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A COMPARATIVE STUDY BETWEEN THE EFFECT OF PLATELET RICH FIBRIN AND CONCENTRATED GROWTH FACTORS ON OSSEOINTEGRATION OF IMMEDIATE IMPLANTS (A RANDOMIZED CLINICAL TRIAL)

Shady A. Khalifah [1]* *BDs* Mostafa M. Eldibany[2] *PhD,* Marwa G. Nouredin[3] *PhD*

ABSTRACT

INTRODUCTION: A lot of studies covered the use of growth factor-containing products as enhancers of osseointegration. Concentrated growth factors or CGF is a third generation platelet concentrate that is used to improve osseointegration of implants.
AIM OF THE STUDY: to compare the effect of CGF on implant stability, bone density, and the horizontal dimension of the bone adjacent to the implant to that of platelet rich fibrin (PRF).
MATERIAL AND METHODS: Fourteen participants with mandibular premolars that needed extraction and replaced immediately were assigned into two groups; a study group and a control group. A CGF membrane was laid in the implant osteotomies of the study group while a platelet-rich fibrin (PRF) membrane was placed in the osteotomies of the control group. The space in between the socket and the implant was filled with bone graft. To assess implant stability, a resonance frequency analysis (RFA) was performed immediately. After one week and after three months, a follow-up RFA was conducted. Preoperatively, directly after surgery, and three months afterwards, cone beam computed tomography (CBCT) was performed.
RESULTS: Implant stability and bone density improved significantly in both groups after three months with no significant change in the horizontal dimension of bone for both groups. While higher implant stability and bone density readings were recorded in the CGF group, there was no change between the two groups that had statistical significance.
CONCLUSION: CGF enhances osseointegration more than PRF when evaluated radiographically and with resonance frequency analysis but with no statistical significance.
KEYWORDS: Dental implants, Growth factors, Osseointegration, Osteogenesis, Wound healing.
RUNNING TITLE: Comparing CGF with PRF on osseointegration.

1 BDS, 2012, Faculty of Dentistry, Alexandria University, Egypt.
2 Professor of Oral and Maxillofacial Surgery, Department of Oral and Maxillofacial Surgery Faculty of Dentistry, Alexandria University, Egypt.
3 Assistant professor of Oral and Maxillofacial Surgery, Department of Oral and Maxillofacial Surgery Faculty of Dentistry, Alexandria University, Egypt.

* *Corresponding Author:*

E-mail: *shady.5alifah@gmail.com*

INTRODUCTION

Osseointegration is the most crucial event for the success of dental implants. And the time required for it to happen varies between three and six months. So there is no standard timing for osseointegration nor prosthetic loading (1).
Techniques have been devised to reduce the amount of time needed for this process. Changing implant surface treatment and design has improved the primary stability of implants. Also, bone healing modulation through bioactive molecules has been used. Bioactive molecules are proteins in the form of growth factors that control the healing process (2).

Platelet rich plasma (PRP), PRF, and CGF are all platelet-rich preparations derived from human venous blood. These products contain growth factors such as bone morphogenetic protein (BMP), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), transforming growth factor-1 (TGF-1), and transforming growth factor-2 (TGF-2). These factors all contribute to the promotion of chemotaxis, angiogenesis, and cell differentiation (3, 4).
In 2009, Sohn et al. demonstrated that CGF has a greater capacity for tissue regeneration (5). This preparation's fibrin network contains platelets,

leukocytes, fibroblasts, and endothelial cells, as well as growth factors, and serves as a matrix for cellular migration, thereby facilitating tissue regeneration and remodeling (6).

A dental implant needs stability during the healing period sufficient to allow the healing process thus achieving osseointegration (7). Resonance frequency analysis can be used to keep a record of implant stability during different time periods of bone healing around implants. Additionally, cone beam computed tomography enables the measurement of changes in bone density in the vicinity of implants, indicating the process of new bone formation (8).

