexion contractures >10°; (5) inflammatory arthritis, such as rheumatoid arthritis and ankylosing spondylitis; (6) <5-year follow-up; (7) abnormal muscle activity or ambulatory difficulties, such as those observed in patients with parkinsonism, other neuromuscular diseases, or other diseases such as hematological disorders, coagulopathy, and immune deficiency; and (8) inability of patients to accurately record results of preoperative- or post-operative questionnaire scores owing to issues such as a history of stroke, dementia, or medical illness requiring intensive treatment.

2.3. Bone Marrow Aspirate Concentrate

All procedures were performed after informed consent had been obtained from all patients. The BM and adipose tissues of patients were obtained under Good Manufacturing Practices (GMP) conditions [8]. The patient was placed in a supine position. After preparation and draping of the anterior superior iliac spine (ASIS) or the posterior superior iliac spine (PSIS), local anesthesia was administered ensuring infiltration from the skin to the periosteum. Autologous BM (120 cc) was aspirated from the ASIS or PSIS using the SmartPReP2 Bone Marrow Procedure Pack BMAC2 kit (Harvest Technology, Plymouth, MA, USA). The aspirated BM was collected in a plastic bag containing an anticoagulant added to the kit and was thoroughly mixed. The SmartPReP2 Platelet Concentrate System (Harvest Technology) was used to reduce the increased temperature of the BM and to separate 14 cc of the platelets, including autologous stem cells and growth factors. In addition, under local anesthesia, abdominal subcutaneous fat was aspirated using the tumescent technique. Approximately
20 cc of adipose tissue was harvested. Finally, 7 cc of autologous BM-derived mesenchymal stem cells (BM-MSCs) and 10 cc of adipose tissue were injected into each knee joint. Patients who received bilateral injections underwent the procedure simultaneously.

After the procedure, the patients were prescribed 6 h of bed rest, following which they could return home and perform their daily activities. A rescue analgesic was defined as approved medications prescribed for pain control. The rescue medication prescribed was acetaminophen (≤4000 mg/day) and the use of other analgesics was not permitted. There was no limitation with respect to the patients’ daily living except that they were advised to avoid severe exercise for 6 weeks postoperatively.

2.4. Outcome Measures

The primary outcome measure was pain intensity in the injected knee joint. Pain evaluation was performed using the visual analogue scale (VAS). Patients were instructed to record their pain on a horizontal 10-point VAS sheet with “no pain” at the far left of the sheet and “greatest pain possible” at the far right of the sheet. The values were obtained preoperatively, at 6 months, and 1, 3, and 5 years postoperatively. The pain scores were collated and analyzed by a research coordinator who was not involved in this study.

The secondary outcome measures were the clinical outcomes, BMAC injection-induced complications, and 5-year treatment success rates. Clinical outcomes were assessed using the following scales representing the patient-reported outcomes and knee function: The International Knee Documentation Committee (IKDC), the 36-Item Short Form Health Survey (SF-36), the Knee injury and Osteoarthritis Outcome Score (KOOS), and the Lysholm Knee Questionnaire/Tegner Activity (LKQ) scale. Detailed information regarding the BMAC injection-induced complications was obtained from the patients via telephonic interviews and outpatient visits by a research coordinator who was not involved in the study. “Treatment success” after BMAC injection was defined as knee joint pain that was tolerable and corresponded to <4 points on the VAS and pain that did not necessitate the use of pain medication, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, during a 5-year follow-up period. “Treatment failure” was defined as severe intolerable knee pain that corresponded to >5 points on the VAS despite the use of pain medication, necessitating surgical treatment, including total knee arthroplasty (TKA) and corrective osteotomy, during the 5-year follow-up period.

