



# A Systematic Review of the Use of Bone Marrow Cells and Platelet Rich Plasma for Enhancement of Bone Healing in Distraction Osteogenesis

A Systematic Review of Literature

**Submitted for Partial Fulfillment of Master Degree in Orthopaedic Surgery**

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لسبب أنك لا تعلم لنا  
إلا ما علمتنا إنك أنت  
العليم العظيم

صدق الله العظيم

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# List of Abbreviations

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Abb.	Full term
<i>DO</i> .....	<i>distraction osteogenesis</i>
<i>BMC</i> .....	<i>bone marrow cells</i>
<i>PRP</i> .....	<i>platelet rich plasma</i>
<i>BMP</i> .....	<i>bone morphogenetic proteins</i>
<i>GFs</i> .....	<i>growth factors</i>
<i>bFGF</i> .....	<i>basic fibroblast growth factor</i>
<i>PDGF</i> .....	<i>platelet derived growth factor</i>
<i>VEGF</i> .....	<i>vascular endothelial growth factor</i>
<i>TGF-<math>\beta</math> 1</i> .....	<i>transforming growth factor <math>\beta</math> 1</i>
<i>EGF</i> .....	<i>epidermal growth factor</i>
<i>IGF</i> .....	<i>insulin growth factor</i>
<i>PPP</i> .....	<i>platelet poor plasma</i>
<i>EDTA</i> .....	<i>ethylenediaminetetraacetic acid</i>
<i>TXA 2</i> .....	<i>thromboxane A 2</i>
<i>ADP</i> .....	<i>adenosine diphosphate</i>
<i>LLD</i> .....	<i>limb length discrepancy</i>

# ABSTRACT

## **Background**

Distraction osteogenesis is a surgical technique used in reconstruction of bone defects and limb lengthening, but long period of external fixator is the main problem in this technique. We conduct this systematic review to state the efficacy of local injection of platelet rich plasma (PRP) alone or combined with bone marrow cells (BMC) to enhance the consolidation and shorten the time of external fixator.

## **Key words**

"Distraction osteogenesis", "Platelet rich plasma" and "Bone marrow cells"

## **Methods**

The search of literature was conducted using electronic databases of The Cochrane library, MEDLINE, Journal of bone and joint surgery (JBJS), Google scholarly articles and Science direct and after assessment 3 studies were obtained according to inclusion and exclusion criteria; 1 randomized control trials (level II of evidence), and 2 retrospective studies (level III of evidence)

## **Results**

After evaluation of all studies included; local injection of platelet rich plasma (PRP) alone or combined with bone marrow cells (BMC) showed lower healing index and lower time needed for healing, but the rate of complications were almost similar with and without injection. Further studies are needed to get more information about the definite role of PRP and BMC on the healing in DO, and about the efficacy in relation to the cost.

## **Conclusion**



Local injection of PRP and/or BMC decrease the healing index of the distracted bone during DO and enhance the consolidation phase but it had no proven effect in decreasing the rate of complications.

## INTRODUCTION

Bone is one of the very few tissues in the human body that possess intrinsic capacity to heal spontaneously following injury. However, after a certain critical size defect, bone does not have the ability to heal by itself and outside intervention is required. Many techniques are available for the management of these defects, including the autogenous bone grafts, allografts, bone graft substitutes and vascularized fibular bone grafts. All these techniques, however, do have limitations. In such cases of severe bone loss, either due to congenital bony deficiencies or acquired causes, there is a challenge to the treating physicians; Distraction osteogenesis (DO) could offer a viable and successful alternative to these techniques <sup>(1, 2)</sup>.

DO is a surgical technique in which new bone formation is induced by gradual distraction of a fracture callus after low-energy corticotomy, with careful preservation of the soft tissue surrounding the bone <sup>(3)</sup>.

Apart from the phases of fracture healing, there are three phases in the process of DO, which are; latency, distraction, and consolidation <sup>(4)</sup>.

In the consolidation phase, mineralization and remodeling occur, resulting in osseous union of the distraction gap. Variable time is required for complete consolidation; in the pediatric population 1 month is required per centimeter

lengthening, while in adult populations 1,6 or 2 months of consolidation is required per centimeter lengthening <sup>(4)</sup>.

One of the major problems with DO is the prolonged time required for consolidation of the newly formed bone in the distraction gap <sup>(5)</sup>. Numerous attempts at enhancing newly formed bone have been described and include the application of external biophysical stimuli (i.e. mechanical loading), and administration of biological agents, systemically or locally <sup>(1)</sup>.