The purpose of this study is to compare the effect of CGF on implant stability, bone density, and the horizontal dimension of the buccal and lingual bone adjacent to the implant to that of PRF.

METHODS

Study design and setting

This study was conducted as a comparative clinical trial. Patient selection was carried out in the outpatient clinic of the oral and maxillofacial clinic of the faculty of dentistry, Alexandria University. Ethical and legal permissions were given by the faculty. This study has been registered at, Clinicaltrials.gov and granted an ID number: NCT05101954.

Study sample

Fourteen patients were selected for extraction and immediate implant placement of mandibular premolars. Following that, patients were randomly assigned to one of two groups. Group A patients (control group) were to receive one implant with the implant cavity walls covered with PRF membrane. Group B patients (study group) received one implant with the implant cavity walls covered with a CGF membrane.

Subjects who meet the inclusion criteria will be randomly assigned to one of the two arms using a computer-generated list of random numbers (CGF group and PRF group). Allocation will be carried out by a trial-independent individual with the goal of maintaining an equal allocation ratio. Allocation will occur in two-block increments to ensure that each study group has an equal number of subjects. (www.randomizor.org) (9).

Criteria for eligibility

Inclusion criteria

1. Patients who are cooperative and maintain proper oral hygiene (10).
2. Patients having a history of mandibular premolars indicated for extraction and immediate implant placement.
3. The alveolar crest at the implant site should have a minimum width of 4–5 mm (11).
4. A minimum distance of 2.5–3 mm should be present between the implant site and the adjacent teeth (11).
5. D2 or D3 bone type at the implant site is recommended (12).

Exclusion criteria

1. Heavy smokers.
2. Patients who exhibit parafunctional occlusal habits (13).
3. Uncontrolled diabetes.
4. History of chemotherapy or radiotherapy.
5. Abnormalities of the hematological system that impair either implantation or centrifugation.
6. Pregnant female patients.
7. Chronic periapical pathology.

MATERIALS

1. Superline Implant System

Dentium Superline implants (Superline, Dentium CoTM, Double Thread, S.L.A surface, Korea). Have different diameters (3.6, 4.0, 4.4, 4.9, 6.0, 7.0 mm) and different lengths (7, 8, 10, 12, 14 mm). The tapered design and surface treatment (Sandblasting and acid etching) facilitate osseointegration.

2. Resonance Frequency Analysis (RFA) Device (Osstell ™)

Osstell instrument (Integration Diagnostics, Goteborg, Sweden) with Smartpeg™ (Integration Diagnostics, Goteborg, Sweden), RFA was used to evaluate the stability of implants using an implant-compatible transducer. The implant stability quotient (ISQ) was calculated using the measurement data.

3. Bonefill Porous (Bioinnovation Biomedical, Brazil.)

Produced using a multiphase process from natural bone: Fresh bone is crushed and then subjected to a series of baths that dissolve organic structures such as remaining cells, fibers, and proteins–leaving only the mineral portion, thereby avoiding the induction of immunogenic processes in the body.

Presurgical phase

1. Personal information and history

Personal information such as age, name, address, and phone number were collected and documented. Past medical history, chronic systemic diseases, and ongoing medications were also documented.

2. Clinical examination

A thorough dental examination was done, history of past dental procedures and chief complaints were documented.

3. Radiographic examination

A periapical and panoramic x-ray examination was performed initially, followed by cone beam computed tomography (CBCT) analysis for implant dimension and angulation.

Preparation of PRF and CGF

Patients were asked for consent for phlebotomy. 20 ml of venous blood were collected from each patient, dispensed in 10 ml tubes with no additives, and placed into the centrifuge.