2.5. Statistical Analysis

Statistical evaluation was performed using IBM SPSS software (Version 22, IBM Corp., Armonk, NY, USA). Continuous data are expressed as the means with standard deviation. All dependent variables were tested for normality of distribution and equality of variances by using the Kolmogorov–Smirnov test. According to normality, parametric or non-parametric tests were utilized. Fisher’s exact test (or chi-square test) was used for categorical variables. A repeated measures ANOVA was used to analyze significant differences between the groups over the 5-year study period. Post hoc analysis was performed after using paired t-tests with the significance set at p < 0.01 (=0.05/5), incorporating a Bonferroni correction to correct for multiple analysis. GraphPad Prism software version 7.01 (GraphPad, San Diego, CA, USA) was used for all statistical analyses, and a two-sided p-value of <0.05 was considered statistically significant. Numerical values are expressed as the mean ± standard deviation.

3. Results

3.1. Characteristics of the Enrolled Patients

In total, 41 patients (75 knees) with knee OA received an intra-articular BMAC injection into the knee. During the 5-year follow-up, four patients (5 knees) dropped out, and patients who underwent a secondary operation were also excluded to eliminate bias. Finally, the remaining 25 patients (47 knees) were investigated in the present study (Figure 1).
Figure 1. Study cohort.
Baseline data of the enrolled patients are presented in Table 1.

Table 1. Demographic data.

| Enrolled Cases          |
|-------------------------|
| Case                    | 25 patients (47 knees) |
| Follow-up period (month)| 76.2 (range, 62–83)   |
| Age (year)              | 67.5 (range, 58–85)   |
| Gender (male/female)    | 9/16                   |
| Height (cm)             | 162.1 ± 9.3           |
| Weight (kg)             | 69.8 ± 11.4           |
| BMI (kg/m²)             | 26.3 ± 4.2            |
| Smoking status          |                        |
| smoker (%)              | 10 (40)               |
| non-smoker (%)          | 15 (60)               |
| Knee OA severity (by K-L grade) |
| K-L Grade 1             | 1 (2.1%)              |
| K-L Grade 2             | 27 (57.5%)            |
| K-L Grade 3             | 12 (25.5%)            |
| K-L Grade 4             | 7 (14.9%)             |

Note: The time point at which the data were assessed was when all patients had a minimum follow-up of 5 years after BMAC injection. Values are presented as the mean ± standard deviation or median (range). BMI, body mass index; OA, osteoarthritis; K-L grade, Kellgren–Lawrence grade.

3.2. Primary Outcome Measure

The mean VAS score improved over time, with scores decreasing from 6 months (8.3 ± 1.2) to 5 years (4.7 ± 0.5) postoperatively ($p < 0.001$). The most significant improvement was observed in the first 6 months (Post hoc analysis, $p < 0.001$). Based on the severity of the arthritis, the pain improvement was significantly different according to the K-L grades. Patients with knee OA of K-L Grades III and IV had lower pain improvement than those with knee OA of K-L Grades I and II during the follow-up period (ANOVA, $p < 0.01$, Figure 2).
The improvements in pain intensity showed no significant difference according to age (patients aged <60 vs. those aged ≥60 years) and sex (Table 2).

Table 2. Pain intensity.

| Parameters | Preoperative | 6 Months | 12 Months | 36 Months | 60 Months | p * |
|------------|--------------|----------|-----------|-----------|-----------|-----|
| Overall    | 8.0          | 6.7      | 5.4       | 5.1       | 4.9       | -   |
| Sex        |              |          |           |           |           |     |
| M          | 7.6          | 6.4      | 4.8       | 4.3       | 4.2       | 0.43|
| F          | 8.2          | 6.9      | 5.6       | 5.4       | 5.2       |     |
| Age        |              |          |           |           |           |     |
| <60        | 7.5          | 6.3      | 4.7       | 4.6       | 4.8       | 0.19|
| ≥60        | 8.3          | 6.9      | 5.8       | 5.4       | 4.9       |     |
| K-L grade  |              |          |           |           |           |     |
| 1          | 6.0          | 3.0      | 2.0       | 2.0       | 2.0       |     |
| 2          | 6.9          | 5.8      | 4.2       | 4.0       | 3.9       |     |
| 3          | 8.5          | 7.0      | 6.0       | 5.8       | 6.0       |     |
| 4          | 9.1          | 7.3      | 5.8       | 6.2       | 6.9       |     |

Note: *p*-values indicate the time point between the preoperative and 60-month follow-up period. Values are presented as mean values. VAS, visual analogue scale; K-L grade, Kellgren–Lawrence grade.

