



Original Article

Can intra-articular injection of freeze-dried platelet-derived factor concentrate regenerate articular cartilage in the knee joint?

Tomohiko Shirata ^a, Yuki Kato ^{b,*}^a Department of Orthopaedic Surgery, Nihon University, School of Medicine, Tokyo, Japan^b Department of Sports Medicine, Kameda Medical Center, Chiba, Japan

ARTICLE INFO

Article history:

Received 14 November 2018

Received in revised form

1 March 2019

Accepted 20 March 2019

Keywords:

Intra-articular injection

Knee osteoarthritis

Platelet-derived factor concentrate

Platelet-rich plasma

ABSTRACT

Freeze-drying methods not only enable the delivery of growth factors using platelets, but also extend the shelf-life of platelet concentrates. The present study shows the clinical results of treating knee osteoarthritis with freeze-dried platelet-derived factor concentrate (PFC). While it improved pain, activities of daily living, sports and recreational activities, and knee-related quality of life, it did not significantly improve symptoms other than pain, such as restricted range of motion and mechanical symptoms. As such, the treatment effect may be attributed to anti-inflammatory action rather than actual cartilage regeneration.

© 2019, The Japanese Society for Regenerative Medicine. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

The use of regenerative therapies for degenerative orthopedic conditions such as osteoarthritis is increasing. As surgical treatment options such as autologous chondrocyte implantation are now widely used [1,2], so are clinical procedures such as the use of mesenchymal stem cells [3], platelet-rich plasma (PRP) [4], and platelet-derived factor concentrate (PFC) [5]. Although intra-articular PRP injection has already been shown to be effective in treating knee osteoarthritis (OA) [6–8], the present study is the first to use freeze-dried PFC and describe the clinical results.

2. Methods

In this retrospective case series, we evaluated 11 patients (5 males and 6 females) with knee OA who were given intra-articular PFC injections. The average age was 71.2 ± 16.6 years (range, 30–90). The Kellgren and Lawrence (KL) system was used to

radiographically grade knee OA severity. Three patients had beginning OA changes (KL grade 1); 4 had mild changes (KL grade 2); 2 had moderate changes (KL grade 3); and 2 had severe changes (KL grade 4).

The process of preparing freeze-dried PFC begins with the extraction of 49 ml of autologous blood from each patient. Sterility testing was performed on a 9 ml portion of the blood sample. Platelet-rich plasma was prepared from the remaining 40 ml by centrifugation. PFC was then prepared according to a method described by Araki et al. [9], and was subsequently freeze-dried and powdered. The resulting product could be preserved for 6 months at room temperature. In order to create a solution for injection into the knee joint, the freeze-dried PFC was dissolved in 6 ml of physiological saline.

Since the freeze-dried PFC was decellularized, approval from the MHLW was not required to use it at our clinic. As the patients in this study were seen in a private clinic, institutional review board approval was not sought. However, informed consent was obtained from each patient in this study.

Assessment was conducted before the procedure, as well as 1, 3, and 6 months after the procedure, using the Knee Injury and Osteoarthritis Outcome Score (KOOS) and each of its 5 subscales: pain, other symptoms, activities of daily living (ADL), function in sport and recreation (Sport/Rec), and knee-related quality of life (QOL). One way analysis of variance was used for statistical analysis. Statistical significance was assumed when p-value was less than 0.05.

Abbreviations: PRP, platelet-rich plasma; PFC, platelet-derived factor concentrate; OA, osteoarthritis; KOOS, Knee Injury and Osteoarthritis Outcome Score.

* Corresponding author. Department of Sports Medicine, Kameda Medical Center, 929 Higashi-cho, Kamogawa City, Chiba Prefecture, 296-8602, Japan. Fax: +81 4 7099 1191.

E-mail address: kato.yuki.0@kameda.jp (Y. Kato).

Peer review under responsibility of the Japanese Society for Regenerative Medicine.

<https://doi.org/10.1016/j.reth.2019.03.005>

2352-3204/© 2019, The Japanese Society for Regenerative Medicine. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