For PRF preparation the centrifuge was set to 3000 RPM for 10 minutes (14). And for CGF preparation the centrifuge is set to accelerate and then alternate speeds between 2700 and 2400 in the following

manner: accelerated for 30 seconds, centrifuged at 2700 rpm for 2 min, 2400 rpm for 4 min, 2700 rpm for 4 min, and 3000 rpm for 3 min, and decelerated for 36 s to stop (15).
When tubes are removed from the centrifuge three layers appear which are:

1. Layer of red blood cells at the bottom.
2. Fibrin gel with platelet aggregate and concentrated growth factors in the middle.
3. Platelet poor plasma at the top.

The middle gel layer was separated from the RBC layer by a pair of scissors and compressed into a membrane using two metal slabs, one of which is fenestrated (Figure 1).

Surgical Procedure

1. Prior to surgery, all patients were instructed to rinse with chlorhexidine mouthwash for two minutes.
2. Local anesthesia administration was done using 4% articaine (1:100000 adrenaline).
3. Periotome atraumatic extraction of the teeth was performed (Figure 2).
4. Implant osteotomies were prepared according to implant system guidelines.
5. Each patient received one osteotomy for one implant, with the implant cavity laid with a CGF membrane in the study group or a PRF membrane in the control group according to patient randomized allocation (Figure 3).

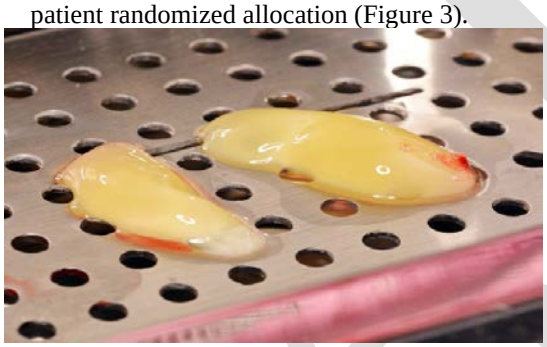

Figure (1): CGF before compression into a membrane.

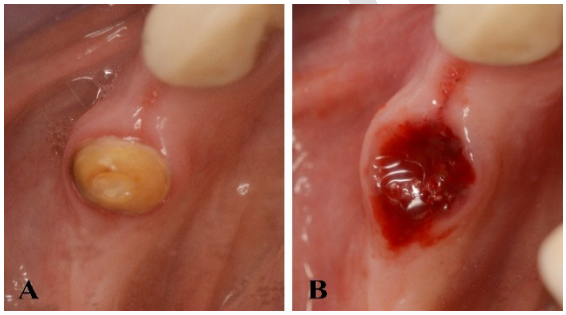

Figure (2): (A) Initial situation. (B) Fresh extraction socket.

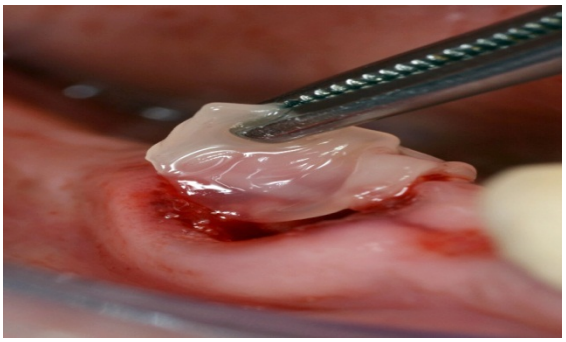

Figure (3): CGF membrane in osteotomy.

6. Implant fixtures were irrigated with platelet poor plasma (PPP) and then placed in the planned osteotomy.
7. Bone graft material was inserted into the socket to fill the empty parts around the implant (Figure 4).

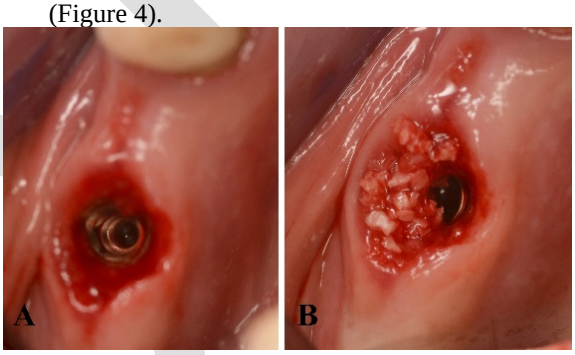

Figure (4): (A) implant fixture secured in place. (B) Bone graft used to fill the empty parts of the socket.