3.3. Secondary Outcome Measures

The mean IKDC score improved from 28.5 ± 4.3 preoperatively to 68.2 ± 6.0 at the 5-year follow-up (p = 0.02). The improvements in IKDC scores showed no significant differences in terms of age distribution (patients aged < 60 vs. those aged ≥ 60 years) and sex. However, the severity of knee OA was significantly associated with IKDC scores observed during the follow-up. Patients with high grades of knee OA (K-L Grade III or IV vs. K-L Grade I or II) showed low IKDC scores at the final follow-up visit, and this difference was statistically significant (Post hoc analysis, p < 0.001, Figure 3).
Figure 3. International Knee Documentation Committee (IKDC) score according to the K-L grade.

The mean SF-36 score also improved from 26.8 ± 4.3 preoperatively to 48.2 ± 6.0 at the 5-year follow-up ($p < 0.001$). However, this improvement did not significantly differ in terms of age and sex. The severity of OA was significantly associated with the outcomes of the SF-36; the improvement in patients with knee OA of K-L Grade I, II, and III was significantly greater than that in patients with K-L Grade IV (ANOVA, $p = 0.02$, Figure 4).

Figure 4. 36-Item Short Form Health Survey (SF-36) score according to the K-L grade.

The KOOS and LKQ scores showed similar trends as the IKDC scores; the mean preoperative KOOS and LKQ scores improved significantly at the final follow-up visit ($p < 0.001$). Similarly, high grades of knee OA were associated with poor scores at the final follow-up visit (Post hoc analysis, $p = 0.001$, and 0.002, respectively, Figures 5 and 6).
Secondary operations were performed in 12 patients (23 knees). Among them, 10 (19 knees) underwent TKA owing to arthritic progression and two patients (four knees) underwent a high tibial osteotomy (HTO) for progressed pain and varus alignment. The mean period for secondary operations after the BMAC injection was 28.7 months (8.5–68.5 months). The rate of secondary operations in patients with K-L Grade III or IV was significantly higher than that in patients with K-L Grade I or II ($p = 0.02$, Table 3).

**Table 3. Secondary operation.**

| OA Severity (by K-L Grade) | Secondary Operation * | No Treatment | $p$  |
|----------------------------|-----------------------|--------------|------|
| K-L Grade 1 (n = 1)        | 0 (0%)                | 1            |      |
| K-L Grade 2 (n = 33)       | 6 (18%)               | 27           |      |
| K-L Grade 3 (n = 20)       | 8 (40%)               | 12           | 0.02 |
| K-L Grade 4 (n = 16)       | 9 (56%)               | 7            |      |
| Total (70 knees)           | 23 knees              | 47 knees     |      |

Note: Values are presented as the mean ± standard deviation. K-L grade, Kellgren–Lawrence grade. * Patients underwent secondary operation during the follow-up (total knee arthroplasty in 19 knees and high-tibial osteotomy in four knees).
The treatment failure rate was 53% (Table 4), which was determined as cases that underwent secondary surgical treatment (23 knees) and cases in which pain could not be managed with the usual medication (14 knees). The latter cases were recommended surgical treatment, but this could not be performed owing to the patients’ personal reasons.

Table 4. Treatment failure rate of the BMAC injection (5-year follow-up).

| K-L Grade | Secondary Operation * | Medication # | Total | p |
|----------|-----------------------|--------------|-------|---|
| 1 (1 knee) | 0                     | 0            | 0 (0%) |   |
| 2 (33 knees) | 6                     | 2            | 8 (24%) | 0.01 |
| 3 (20 knees) | 8                     | 6            | 14 (70%) |   |
| 4 (16 knees) | 9                     | 6            | 15 (94%) |   |
| Total (70 knees) | 23                | 14            | 37 (53%) | Failure rate = 53% |

Note: Values are presented as the mean ± standard deviation. K-L grade, Kellgren–Lawrence grade. * Patients who underwent a secondary operation during the follow-up. # Patients with intolerable pain that could not be managed with the usual medication.

