

Clinical Evaluation of Platelet Rich Growth Factors (PRGFs) in Treatment of Temporomandibular Joint Disc Displacement—Study Report

Lahaou Baladji Touré^{1*}, Oumar Ongoïba¹, Djibril Kassogué¹, Wael Ahmed Elmohandes²,
Elsaed Mohamed Abdellatif²

¹Department of Surgery, Regional Hospital of Tombouctou, Tombouctou, Mali

²Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Al Azhar University, Cairo, Egypt

Email: *lahaou@hotmail.com

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Abstract

Objective: The aim of the study was to evaluate the effect of platelet rich growth factors (PRGFs) in treatment of temporomandibular joint disc displacement. **Materials and Methods:** The study subjects included 8 females having bilateral anterior disc displacement with reduction and 1 female having bilateral anterior disc displacement without reduction with the age range between 20 - 35 years. The process of obtaining PRGFs was carried out following the Anitua Technique. **Results:** Clinical parameters of Interincisal distance, Lateral excursion of mandible using digital caliper in millimeters and Visual Analogue Scale (VAS 0/10) for pain intensity score were used. All of these parameters were running through the intervals of two, four, and eight weeks till the end of the follow-up period at twenty-six weeks (six months). The participated patients showed the clinical improvement in the different clinical statuses such as interincisal distance; lateral excursion of mandible and Pain Score. **Conclusion:** the study reported early efficacy of PRGFs after the arthrocentesis of the joint in treatment of TMJ disc displacement, and according to our results, the injection of PRGFs could be a possible alternative treatment for patients who did not respond to standard treatment.

Keywords

Platelet Rich Growth Factors, Platelet Rich Plasma,
Temporomandibular Joint

1. Introduction

Temporomandibular joint disc displacement is defined as abnormal anatomical relationship amongst three structures, glenoid fossa, articular disc, and condyle. All patients especially those with disc displacement either with or without reduction should be initially managed with a conservative regime consisting of rest, NSAIDs and bite splint for a reasonable period of at least 6 weeks [1].

Patients who fail to respond to routine conservative measures for joint related pain (confirmed by relief of pain following local analgesic injection into joint) are submitted to arthrocentesis [2] [3] [4] [5]. Many different materials have been proposed for injection such as hyaluronans (1% sodium hyaluronate; sodium hyaluronate; high-molecular-weight hyaluronan; hylan G-F20); [6] [7] [8] steroid [9]; platelet rich plasma (PRP) [10]; platelet rich fibrin [11]. However none of these materials proved to have full satisfaction for most patients regarding tissue regeneration and pain relief, a factor that initiates the use of platelet rich growth factors which regulate healing in the complex processes [12].

Growth factors are proteins which play a main role on cell migration, cell proliferation and angiogenesis in tissue regeneration phase [13]. These growth factors are mainly located in blood plasma and platelet. So platelet aggregate has been widely used to accelerate tissue regeneration and repair in dental and medical areas. Moreover, platelet rich growth factors (PRGFs) possess certain more distinct advantages as it has a lower infection risk, accelerated healing process as well as safety and convenience. Additionally, it has no allergic reactions and reduces inflammation and pain [13] [14]. As the first generation of platelet concentrate, platelet rich plasma (PRP) and platelet rich growth factors (PRGFs) were well known. PRP was introduced by Marx [12]. But the effect of PRP shows weak effect regarding hard tissue regeneration [15]. PRGFs were introduced by Anitua [16]. Moreover, the second generation of platelet aggregation, platelet rich fibrin was first introduced by Choukroun [17].

The term “PRGFs” identifies exclusively 100% autologous and biocompatible formulation elaborated by a one-step centrifugation process and using sodium citrate as the anticoagulant and calcium chloride as the activator [18] [19]. PRGFs have a moderated platelet concentration and do not contain leukocytes, with the aim of avoiding the pro-inflammatory effects of the proteases and acid hydrolases contained in white blood cells [12]-[19].

2. Patients and Methods

The study subjects included were 9 females with age range between 20 - 35 years. The participated patients in this study were complaining of bilateral anterior disc displacement with or without reduction. All of those patients underwent three months of conservative treatment (soft diet, analgesics, rest, and occlusal splint). Subsequently, patients who didn't respond to conservative treatment were enrolled in the present study. They were free from any systemic disease or conditions that may compromise the treatment (previous open surgery; severe

malocclusion; and history of recent injury of joint).