8. Gingival formers were attached to implants (Figure 5).
9. Resonance Frequency Analysis (RFA): During measurement, The SmartpegTM was positioned over the implant prosthesis's position and the Osstell probe was used to approach it from the buccal, palatal, mesial, and distal aspects of the implant, yielding four ISQ readings. A mean ISQ was then determined for each implant by averaging the four readings. The ISQ values of the implants were determined during surgery, one week after surgery, and three months following surgery.

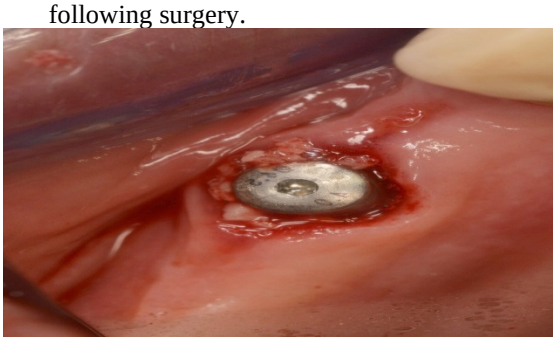

Figure (5): Gingival formers in place.

Post-surgical phase

1. Postoperative care and instructions

Patients were prescribed antibiotic, analgesic, and antiseptic mouth wash for 1 week. The patients were followed up after the 1st week, 4th week, and after 3 months.

2. Postoperative follow up

a. Clinical evaluation

All of the cases when followed up proved uneventful and there were no major complications related to the implant eg. edema, severe pain, or infection.

b. Implant stability evaluation

RFA was done by Osstell ™and Smartpeg™ after the first week and after three months.

c. Radiographic evaluation

Patients were asked to undergo CBCT immediately following surgery and again three months later to measure bone density and the horizontal bone dimension– buccal and lingual to the implant.

Radiography was performed using a cone beam 3D imaging system (Morita 3DX; J Morita, Kyoto, Japan) and CBCT analysis software (OnDemand 3D version 1.0, Win 32 edition), To begin, we standardized the CBCT device settings (preoperative and 3 months postoperative); the scan was performed with a field of view (FOV) of W 100mm x H 50mm and an isometric voxel size of 0.160mm. 90KV (kilovoltage), 8 mA (milliampere), and a 20-second exposure time were used for the tube voltage. To minimize error bias, all CBCT scans were performed at the same radiology center and with the same device.

Bone density

Using the viewer app tools three 4 mm2 regions of interest (ROI) were defined using the rectangular tool around three aspects of the implants i) one buccal to the implant coronal to the second thread from the bottom of the implant. ii) one lingual to the implant coronal to the second thread from the bottom of the implant. iii) one directly apical to the bottom of the implant. Then an average of the readings was calculated (16) (Figure 6).

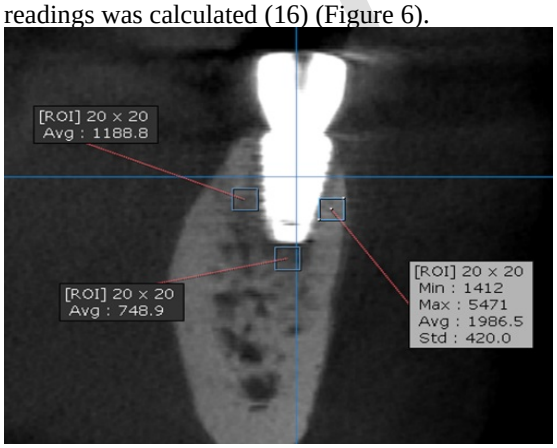

Figure (6): Radiographic bone density evaluation.