4. Discussion

4.1. Study Highlights

The most important finding of this study was that an intra-articular injection of BMAC led to favorable outcomes in terms of pain and patient-reported clinical outcomes in patients with early-to-moderate knee OA (K-L Grade I or II). The degree of improvement and treatment success rate was significantly lower and the rate of secondary operations was significantly higher in patients with K-L Grade III or IV than in those with K-L Grade I or II. Based on the outcomes of the current study, it is reasonable to conclude that an intra-articular BMAC injection can be useful to manage patients with knee OA of K-L Grade I or II.

4.2. Potential Biomechanical Factors of Bone Marrow Aspirate Concentrate for Knee Osteoarthritis

The molecular and cellular mechanisms involved in the development and progression of OA are well known. First, immunogenic cells, such as macrophages, initiate or aggravate OA, resulting in the early inflammatory phase of OA [8]. Next, pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β, shift tissue homeostasis toward catabolism by degradation, resulting in cartilage resorption [19]. Biomolecular mechanisms, such as an increased level of proinflammatory cytokines (e.g., IL-1 or TNF-α), decreased levels of growth factors, such as TGF-β, activation of matrix metalloproteinase, and ultimately chondrocyte senescence can be observed at the molecular level [20,21].

Considering the biomechanical aspects of OA, BMAC can be an effective therapeutic agent for managing OA [22,23]. BMAC contains MSCs, hematopoietic stem cells, growth factors, and cytokines [6,7,15]. Particularly, several studies have proven that BMAC contains several anti-inflammatory growth factors, such as PDGF, TGF-β, and VEGF, within α-granules of the platelets and MSCs that possess high chondrogenic ability. Moreover, PDGF, TGF-β, and other factors, such as IGF-I, also serve as chemoattractants. Further, MSCs have the potential for local tissue regeneration, as well as paracrine and anti-inflammatory actions through their interaction with several growth factors and cytokines [8,24–27]. In addition, by modulating the activation of immune cells, such as natural killer cells, macrophages, and T and B lymphocytes, MSCs also exert an immunosuppressive effect [28,29]. The pathological mechanism of OA can be attributed to both degenerative changes and inflammatory responses. Therefore, MSCs could improve the intra-articular environment secondary to their potential role as a disease-modifying biological tool [8,29]. On the basis of the positive outcomes observed in previous studies with the use of MSCs for OA, a few studies have investigated the outcomes of an intra-articular MSC injection to treat knee OA [1,30,31]. A study using high-dose
autologous BM-MSCs injections reported significant improvement in clinical outcomes and cartilage quality over 24 months after administering the injection [32]. However, the number of cells was increased by 1–2 weeks of laboratory culture. Additionally, the sample size was too small to investigate the statistical significance of the results. Although the expansion procedure to culture MSCs can provide a sufficient number of cells, the process is usually time consuming and expensive and requires specialized facilities [33,34]. Moreover, during culture, the cells may lose their ability to differentiate or may transform into malignant cells [17]. Another study reported the outcomes of injection of allogeneic BM-MSCs in patients with OA of K-L Grade II to IV, which showed a significant improvement in pain and cartilage quality [26]. Although the study reported no major adverse events, the risk of host immune rejection, tumorigenesis, and disease transmission with the use of allogeneic MSCs cannot be excluded [35]. Further studies are needed to investigate the safety and efficacy of allogeneic MSCs in clinical applications.