3. The Study Design

- Injection of platelet rich growth factors after arthrocentesis of the joint.
- Before treatment each patient signed written consent having all the details about the following procedure.

4. Preoperative Assessment

- Radiographically; Orthopantogram was done for assessment of bony compartment of TMJ (**Figure 1**). Also MRI was done for assessment of soft tissue compartment (**Figure 2**).
- Clinically before the procedure of arthrocentesis the following parameters were used for assessment interincisal distance (**Figure 3**), lateral excursion using a digital caliper in millimeters, and pain using Visual Analogue Scale (VAS; scale 0-10).



Figure 1. Panoramic view for assessment of bony compartment of TMJ.

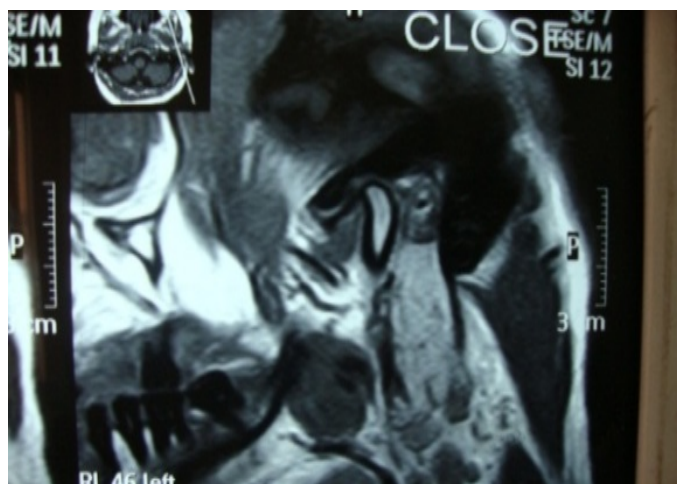


Figure 2. MRI for assessment of soft tissue compartment of TMJ.



Figure 3. Preoperative Interincisal distance using a digital caliper in millimeters.

5. Procedure of Arthrocentesis and Injection of PRGFs

Each patient was anaesthetized through the induction of light general anesthesia. Palpation across Zygomatic arch and the manipulation of the mandible was done in order to facilitate the localization of superior joint space. Prophylactic broad spectrum antibiotic (amoxicillin 1 gm) ** was given intravenously. The procedure of arthrocentesis was done routinely according to the technique of McCain [3].

A total of 60 - 100 ml solution was used to lavage the superior joint space and the needle of second point is removed; leaving the needle of the first point for injection of Platelet Rich Growth Factors (PRGFs). Then the needle of the first point is removed after the injection of PRGFs. Both points were covered by surgical pad. At the end of the procedure, the mandible was opened and closed several times for a minute to ensure equal distribution of PRGFs before it converts into gel.

**E.I.P.I.C.O (Egyptian Int. Pharmaceutical Industries Co.) (Tenth of Ramadan City A.R.E).

6. Preparation and Injection of Platelet Rich Growth Factors (PRGFs)

The preparation of PRGFs was done according to the description of Eduardo Anitua [16]. The blood was compartmentalized into the following four components after centrifugation:

- Plasma is poor in growth factors (PPGFs), located in the most superior 1 cc layer;
- Plasma with growth factors (PGFs), located just below the most superior layer 0.5 cc layer;
- PRGF (0.5 cc) is located immediately above the red blood cell fraction in the tube;

- Red blood cell concentrate.

The PPGFs located in the upper part of the plasma in the tube were eliminated through the aspiration of 1 cc. PPGFs have the lowest quantity of platelets in the plasma. The functional fraction is usually 0.5 cc of PRGFs located immediately above the red blood cell fraction. The PRGFs separated with 3 cc syringe and transported to an independent tube collecting 2 cc of PRGFs of every 20 cc of venous blood. Next, 2 cc of the PRGFs was activated using 100 µL of 10% calcium chloride. Immediately the mixture of PRGFs and calcium chloride is injected through the needle of the first point before being removed when PRGFs are in liquid form.