The horizontal dimension of the alveolar bone

The bone buccal and lingual to the implant was measured horizontally from two fixed points on the buccal and lingual surfaces of the implant and midway through the length of the implant. Then the ruler tool was used to measure the distance from each point to the respective outer cortical border with the ruler line parallel to the horizontal axis of the section.

Statistical Analysis of the Data

The Shapiro Wilk test, box plots, and descriptive statistics were used to determine normality. The mean and standard deviation (SD) were used to present the data. Groups were compared regarding all measured outcomes using independent t-tests. Repeated measures ANOVA was applied to assess changes across time regarding bone density and implant stability while Paired t-test was used to assess changes within each group for horizontal and vertical bone formation.

Percent change was calculated according to the following formula:

[(values after – values before) / values before] × 100.

The Mann Whitney U test was used to compare all percent change values between groups. The significance level was set at a p value of 0.05 All tests used a two-tailed design. SPSS for Windows version 23 was used to analyze the data (17).

RESULTS

Patients' demographic data

The selected patients were twenty nine to fifty nine years of age with a mean age of 41.5 years for the control group and 46.17 for the study group and were of both genders (six males and eight females).

Implant stability measurement by Osstell™

Data were collected immediately (Primary stability), after one week from implant placement, and after three months (Secondary stability). The mean of implant stability for the study group immediately after implant insertion was 64.29±14.09 ISQ. The mean of implant stability after one week following surgery was 73.43±11.32. When readings were collected after 3 months the mean ISQ was 80.86±10.49. This difference between primary and secondary stability at all time intervals had statistical significance with a p value <0.05 (Table 1).

Table (1): Implant stability between group A and B at different follow up intervals.

Follow up	Group A (n=7)	Group B (n=7)	Test (*P* value)
	Mean±SD		
Immediate	67.14±17.63	64.29±14.09	0.335 (0.744)
1 week	71.57±14.43	73.43±11.32	0.268 (0.793)
3 months	78.57±10.69	80.86±10.49	0.404 (0.694)
Test (*P* value)	19.217 **(<0.0001*)**	95.248 **(<0.0001*)**	
Post hoc test	P_1**=0.032*** P_2**=0.014*** P_3**=0.008***	P_1**=0.002*** P_2**<0.0001*** P_3**<0.0001***	

*Statistically significant different at *p* value≤0.05

For the control group, the mean of implant ISQ for the control group immediately following implant insertion was 67.14±17.63 ISQ. The mean of implant stability after one week of implant insertion was 71.57±14.43 ISQ. The mean after three months was found to be 78.57±10.69 ISQ. This difference between primary and secondary stability at all time intervals was found to be statistically significant with a p value <0.05 (Table 1).

On the other hand, when implant stability was compared between groups A and B, there was no statistically significant difference between the two groups at any time interval.

Radiographic bone density analysis

For the study group, immediately post-operative, the mean peri-implant bone density value was 902.97±106.22 HU. At 3 months postoperative, the mean peri-implant bone density value was 1248.31±247.22 HU. The difference in bone density was statistically significant between immediate post-operative values and after 3 months post-operative (p <0.05) (Table 2).

Table (2): Bone density between group A and B at different follow up intervals.

Follow up	Group A (n=7)	Group B (n=7)	Test (*P* value)
	Mean ±SD		
Immediate	743.21± 222.27	902.97± 106.22	1.716 (0.112)
3 months	811.17± 209.45	1248.31± 247.22	3.570 **(0.004*)**

*Statistically significant different at *p* value≤0.05

For the control group immediately post-operative, the mean peri-implant bone density value was 743.21±222.27 HU. At 3 months postoperative, the mean peri-implant bone density value was 811.17±209.45 HU. The differences were statistically significant between bone density values immediately post-operative and after 3 months post-operative (p <0.05) (Table 2).