4.3. Clinical Studies using BMAC for Knee Osteoarthritis

To date, few clinical studies have reported the outcomes of intra-articular BMAC injections in patients with knee OA [16–18]. Centeno et al. [16] used autologous BMAC for intra-articular injection with or without adipose grafts. They reported that patients with K-L Grade I or II showed significantly better improvement in clinical outcomes than K-L Grade III or IV. This finding concurs with the results of the current study. Moreover, the results of the current study suggest that clinical improvement can be maintained over 5 years (mean follow-up of 6.3 years) with a single intra-articular BMAC injection. Therefore, intra-articular BMAC injection could be a viable and simple treatment method for knee OA. However, it is difficult to directly compare the differences because of heterogeneity across studies in the study design, sources and doses of cells, and administration of adjuvant therapy. According to one study [12], the optimal number of cells required for adequate cartilage regeneration is approximately $1 \times 10^8$ cells. In the current study, the estimated number of cells was calculated as $2.4 \times 10^7$ adult stem cells and $1.8 \times 10^9$ mononuclear cells [26]. Although this number was lesser than that required for regenerative action, it is reasonable to presume that the effect of MSCs could be maximized within the osteoarthritic joint because an adipose tissue that served as a scaffold was used in this study [1]. Moreover, adipose tissue-derived MSCs (AD-MSCs) are easy to harvest, plentiful in number, and less affected by donor age than other cells. Particularly, a recent study showed that AD-MSCs could function intra-articularly in patients with arthritic knee [24]. Ultimately, both BM-MSCs and AD-MSCs in the BMAC might produce synergic effects [17]. Based on this observation, it can be inferred that a relatively small number of cells in BMAC could maintain the clinical efficacy of this treatment over a 5-year follow-up. However, the optimal number of cells and dose of BMAC for the treatment of knee OA has not been standardized. Further research is needed to determine the optimal number and dose of cells that can maximize the effect of the BMAC injection.

4.4. Study Limitations and Strengths

In the current study, patients with K-L Grade III or IV showed a lower rate of improvement in clinical outcomes and a higher rate of secondary operations, such as a conversion to TKA and treatment failure, than those with K-L Grade I or II. Thus, it can be concluded that BMAC injections would not be useful in patients with K-L Grade III or IV. Despite the meaningful results, the following limitations of this study need to be considered. First, the study had a retrospective study design with no control group. Prospective randomized controlled trials are needed to understand the effects of the BMAC injection. Secondly, radiological and/or other imaging information, including a follow-up MRI or arthroscopy, would be needed to obtain objective data regarding the efficacy of this injection. Thirdly, a female predominance was observed in this study because women in South Korea show a higher rate of knee OA than women in Western countries [36]. Fourth, this was a mid-term follow-up study. Thus, it is possible that long-term follow-up might reveal different outcomes with regard to clinical efficacy. Therefore, long-term studies are needed in the future. Fifth, adverse events of this procedure should be
considered, including joint pain, swelling and skin rash or itching [15]. Although most of the reported complications for BMAC might be self-limited and generally resolved without specific intervention, they should be explained and recognized prior to administration. Nevertheless, the strengths of this study are as follows. First, to our knowledge, this is the first study to report on the 5-year follow-up after an intra-articular BMAC injection. Secondly, a variety of clinical assessments were performed; therefore, the patient-reported outcomes can be considered sufficiently reliable. A BMAC injection can be a relatively simple and less invasive alternative treatment for knee OA.

5. Conclusions

The current retrospective study evaluated the mid-term effects of intra-articular BMAC injections in patients with knee OA. Based on the outcomes of a >5-year follow-up, an intra-articular BMAC injection could be considered an effective and feasible treatment option for early-to-moderate knee OA (K-L Grade I or II). However, it is not recommended for moderate-to-severe knee OA (K-L Grade III or IV) because of undesirable outcomes. To our knowledge, this is the first study to report the 5-year follow-up results after an intra-articular BMAC injection. Further studies with larger sample sizes and a longer follow-up than those in the current study are needed to determine the effect of an intra-articular BMAC injection on knee OA.

Author Contributions: Conceptualization, G.W.L and J.-D.K; methodology, J.-D.K.; validation, G.W.L., G.B.K., Y.C. and C.H.C.; formal analysis, J.-D.K and G.B.K.; investigation, C.H.C. and Y.C.; resources, G.W.L. and J.-D.K.; data curation, G.W.L., Y.C. and C.H.C.; writing—original Draft Preparation, G.W.L. and G.B.K.; writing—review and Editing, G.W.L., G.B.K., and J.-D.K.; visualization, C.H.C.; supervision, J.-D.K. and G.W.L.; project administration, G.W.L.; funding acquisition, G.W.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Ministry of Science & ICT (2019M3E5D1A02068105).