7. Postoperative Assessment

On the first day of injection the patients are discharged with a list of recommendations including the following:

- Cold fomentation on injection site during the first 24 hours; then hot fomentation for subsequent 5 days accompanied with (paracetamol 500 mg, 3 times daily), they were also instructed to continue the oral soft diet and to resume gradually to normal diet after the second week.
- All subjects in the study were informed to wear an occlusal splint at least eight hours before going to bed at night until morning.
- Then Patients were recalled at intervals of 2, 4, 8 weeks and 6 months postoperative to follow Interincisal distance, lateral excursion using an electronic digital caliper in millimeters, and VAS for pain score using.
- Finally, MRI was done for soft tissue evaluation at 6 months postoperative.
- All the post-operative complications and adverse effects were recorded.
- The resulted data was recorded and statistically analyzed using One-way ANOVA in order to obtain mean reading and P. value.
- The result is statistically significant where P. value < 0.05.

8. Results

The participated patient had moderate to severe preoperative pain. Those patients postoperatively showed the clinical improvement in the different clinical statuses such as Interincisal distance; lateral excursion of mandible and Pain Score for pain intensity. On orthopantogram findings, no remarkable change was observed on bony compartment of joint (TMJ) postoperatively in comparison to preoperative panoramic view taken at three months and six months follows up. Although MRI findings at six months postoperative, did not show any remarkable difference compared to preoperative MRI. However, the clinical outcomes showed remarkable improvement concerning Maximum mouth opening, Lateral excursion of mandible, and also pain score reduction.

9. Statistical Analysis

The mean readings of the study on different levels of clinical status; were statis-

tically significant where ($P < 0.05$), based on One-way ANOVA analysis: The mean of maximum mouth opening preoperatively was (28.8 ± 7.6 mm) and after treatment was (39.5 ± 1.8 mm) at six months the end of the follow-up period with P . value = 0.000 (Figure 4). The mean of lateral excursion of the mandible preoperatively was (4.4 ± 2.6 mm) and after treatment was (10.4 ± 1.2 mm) at six months the end of the follow-up period with P . value = 0.000 (Figure 5). The mean pain score preoperatively was (5.8 ± 0.7 mm) and after treatment was (0.0 ± 0.0 mm) at six months the end of the follow-up period with P . value = 0.000 (Figure 6).

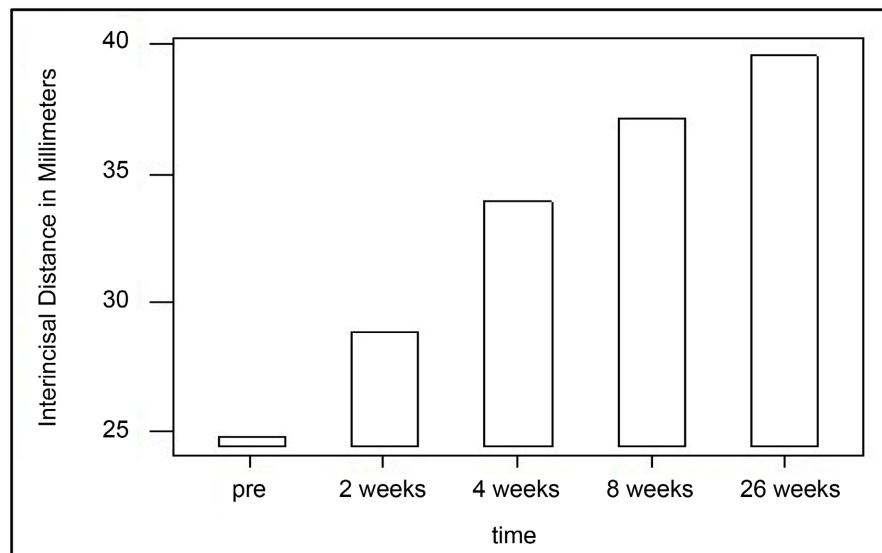


Figure 4. Chart graph showing interincisal distance in millimeters at preoperative, 2 weeks; at 4 weeks; at 8 weeks; and at 26 weeks postoperatively.

