Enhancing bone healing during distraction osteogenesis with platelet-rich plasma

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ABSTRACT

Gradual limb lengthening with external fixators using distraction osteogenesis principles is the gold standard for treatment of limb-length discrepancy. However, long treatment time is a major disadvantage of the current lengthening procedures. Efforts to decrease the treatment include biological and biomechanical factors. Injection of platelet-rich plasma (PRP) is a biological method to enhance bone healing during distraction osteogenesis. We hypothesized that PRP can enhance bone healing during limb lengthening. We report our experience with the use of PRP during distraction osteogenesis. This retrospective study included 19 patients divided into the standard group of 10 patients who did not receive PRP and the PRP group of nine patients who received PRP at the end of the distraction phase. The study variables included external fixator time, external fixation index, and complications during treatment. The PRP group had statistically significantly shorter treatment time (p = 0.0412). Injection of PRP into regenerate bone might be an effective method to shorten treatment time during limb lengthening and lead to better functional outcomes and improved patient satisfaction.

Level of evidence: Level IV, therapeutic study.

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Introduction

Limb-length inequality can occur secondary to congenital, traumatic, or infectious causes. Gradual limb lengthening with external fixators is the gold standard for correction of limb-length discrepancy (LLD) at many centres worldwide. Although gradual limb lengthening has been reported to achieve good results, the method is not without drawbacks. The main disadvantage of limb lengthening is the long treatment time which sometimes is not well tolerated by patients and which is associated with bony and soft-tissue complications. Several reports have proposed mechanical and biological methods for decreasing the treatment time associated with limb lengthening, resulting in better functional outcomes and increased patient satisfaction.

Platelet-rich plasma (PRP) is an autologous concentration of human platelets in a small volume of plasma. PRP has very high concentrates of platelet-derived growth factors that can stimulate the growth of bone-forming cells. Several animal studies have shown the efficacy of PRP in enhancing bone and tissue healing. PRP contains multiple growth factors for osteoinduction and tissue healing and cell adhesions molecules (fibrin, fibronectin, and vitronectin) that act as a scaffold for osteoconduction. Currently, few reports are available regarding the application of PRP for the enhancement of bone healing during limb-lengthening procedures.

We conducted a retrospective study of our clinical experience with the use of PRP to enhance bone healing during distraction osteogenesis, including treatment time and reported complications. The study hypothesized that PRP with its growth factors can effectively enhance bone healing during distraction osteogenesis and subsequently shortens the time necessary for regenerate consolidation during limb-lengthening procedures.

Patients and methods

This retrospective study was approved by our institutional review board. The study population included 19 patients with LLD.
All patients had undergone limb lengthening with external fixation between 2004 and 2008. The study population included eight male and 11 female patients. The mean age at the time of surgery was 15.2 years (range, 12–18 years). The study population was divided into two groups: (1) the standard group of 10 patients who underwent gradual limb lengthening with external fixation but without PRP injection into the regenerate site, and (2) the PRP group of nine patients who received PRP enhancement during the same procedures. A total of 19 limb segments were included in this study: 12 femora and 7 tibiae. The causes of LLD were congenital (11 cases) and traumatic (eight cases). The indications for surgery were LLD greater than 3 cm secondary to posttraumatic or congenital causes. A unilateral external fixator was used for nine patients, and a ring fixator was used for 10 (Table 2).

The criteria used to evaluate the results were the external fixation index (duration of external fixation per length gained) and external fixation time (total time in external fixator). Consolidation was considered complete when three of four cortices of regenerated bone were noted to be intact on the anteroposterior and lateral view radiographs. The decision to remove the fixator was made by three surgeons based on the radiological appearance of the regenerated bone.26 The complications were classified according to the system proposed by Paley20 (problems, obstacles and sequelae).

### Operative technique

Initially, the frame was applied in standard fashion and corticotomy was performed for distraction osteogenesis. The corticotomy was accomplished with a small (5 mm) sharp osteotome through a small skin incision, as originally described by Ilizarov.7,8 Gradual distraction was started after a 3- to 7-day latent period. The distraction rate was determined by monitoring the regenerate bone quality with radiography and ultrasonography (using power Doppler sonography).17 Partial weight bearing with crutches was allowed throughout the treatment period and was adjusted according to the patients’ tolerance. In the PRP group, 30 ml of PRP was injected into the regenerate bone 1 week after the beginning of the consolidation phase. The injection was performed once during the consolidation phase in the operating room with the patient under general anaesthesia. The image intensifier was used to localise the regenerate site (Fig. 1).