Conflicts of Interest: The authors declare no conflict of interests.

References

1. Orozco, L.; Munar, A.; Soler, R.; Alberca, M.; Soler, F.; Huguet, M.; Sentis, J.; Sánchez, A.; García-Sancho, J. Treatment of knee osteoarthritis with autologous mesenchymal stem cells: A pilot study. Transplant 2013, 95, 1535–1541. [CrossRef] [PubMed]

2. Shin, Y.-S.; Yoon, J.-R.; Kim, H.-S.; Lee, S.-H. Intra-articular injection of bone marrow-derived mesenchymal stem cells leading to better clinical outcomes without difference in MRI outcomes from baseline in patients with knee osteoarthritis. Knee Surg. Relat. Res. 2018, 30, 206. [CrossRef] [PubMed]

3. Kim, S.S.; Kang, M.S.; Lee, K.Y.; Lee, M.J.; Wang, L.; Kim, H.J. Therapeutic effects of mesenchymal stem cells and hyaluronic acid injection on osteochondral defects in rabbits’ knees. Knee Surg. Relat. Res. 2012, 24, 164. [CrossRef] [PubMed]

4. Hong, S.H.; Nam, J.; Kim, H.J.; Yoo, J.J. Platelet-rich plasma pretreatment on grit-blasted titanium alloy for enhanced osteogenic differentiation of human adipose-derived stem cells. Clin. Orthop. Surg. 2019, 11, 361–368. [CrossRef] [PubMed]

5. Lee, H.W.; Choi, K.-H.; Kim, J.-Y.; Kim, K.-O.; Haotian, B.; Yuxuan, L.; Noh, K.-C. Proteomic classification and identification of proteins related to tissue healing of platelet-rich plasma. Clin. Orthop. Surg. 2020, 12, 120–129. [CrossRef]

6. Fortier, L.A.; Potter, H.G.; Rickey, E.J.; Schnabel, L.V.; Foo, L.F.; Chong, L.R.; Stokol, T.; Cheetham, J.; Nixon, A.J. Concentrated bone marrow aspirate improves full-thickness cartilage repair compared with microfracture in the equine model. J. Bone Joint Surg. 2010, 92, 1927–1937. [CrossRef]

7. Saw, K.-Y.; Hussin, P.; Loke, S.-C.; Azam, M.; Chen, H.-C.; Tay, Y.-G.; Low, S.; Wallin, K.-L.; Ragavanaidu, K. Articular cartilage regeneration with autologous marrow aspirate and hyaluronic acid: An experimental study in a goat model. Arthroscopy 2009, 25, 1391–1400. [CrossRef]

8. Acharya, C.; Adesida, A.; Zajac, P.; Mumme, M.; Riesle, J.; Martin, I.; Barbero, A. Enhanced chondrocyte proliferation and mesenchymalstromal cells chondrogenesis in coculture pellets mediate improved cartilage formation. J. Cell Physiol. 2012, 227, 88–97. [CrossRef]
9. Wu, L.; Prins, H.-J.; Helder, M.N.; van Blitterswijk, C.A.; Karperien, M. Trophic effects of mesenchymal stem cells in chondrocyte co-cultures are independent of culture conditions and cell sources. *Tissue Eng. Part A* 2012, 18, 1542–1551. [CrossRef]

10. Gobbi, A.; Karnatzikos, G.; Sankineanei, S.R. One-step surgery with multipotent stem cells for the treatment of large full-thickness chondral defects of the knee. *Am. J. Sports Med.* 2014, 42, 648–657. [CrossRef]