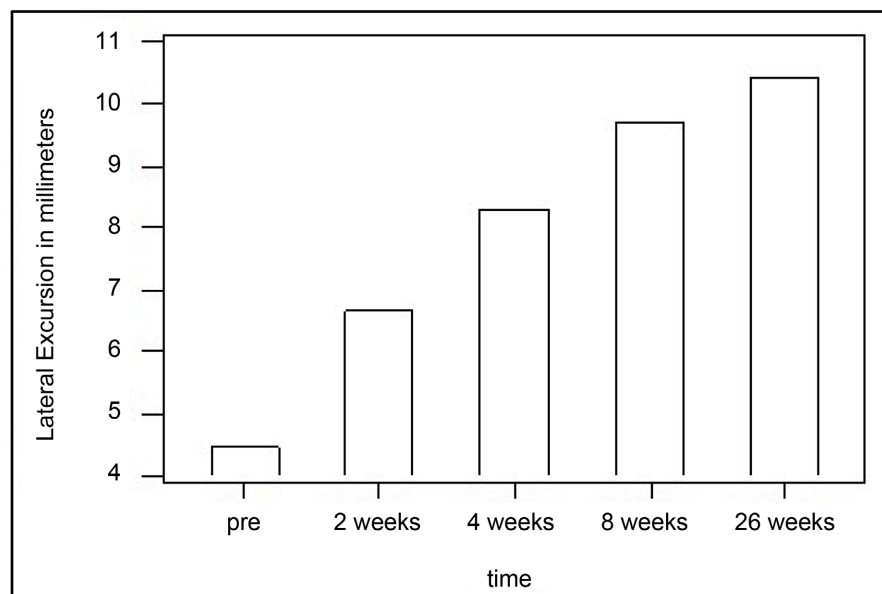


Figure 5. Chart graph showing lateral excursion of mandible in millimeters; at preoperative; at 2 weeks; at 4 weeks; at 8 weeks; at 26 weeks postoperatively.

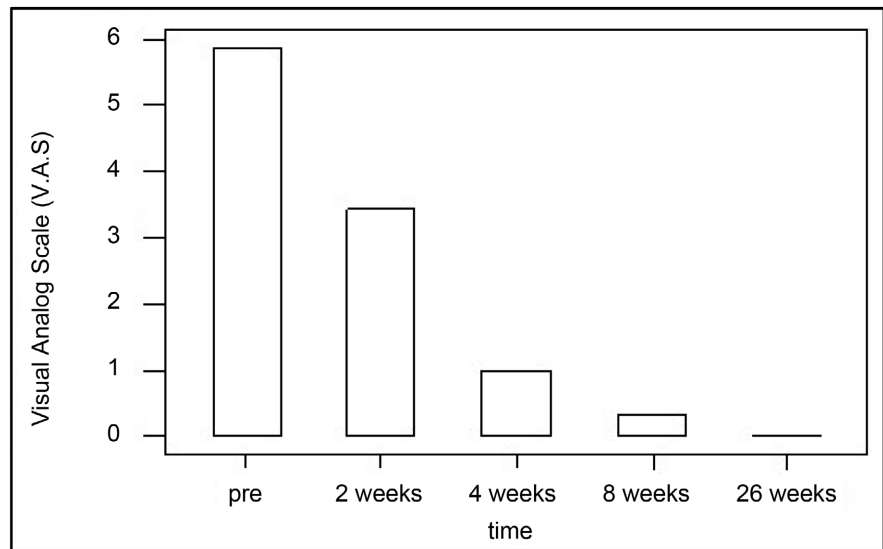


Figure 6. Chart graph showing pain intensity, reflected by visual analog scale VAS 0/10 at preoperative, at 2 weeks; at 4 weeks; at 8 weeks; and at 26 weeks postoperatively.

10. Discussion

There appeared to be strong female prevalence to temporomandibular disorders. In our study all of the subjects were female (9 females, 18 joints). This female prevalence prompted some to suggest that cellular activities in the TMJ may be modulated by sex hormones. Estrogen inhibits cartilage synthesis in animal models of osteoarthritis, and it also increases the production of inflammatory cytokines in tissues [20]. Estrogen and prolactin [21] may adversely affect the adaptive capacity of articular tissues of the TMJ by inhibiting fibro-cartilage synthesis and enhancing cellular matrix degradation. The number of patients in the present study was not sufficient to come to the conclusion regarding female prevalence.