Biological Adjuncts to promote callus formation have been administered either systemically or locally at the osteotomy site. Acceleration of osseous healing may, in turn, increase limb lengthening potential and may decrease the time that patients must wear a bulky external fixator <sup>(4)</sup>.

Local application of bone marrow cells (BMC), platelet rich plasma (PRP), demineralized bone matrix, and bone morphogenic proteins have been tried in DO models. Furthermore, systemic applications of parathyroid hormone, growth hormone, and bisphosphonate have been investigated <sup>(6)</sup>.

Among the locally applied substances, BMC are rich in mononucleated cells, which are reported to have high potentiality in bone healing; also, platelet-rich plasma has many osteoinductive growth factors that are released from platelets <sup>(6)</sup>.

Although being approved - theoretically - that PRP and BMC can enhance bone consolidation, yet there are few clinical studies testing their efficacy, regimen of injection and impact on healing indices of the patients. They have not been extensively discussed in literature <sup>(v)</sup>.

The purpose of this review is to focus on the clinical studies that were held in this field, trying to answer the question about whether it is effective or not to inject PRP and/or BMC in patients undergoing DO.

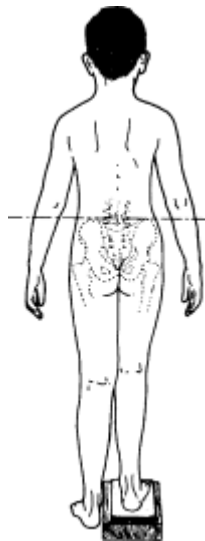
## **AIM OF THE WORK**

A systematic review of literature and meta-analysis of the results of the use of platelet rich plasma and/or bone marrow cells for enhancement of bone consolidation in distraction osteogenesis in terms of healing time and complications rates.

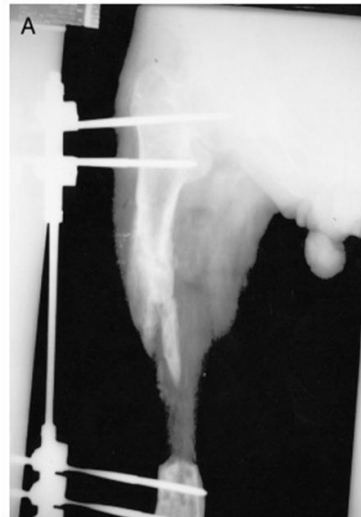
## REVIEW OF LITERATURE

### ▪ Distraction Osteogenesis

Distraction osteogenesis is a surgical technique used in reconstruction of the skeletal deformities that occur with fracture malunion, congenital deformities and developmental conditions, limb-length discrepancies (figure ١) , and bone defects (figure ٢) <sup>(١)</sup>.



**Figure (١):** Limb length discrepancy <sup>(١)</sup>.



**Figure (٢):** post traumatic femoral bone defect <sup>(١)</sup>.

In DO, initially osteotomy is done then it is followed by gradual distraction to get use of mechanical strain that induce the integration of cells, growth factors, and extracellular matrix to form bone. In many cases, DO creates an environment that suppresses the formation of cartilage and enhances angiogenesis with subsequent intra-membranous

bone formation; in some cases, instability results in callus and partial endochondral bone formation <sup>(4)</sup>.

▪ **Phases of distraction osteogenesis**

As shown in Figures (3) and (4), DO consists of the following phases:

- 1- **Latency phase:** the phase that just follows the osteotomy, there is no distraction in this phase. It takes about 5 to 10 days <sup>(11)</sup>.
- 2- **Distraction phase:** gradual distraction start at a rate of 1 milli meter each day, till we reach the wanted amount of lengthening. Ilizarov stated that the best rate was 1 milli meter every day with the best rhythm of distraction of 0.25 milli meter every 6 hours. Distraction must be done with cautious because over distraction (beyond 2 milli meter /day) can lead to slowing of osteogenesis, also very slow rate of distraction (less than 0.5mm/day) can lead to premature consolidation. Auto-distractor can be used to make continuous gradual and slow distraction of 1.0 mm/day instead of manual distraction <sup>(11)</sup>.
- 3- **Consolidation phase:** in this phase, distraction is stopped and the both bones are kept in place till mineralization and remodeling is completed and the end of consolidation is noticed by follow up X rays <sup>(12)</sup>.