### Preparation of PRP

The Autologous Platelet Separator System (Medtronic©, Minneapolis, MN) consists of microprocessor-controlled centrifuge and syringe pumps and the necessary single-use processing components. The system works by separating anti-coagulated whole blood into individual components using centrifugation (Fig. 2A). Each procedure required a single-use kit, which included the necessary components for platelet separation for one patient. The components were as follows: a 30-ml vial of Anticoagulant Citrate Dextrose Solution; Solution A as an anticoagulant; 60-ml, 10-ml, and 5-ml syringes; an intravenous site preparation kit; a separation chamber with attached tubing; 18-gauge × 3.8 cm (1.5 in.) and 17-gauge needles; and intravenous tubing. A double-syringe pump was used for mixing the anticoagulant with the platelets (Fig. 2B).

### Statistical analysis

Means and standard deviations were calculated for all continuous variables. The outcome variables were statistically analysed by conducting the Mann–Whitney U test for nonparametric data and an unpaired t test for continuous variables. A P value of <0.05 was set as the level of statistical significance. The

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**Table 1**

Platelet-derived growth factors with potential effects on bone healing.18

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard group</th>
<th>PRP group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>15.3 ± 1.76</td>
<td>15.1 ± 1.96</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Limb segments (n = 19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femur</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Tibia</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lengthening (cm)</td>
<td>5.05 ± 1.23</td>
<td>5.55 ± 1.47</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mean external fixation index (days/cm)</td>
<td>38.5 ± 9.91</td>
<td>29.9 ± 6.81</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*p < 0.05 was statistically significant.

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**Fig. 1.** Showing radiographs of 15 years old boy with LLD secondary to congenital short left femur. Five centimetre was achieved with Orthofix© monolateral external fixator. PRP (30 ml) was injected into the regenerate one week after the beginning of the consolidation phase. EFI was 23 days/cm. (A) Radiograph at the end of distraction phase and PRP administration. (B) Radiograph four weeks after PRP injection. (C) Radiograph after 11 weeks after injection showing complete consolidation.
Instat+ statistical package (Version 3.36; Statistical Services Centre, University of Reading, Berkshire, UK) was used for analysis of the results.

**Results**

The mean limb length gained was 5.26 cm (standard group, 5.05 cm; PRP group, 5.5 cm; range, 3–8 cm). The mean external fixator time was 189.5 days (range 66–427 days). The mean external fixation index was 34.42 days/cm: standard group, 38.5 days/cm (range, 30–61 days/cm) and PRP group, 29.8 days/cm (range, 22–43 days/cm). The external fixation index was statistically significantly shorter in the PRP group than in the standard group (p = 0.0412) (Table 2). The desired length of the lower extremity was obtained in all patients. Table 3 shows the difference of external fixator time and healing index of different study population between PRP and non-PRP study groups. Three complications occurred, including two problems and one obstacle but no sequelae according to the Paley’s criteria for difficulties during limb lengthening. Five patients (three in the standard group and two in the PRP group) experienced signs of pin-tract infections that resolved with local pin care and orally administered antibiotics. No patient developed a deep infection. During treatment, all patients experienced limited range of motion in adjacent joints; however, full range of motion was recovered in the affected joints of all patients after removal of the external fixators and after intensive physiotherapy. Premature consolidation occurred in one patient in the PRP group, and the patient underwent subsequent osteotomy. The patient achieved the required length without further complications.

**Discussion**

Several factors influence bone formation during limb lengthening, including age, limb segment, rate and rhythm of distraction, osteotomy site, and frame stability. Although limb lengthening is associated with many complications, the long treatment time remains the main disadvantage of current limb-lengthening procedures. Treatment time can be shortened by increasing the distraction rate during the distraction phase or by shortening the time necessary for bone consolidation after achieving the required length to allow frame removal. Tension stress law, as proposed by Ilizarov, postulated 1 mm per day as the optimum rate for bone regeneration during distraction osteogenesis. Increasing distraction rate is associated not only with poor bone formation but also with severe soft-tissue contractures and nerve problems.