The participated subjects were completely free from any condition that contraindicates the use of Platelet-rich growth factors (PRGFs). **However**, some contraindications for the use of PRGFs are platelet dysfunction syndrome, critical thrombocytopenia, hypofibrinogenemia, and hemodynamic instability [22].

Arthrocentesis is the primary treatment for patients who did not respond to conservative methods of management of TMJ pain, restriction and locking [23]. The debate continues about whether arthrocentesis alone is sufficient for the management of Internal Derangement of TMJ [1]. Arthrocentesis was used in this study according to the technique described by Mc Cain [3]. This is because, it was a standard technique, simple, more reliable to approach upper joint space without complication. In this study arthrocentesis was used after failure of conservative treatment for three months as therapeutic procedure; combined immediately with injection of Platelet Rich Growth Factors (PRGFs) to offer better results. Double needle technique of arthrocentesis [3] [5] was used for each patient as a minimally invasive technique that involves placing ports (Needles or

small Canulas) into the TMJ to lavage the joint and to break up any adhesions, the needles were used in this study instead of Canula, which it can be more difficult to enter the narrow joint spaces [5], also other studies used single needle which is indicated for hypermobile joints, with strong adhesions, or for joints with degenerative changes which make difficult insertion of the second needle [24]. Double needle technique is more efficient in washing out of the joint, for this point this technique was chosen for the procedure of this study.

Up to date no one injected Platelet Rich Growth Factors (PRGFs) after washing out the superior joint space of TMJ in treatment of temporomandibular joint disc displacement. In this study Platelet Rich Growth Factors (PRGFs) were injected just one time with six-month follow-up, having similar benefic results particularly in reduction of pain. While other studies used 3 intra-articular injection of autologous PRGFs. This was administered at 2-week intervals in treatment of osteoarthritis of the knee [25]. However, many orthopedic studies reported a greater number of repeated applications, mostly 3 times at an interval of 3 - 5 weeks [26] [27]. This revealed better, satisfactory results versus repeated injections of PRP [26] [27], and that could be attributed to the combination of injection of PRGFs immediately after washing out of the joint.

In the study the bony compartment was assessed preoperatively, at three months, and six months postoperatively, using panoramic radiograph [28] as a screening tool for the entire maxillo-mandibular region. In order to evaluate any bony defect presence which can compromise the procedure, and no remarkable change was observed on bony compartment of joint (TMJ) postoperatively in comparison to preoperative panoramic view taken at three, and six months. This view was unable to determine the exact condylar fossa disc relationship, and is unable to provide diagnostic information on the position and the status of the disc. For these disadvantages of panoramic view concerning the soft tissues of TMJ, the joint was evaluated also using Magnetic Resonance Imaging (MRI) [29] for soft tissues assessment preoperatively and postoperatively at six month. MRI is used due to its superior resolution of both soft tissues as well as hard tissues of the temporomandibular joint; it is considered as the imaging of choice in the diagnosis of temporomandibular joint disc displacement [29]. For soft tissues compartment evaluation at six-month follow-up, postoperatively no remarkable differences were noted in MRI results in comparison to the preoperative results of MRI. These negative results could be due to the short period follow-up. And because the actual image of MRI needs at least 9 months to show any soft tissue changes.

In the present study, arthrocentesis was done routinely using Ringer's lactate due to its positive physiologic effect, it is considered one of the balanced fluids, and has better safety profile compared to other non-balanced fluids due to decreased chloride intake [30]. The fibrous tissue of the articular disc has a better tolerance for Ringer's solution than for an isotonic saline solution [31]. The composition of the solution of other types of crystalloid has no effect in influen-

cing the result of the procedure [32]. However, the idea of the procedure of arthrocentesis is to distend the joint and cause lavage without altering the structure or position of the disc. Release of the negative forces, reduction in the surface friction and release of the stuck disc phenomenon also, have been attributed to the possible correction of the jaw joint disorder [32]. The possibility to complete the treatment as an outpatient procedure with minimal complications makes it the first choice treatment for the jaw joint problem [32]. Combination of these two modalities of treatment; the arthrocentesis and injection of PRGFs; was to have better results as advised by Hegab [33].