11. Gobbi, A.; Chaurasia, S.; Karnatzikos, G.; Nakamura, N. Matrix-induced autologous chondrocyte implantation versus multipotent stem cells for the treatment of large patellofemoral chondral lesions: A nonrandomized prospective trial. *Cartilage* 2015, 6, 82–92. [CrossRef] [PubMed]

12. Chahla, J.; Dean, C.S.; Moatshe, G.; Pascual-Garrido, C.; Serra Cruz, R.; LaPrade, R.F. Concentrated bone marrow aspirate for the treatment of chondral injuries and osteoarthritis of the knee: A systematic review of outcomes. *Orthop. J. Sports Med.* 2016, 4, 2325967115625481. [CrossRef] [PubMed]

13. McCarrel, T.; Fortier, L. Temporal growth factor release from platelet-rich plasma, trehalose lyophilized platelets, and bone marrow aspirate and their effect on tendon and ligament gene expression. *J. Orthop. Res.* 2009, 27, 1033–1042. [CrossRef] [PubMed]

14. Schnabel, L.V.; Mohammed, H.O.; Miller, B.J.; McDermott, W.G.; Jacobson, M.S.; Santangelo, K.S.; Fortier, L.A. Platelet rich plasma (prp) enhances anabolic gene expression patterns in flexor digitorum superficialis tendons. *J. Orthop. Res.* 2007, 25, 230–240. [CrossRef]

15. Kim, G.B.; Seo, M.-S.; Park, W.T.; Lee, G.W. Bone marrow aspirate concentrate: Its uses in osteoarthritis. *Int J. Mol. Sci.* 2020, 21, 3224. [CrossRef]

16. Centeno, C.; Pitts, J.; Al-Sayegh, H.; Freeman, M. Efficacy of autologous bone marrow concentrate for knee osteoarthritis with and without adipose graft. *Biomed. Res. Int.* 2014, 2014. [CrossRef]

17. Kim, J.-D.; Lee, G.W.; Jung, G.H.; Kim, C.K.; Kim, T.; Park, J.H.; Cha, S.S.; You, Y.-B. Clinical outcome of autologous bone marrow aspirates concentrate (bmac) injection in degenerative arthritis of the knee. *Eur. J. Orthop. Surg. Traumatol.* 2014, 24, 1505–1511. [CrossRef]

18. Hauser, R.A.; Orlofsky, A. Regenerative injection therapy with whole bone marrow aspirate for degenerative joint disease: A case series. *Clin. Med. Insights Arthritis Musculoskelet. Disord.* 2013, 6, CMAMD-S10951. [CrossRef]

19. Harrell, C.R.; Markovic, B.S.; Fellabaum, C.; Arsenijevic, A.; Volarevic, V. Mesenchymal stem cell-based therapy of osteoarthritis: Current knowledge and future perspectives. *Biomed. Pharm.* 2019, 109, 2318–2326. [CrossRef]

20. Martin, J.A.; Buckwalter, J.A. The role of chondrocyte senescence in the pathogenesis of osteoarthritis and in limiting cartilage repair. *J. Bone Joint Surg.* 2003, 85 (Suppl. 2), 106–110. [CrossRef]

21. Roach, H.I.; Yamada, N.; Cheung, K.S.; Tilley, S.; Clarke, N.M.; Oreffo, R.O.; Kokubun, S.; Bronner, F. Association between the abnormal expression of matrix-degrading enzymes by human osteoarthritic chondrocytes and demethylation of specific cpg sites in the promoter regions. *Arthritis Rheum.* 2005, 52, 3110–3124. [CrossRef] [PubMed]

22. Lee, G.W.; Seo, M.-S.; Kang, K.-K.; Oh, S.-K. Epidural fat-derived mesenchymal stem cell: First report of epidural fat-derived mesenchymal stem cell. *Asian Spine J.* 2019, 13, 361. [CrossRef] [PubMed]

23. Yang, S.-H.; Yang, K.-C.; Chen, C.-W.; Huang, T.-C.; Sun, Y.-H.; Hu, M.-H. Comparison of transforming growth factor-beta1 and lovastatin on didermal mesenchymal stem cells toward nucleus pulposus-like phenotype: An in vitro cell culture study. *Asian Spine J.* 2019, 13, 705. [CrossRef]