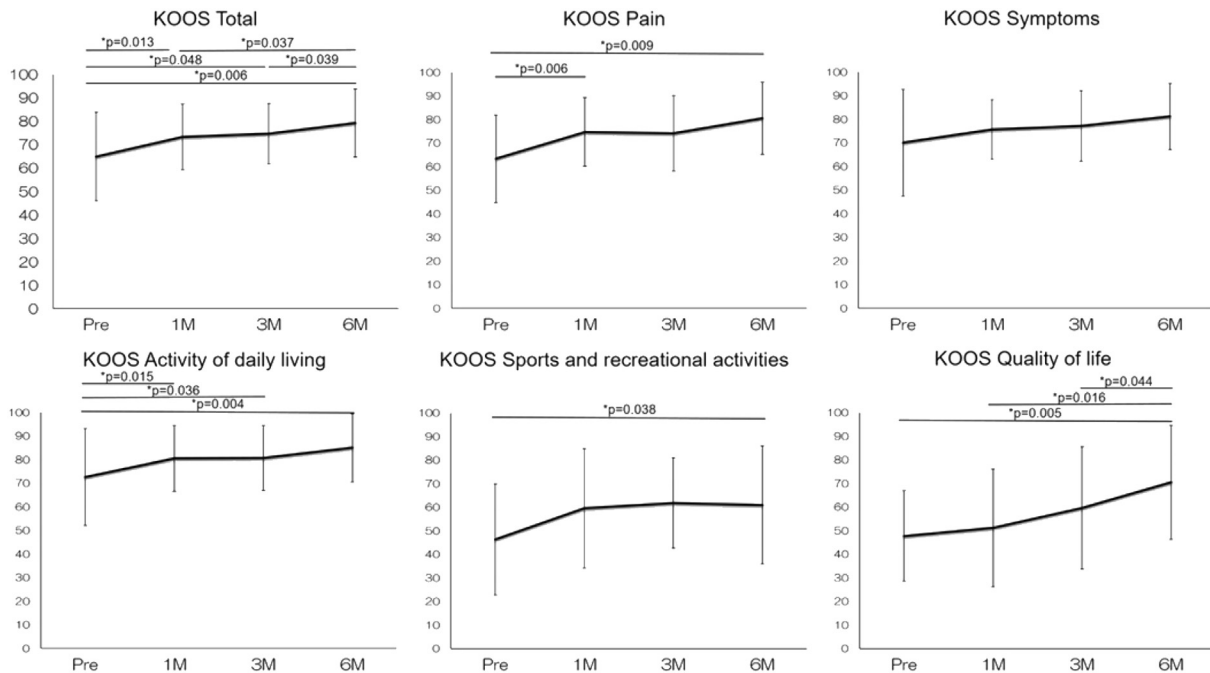


Fig. 1. Assessment of intra-articular platelet-rich plasma injection for patients with knee osteoarthritis (n = 11) using the Knee Injury and Osteoarthritis Outcome Score.

3. Results

General improvement was noted with respect to the KOOS. Total KOOS was significantly improved from pre-injection and 1, 3, and 6 months after injection ($p = 0.013$, 0.048 , and 0.006 , respectively), from 1 to 6 months ($p = 0.037$), and from 3 to 6 months ($p = 0.039$). KOOS pain was significantly improved from pre-injection to 1 and 6 months ($p = 0.006$ and 0.009 , respectively). KOOS ADL was significantly improved from pre-injection to 1, 3, and 6 months ($p = 0.015$, 0.036 , and 0.004 , respectively). KOOS Sport/Rec was significantly improved from pre-injection to 6 months ($p = 0.038$). KOOS QOL was significantly improved from pre-injection, 1 and 3 months to 6 months ($p = 0.005$, 0.016 , and 0.044 , respectively). However, no significant improvement was noted in “other symptoms” (Fig. 1). There were no adverse events throughout the follow-up period in all patients.

4. Discussion

There are few clinical reports on intra-articular injection of freeze-dried PFC. Freeze drying has been shown to be the most suitable technique for preserving PRP bioactivity because both platelet counts and growth factor levels are preserved [10]. However, it is still unclear that freeze-dried PRF can preserve its bioactivity. The present study showed that the use of freeze-dried PFC brought about no significant improvement in “other symptoms” in the KOOS, indicating that the procedure may be ineffective for patients with mechanical symptoms due to meniscal tears or articular cartilage defects. Therefore, the general improvement in scores on the other subscales may be due to the anti-inflammatory effect of the product [11] rather than its regenerative potential. The perceived improvement was caused by the relief of the symptoms and not by treatment of the actual cause of the symptoms. As an analogy, the effect may be similar to experiencing temporary relief by taking antipyretics for fever instead of antibiotics to treat the underlying cause of the fever.

Consequently, it remains difficult to justify the high cost of PRP or PFC injection since they only treat the symptoms of OA, and not the underlying disease itself. In Japan, as in most other countries, these injections are not covered by the national health insurance. Thus, the cost to patients would be at least JPY 10,000, depending on the treating center. Most government and insurance companies believe that while the potential benefit of treatment is acknowledged, more outcomes should be collected to investigate its effectiveness [12]. Moreover, the literature contains conflicting evidence regarding the effectiveness of PRP injection compared to options such as hyaluronic acid [13–16]. Patients may end up seeking affordable alternatives such as steroids, which cause cartilage degeneration and volume loss with long-term use, if the high cost of PRP injection continues to make it less accessible [17].