Therefore, the main way to decrease treatment time during limb-lengthening procedures is to shorten the time necessary for bone consolidation. Several studies have suggested both mechanical and biological methods to shorten the consolidation phase during limb lengthening. The mechanical methods include the use of a combination of external fixators and internal fixation devices. Biological methods include low-intensity pulsed ultrasound, electric stimulation, hyperbaric oxygen exposure, systemic administration of recombinant growth hormone, transplantation of fresh bone marrow cells, the concentrate of bone marrow aspirate, recombinant human bone morphogenetic proteins, and PRP.

To the best of our knowledge, this is the first report in the English literature of the use of PRP concentrate from autogenous sources alone to enhance bone healing during distraction osteogenesis. The main finding of the current study is the short treatment time in the PRP group. Comparing the standard group with the PRP group, the treatment time in the PRP group was statistically significantly shorter.

The study finding is supported by the work of Kitoh et al. The authors observed a short treatment time in three patients after the application of expanded bone marrow cells and PRP during the consolidation phase. The same finding was echoed by the same group in a recent report of a large series. The study included 20 patients (56 bones) treated with lengthening procedures for short stature (achondroplasia/hypochondroplasia). The patients were

**Table 3**

Data comparing the healing index and external fixator time (days) of different study population between PRP and non-PRP groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PRP</th>
<th>Non PRP</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healing index</td>
<td>Ex fix time</td>
<td>Healing index</td>
</tr>
<tr>
<td>Congenital</td>
<td>30</td>
<td>169.83</td>
<td>39.86</td>
</tr>
<tr>
<td>Post traumatic</td>
<td>29.67</td>
<td>178.67</td>
<td>35.33</td>
</tr>
<tr>
<td>Ring fixator</td>
<td>23.5</td>
<td>89</td>
<td>41.86</td>
</tr>
<tr>
<td>Monolateral</td>
<td>31.71</td>
<td>196.71</td>
<td>30.67</td>
</tr>
<tr>
<td>Femur</td>
<td>31.71</td>
<td>196.71</td>
<td>38.6</td>
</tr>
<tr>
<td>Tibia</td>
<td>23.5</td>
<td>89</td>
<td>38.4</td>
</tr>
</tbody>
</table>
divided into two groups: one group treated with culture expanded marrow cells and PRP and the other a control group without enhancement. The study showed statically significant shorter treatment time in the group that received enhancement compared with the group that did not.

The beneficial effects of PRP on bone healing during distraction osteogenesis have also been shown by several experimental studies. Choi et al.\textsuperscript{1} reported that the proliferation of alveolar bone cells can be suppressed or stimulated by PRP. Kawasumi et al.\textsuperscript{11} proved that stimulation bone marrow cell proliferation in the distraction gap in rat limb-lengthening models was PRP dose dependent. The study showed that higher concentrations of PRP were related to more favourable effects on osteogenesis in the rat limb-lengthening models. Fang et al.\textsuperscript{12} emphasised the importance of PRP in induction of angiogenesis during distraction osteogenesis for successful bone healing.

PRP injections were successfully able to expand bone marrow cells in cell cultures that can be transplanted into the distraction gap to enhance bone healing during limb lengthening.\textsuperscript{1,4} However, this technique requires extensive equipment and experience with tissue culture, which might not be widely available at all limb-lengthening centres.

The main limitations of our study were the small sample size, the retrospective nature of the study design, and the need for further studies to determine the optimisation of PRP applications in clinical practice regarding bone regeneration (such as the volume of PRP and the method and rhythm of administration). However, the results of the study are promising and showed PRP injection into regenerate site can enhance bone healing during distraction osteogenesis.

In conclusion, biological methods can play a critical role in the future by enhancing bone healing during distraction osteogenesis. PRP injection into the distraction gap is proposed as one of the biological methods that can effectively decrease treatment time during distraction osteogenesis without the need for hardware modifications.

References