24. Barry, F.; Murphy, M. Mesenchymal stem cells in joint disease and repair. *Nat. Rev. Rheumatol.* 2013, 9, 584–594. [CrossRef]

25. Horie, M.; Choi, H.; Lee, R.H.; Reger, R.L.; Ylostalo, J.; Muneta, T.; Sekiya, I.; Prockop, D.J. Intra-articular injection of human mesenchymal stem cells (mscs) promote rat meniscal regeneration by being activated to express indian hedgehog that enhances expression of type ii collagen. *Osteoarthr. Cartil.* 2012, 20, 1197–1207. [CrossRef]

26. Audette, R.V.; Lavoie-Lamoureux, A.; Lavoie, J.-P.; Laverty, S. Inflammatory stimuli differentially modulate the transcription of paracrine signaling molecules of equine bone marrow multipotent mesenchymal stromal cells. *Osteoarthr. Cartil.* 2013, 21, 1116–1124. [CrossRef]

27. Le Blanc, K.; Ringden, O. Immunomodulation by mesenchymal stem cells and clinical experience. *J. Intern. Med.* 2007, 262, 509–525. [CrossRef]
28. Wang, Y.; Chen, X.; Cao, W.; Shi, Y. Plasticity of mesenchymal stem cells in immunomodulation: Pathological and therapeutic implications. *Nat. Immunol.* 2014, 15, 1009. [CrossRef]

29. Pers, Y.-M.; Ruiz, M.; Noël, D.; Jorgensen, C. Mesenchymal stem cells for the management of inflammation in osteoarthritis: State of the art and perspectives. *Osteoarthr. Cartil.* 2015, 23, 2027–2035. [CrossRef]

30. Vega, A.; Martin-Ferrero, M.A.; Del Canto, F.; Alberca, M.; García, V.; Munar, A.; Orozco, L.; Soler, R.; Fuertes, J.J.; Huguet, M. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: A randomized controlled trial. *Transplant* 2015, 99, 1681–1690. [CrossRef]

31. Jo, C.H.; Lee, Y.G.; Shin, W.H.; Kim, H.; Chai, J.W.; Jeong, E.C.; Kim, J.E.; Shim, H.; Shin, J.S.; Shin, I.S. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: A proof-of-concept clinical trial. *Stem Cells* 2014, 32, 1254–1266. [CrossRef] [PubMed]

32. Orozco, L.; Munar, A.; Soler, R.; Alberca, M.; Soler, F.; Huguet, M.; Sentis, J.; Sánchez, A.; García-Sancho, J. Treatment of knee osteoarthritis with autologous mesenchymal stem cells: Two-year follow-up results. *Transplant* 2014, 97, e66–e68. [CrossRef] [PubMed]

33. Kozhevnikova, M.; Mikaelyan, A.; Payushina, O.; Starostin, V. Comparative characterization of mesenchymal bone marrow stromal cells at early and late stages of culturing. *Biol. Bull.* 2008, 35, 132–138. [CrossRef]

34. Centeno, C.J.; Busse, D.; Kisiday, J.; Keohan, C.; Freeman, M.; Karli, D. Regeneration of meniscus cartilage in a knee treated with percutaneously implanted autologous mesenchymal stem cells. *Med. Hypotheses* 2008, 71, 900–908. [CrossRef] [PubMed]

35. Gucciardo, L.; Lories, R.; Ochsenbein-Kölble, N.; Zwijsen, A.; Deprest, J. Fetal mesenchymal stem cells: Isolation, properties and potential use in perinatology and regenerative medicine. *BJOG* 2009, 116, 166–172. [CrossRef]

36. Koh, I.J.; Kim, M.W.; Kim, J.H.; Han, S.Y.; In, Y. Trends in high tibial osteotomy and knee arthroplasty utilizations and demographics in Korea from 2009 to 2013. *J. Arthroplast.* 2015, 30, 939–944. [CrossRef]