This study has certain limitations. First, only a limited sample size of 11 patients was used for the study. A larger sample size may increase the power of the hypothesis and may also demonstrate a correlation between OA severity grade and treatment results. Second, the study utilized subjective outcome measures in the form of the KOOS and its subscores. Future studies should use objective outcome measures, such as magnetic resonance imaging and second-look arthroscopy, to identify correlations with subjective outcome assessments.

5. Conclusion

Intra-articular injection of freeze-dried PFC for knee OA was effective in improving pain, ADLs, sports and recreational activities, and knee-related QOL. However, it was not effective in improving restricted range of motion and mechanical symptoms.

Conflicts of interest

All the authors declare that they do not have any conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.reth.2019.03.005>.

References

- [1] Bauer S, Khan RJ, Ebert JR, Robertson WB, Bredahl W, Ackland TR, et al. Knee joint preservation with combined neutralising high tibial osteotomy (HTO) and matrix-induced autologous chondrocyte implantation (MACI) in younger patients with medial knee osteoarthritis: a case series with prospective clinical and MRI follow-up over 5 years. *Knee* 2012;19:431–9.
- [2] Ochi M, Uchio Y, Kawasaki K, Wakitani S, Iwasa J. Transplantation of cartilage-like tissue made by tissue engineering in the treatment of cartilage defects of the knee. *J Bone Joint Surg Br* 2002;84:571–8.
- [3] Yoshimura H, Muneta T, Nimura A, Yokoyama A, Koga H, Sekiya I. Comparison of rat mesenchymal stem cells derived from bone marrow, synovium, periosteum, adipose tissue, and muscle. *Cell Tissue Res* 2007;327:449–62.
- [4] Dai WL, Zhou AG, Zhang H, Zhang J. Efficacy of platelet-rich plasma in the treatment of knee osteoarthritis: a meta-analysis of randomized controlled trials. *Arthroscopy* 2017;33:659–670 e651.
- [5] Kawase T, Tanaka T. An updated proposal for terminology and classification of platelet-rich fibrin. *Regen Ther* 2017;7:80–1.
- [6] Khoshbin A, Leroux T, Wasserstein D, Marks P, Theodoropoulos J, Ogilvie-Harris D, et al. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis. *Arthroscopy* 2013;29:2037–48.
- [7] Laudy AB, Bakker EW, Rekers M, Moen MH. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. *Br J Sports Med* 2015;49:657–72.
- [8] Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. *J Orthop Surg Res* 2017;12:16.
- [9] Araki J, Jona M, Eto H, Aoi N, Kato H, Suga H, et al. Optimized preparation method of platelet-concentrated plasma and noncoagulating platelet-derived factor concentrates: maximization of platelet concentration and removal of fibrinogen. *Tissue Eng Part C Methods* 2012;18:176–85.
- [10] Shiga Y, Kubota G, Orita S, Inage K, Kamoda H, Yamashita M, et al. Freeze-dried human platelet-rich plasma retains activation and growth factor expression after an eight-week preservation period. *Asian Spine J* 2017;11:329–36.
- [11] Chang KV, Hung CY, Aliwarga F, Wang TG, Han DS, Chen WS. Comparative effectiveness of platelet-rich plasma injections for treating knee joint cartilage degenerative pathology: a systematic review and meta-analysis. *Arch Phys Med Rehabil* 2014;95:562–75.
- [12] Choi HM, Kim SH, Kim CK, Choi HG, Shin DH, Uhm KI, et al. The cheapest and easiest way to make platelet-rich plasma preparation. *Arch Aesthetic Plast Surg* 2015;21:12–7.
- [13] Filardo G, Di Matteo B, Di Martino A, Merli ML, Cenacchi A, Fornasari P, et al. Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial. *Am J Sports Med* 2015;43:1575–82.
- [14] Han YH, Huang HT, Pan JK, Lin JT, Zeng LF, Liang GH, et al. Comparison of platelet-rich plasma vs hyaluronic acid injections in patients with knee osteoarthritis: a protocol for a systematic review and meta-analysis. *Medicine (Baltimore)* 2018;97:e13049.
- [15] Laver L, Marom N, Dnyanesh L, Mei-Dan O, Espregueira-Mendes J, Gobbi A. PRP for degenerative cartilage disease: a systematic review of clinical studies. *Cartilage* 2017;8:341–64.
- [16] Zhang HF, Wang CG, Li H, Huang YT, Li ZJ. Intra-articular platelet-rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: a meta-analysis. *Drug Des Devel Ther* 2018;12:445–53.
- [17] McAlindon TE, LaValley MP, Harvey WF, Price LL, Driban JB, Zhang M, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. *J Am Med Assoc* 2017;317:1967–75.