During the clinical follow-up of the subjects; the maximum mouth opening (Interincisal distance); and lateral excursion of the mandible were measured by Digital caliper. It was used for its accuracy in measurement and to prevent any error during the procedure. Concerning the pain intensity record; Visual Analog Scale (VAS) was used. Patients were invited to complete an original satisfaction of pain assessment form.

Each patient participated in the present study showed early relief of pain during the follow-up period that can be explained as PRGFs therapy is based on the effects of GFs that promote changes in cell proliferation and regulate cellular metabolism. Growth factors have a vital role in modulating chondrogenic expression [34], PRGFs promote healing through regeneration of degenerative changes in cartilage, bone, and synovial tissue [35]. Platelet Rich Growth Factors are widely used in orthopedic surgery, as it promotes healing of wounded tendons and ligaments (medial collateral ligament rupture of the knee, lateral collateral ligament rupture of the ankle and tendon defects) and regenerate OA damage to cartilage and subchondral bone [36] [37] [38]. While articular cartilage has limited regenerative capacity due to its avascularity and low mitotic activity, some GFs especially TGF beta, basic fibroblast growth factor, and bone morphogenic protein show a positive effect on cartilage tissue regeneration [26] [27] [39]. These positive histologic properties of PRGFs were emphasized by Eduardo Anitua [40].

The satisfactory results were obtained in the present study in short duration in comparison to some studies where arthrocentesis alone was used in treatment of Internal Derangement of temporomandibular joint. This was due to the merit of combination of arthrocentesis and lavage immediately followed by injection of PRGFs. On the other hand, Neeli *et al.* [3] obtained less satisfactory results in long duration. Irrespective to material be used for arthrocentesis and lavage gives less this satisfactory results concerning pain regression and or improvement of Maximum mouth opening and or Lateral excursion of mandible. However injection of PRGFs, or even PRP has the main role in pain regression, improvement of Maximum mouth opening and lateral excursion of mandible.

The rapid pain regression in this study just after a week of the procedure was reported by each patient who participated in this study; which can be attributed to the physiologic effect of Platelet Rich Growth Factors (PRGFs), and the same parallel result found in a study done by Pihut *et al.* [41] in the evaluation of pain

regression in patients with Internal Derangement treated by intra-articular platelet-rich plasma. According to the results obtained in Visual Analog Scale in this study; additional intra-articular injections of platelet rich growth factors into the temporomandibular joints have a positive impact on the reduction in the intensity of pain experienced by patients for temporomandibular disc displacement. Failure in pain relief in a case may be due to pain originating from causes other than internal derangement; such as extravasation of fluid into the surrounding tissue; hematoma with risk of infection; tenderness of pre-auricular region; and middle ear effusion.

In the second week of follow-up period of this study the inflammatory signs were completely resolved clinically. This can be explained as PRGFs has a moderated platelet concentration and does not contain leukocytes. No remarkable signs of effusion or exuberant synovitis were noted through MRI. On the other hand, Mallo *et al.* [42] mentioned the presence of Exuberant synovitis after sub-acromial decompression and platelet rich growth factor (PRGF) injection. In a study of porcine knee arthritis, Lippross *et al.* [43] reported that PRP reduced inflammatory mediator synthesis in the synovial membrane. This was confirmed by Liu *et al.* [44] While Sun *et al.* [45] and Ying *et al.* [46] reported a positive effect of TGF in OA of rabbit TMJs. These positive physiologic effects of PRGFs on inflammatory degenerative changes may approve the benefic results obtained in the different levels of the clinical finding.

Several clinical trials have shown that PRGFs therapy is effective for pain reduction and subsequent improvement in joint function; in this study remarkable pain reduction and improvement in joint function were noted. This was confirmed by those studies, Sánchez *et al.* [26], Filardo *et al.* [47], Sampson *et al.* [48], Napolitano *et al.* [34], and Kon *et al.* [49].

11. Conclusion

Arthrocentesis is a minimally invasive technique. It removes all the inflammatory mediators. Arthrocentesis and lavage with immediate injection of PRGFs proved effective in different levels of clinical status. It improves the quality of life. Preparation of PRGFs is a simple procedure. It is autologous no rejections.

Conflicts of Interest

The authors declare no conflict of interest.

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