When the two groups were compared, a significant difference in bone density was observed at three months postoperatively in favour of the study group. However, when comparing immediate and 1 week bone density values, the study group showed higher values but the differences were statistically insignificant.

Horizontal Bone buccal and lingual to the implants

In the study group the mean value for the horizontal dimension of bone after 3 months was 2.17±0.34 mm buccally and 4.71±0.78 mm lingually with an overall mean value of 3.43±0.46 mm with an overall percent decrease of 2.419 percent which was not statistically significant. For the Control group the mean value for the dimension of bone after 3 months was 1.81±0.36 mm buccally and 5.26±0.29 mm lingually with an overall mean value of 3.53±0.26 mm with an overall percent decrease of 2.280 which was not a statistically significant bone loss (Table 3).

Table (3): Horizontal dimensionsional change of alveolar bone between Group A and Group B at different follow up intervals.

Site	Follow up	Group A (n=7)	Group B (n=7)	Test (*P* value)
		Mean±SD		
Buccal	Immediate	1.99±0.25	2.24±0.38	1.516 (0.155)
	3 months	1.81±0.36	2.17±0.34	1.923 (0.079)
Test (*P* value)		2.444 (0.051)	2.236 (0.067)	
Lingual	Immediate	5.36±0.37	4.73±0.78	1.911 (0.080)
	3 months	5.26±0.29	4.71±0.78	1.753 (0.105)
Test (*P* value)		1.580 (0.165)	1.534 (0.176)	
Overall	Immediate	3.67±0.26	3.48±0.46	0.916 (0.378)
	3 months	3.53±0.26	3.43±0.46	0.441 (0.643)
Test (*P* value)		2.280 (0.063)	2.419 (0.054)	

DISCUSSION

This study discusses the abilities of bone grafts and platelet concentrates in enhancing osseointegration, overcoming the challenges of immediate implants, and possibly shortening the period of treatment.

Using bioactive additives such as platelet concentrates as an innovative method to increase the speed of healing has become popular in the dental implant field of dentistry, namely platelet rich plasma (PRP), platelet rich fibrin (PRF), and concentrated growth factors (CGF) each representing a generation respectively. Masuki et al evaluated the growth factor and pro-inflammatory cytokine content in PRP, PRF, and CGF and concluded that PRF and CGF had the advantage of having a complex fibrin network that acted as a meshwork entangling platelets with growth factors on their surfaces modulating the healing process and also serve as a reservoir for certain growth factors to be delivered to the application site (18).

In this study, a comparison was intended between PRF and CGF when used in osteotomies of immediate implants of lower premolars. Both were prepared and compressed into a membrane and then laid in the osteotomy before implant insertion. This surgical technique was utilized and the form of a membrane was chosen over other forms e.g. plug or sticky bone, in order to facilitate the application of PRF or CGF and insertion of the implant. Pirpir et al in a clinical trial utilized the same surgical technique with CGF membranes application in implant osteotomies before implant insertion and also Oncu E. applied the surgical

technique with PRF before immediate implant insertion in a clinical trial to evaluate the effect of PRF on osseointegration and in both studies PRF and CGF improved osseointegration with statistical significance which is consistent with the results in this trial.

Successful immediate implant treatment planning begins with overcoming the challenge of the space between the implant and the socket wall. Since bone healing around an implant begins apical and moves coronal, ignoring this gap would cause bone resorption and incomplete osseointegration around the implant. Regarding this issue, an allograft was used to fill the jumping gap between the implants of the study and control groups due to their osteoconductive properties which resemble that of natural human bone, as well as avoiding donor site complications which lead to preservation of the dimensions of alveolar bone around the implant (19). This was consistent with a radiographic study conducted in dogs by Novaes et al., which evaluated buccal bone plate remodeling following immediate insertion and bone grafting and demonstrated improved buccal bone preservation (20).

This study demonstrated a statistically significant increase in implant stability through the use of resonance frequency analysis in both the study and control groups after three months when compared with the primary stability of the implants immediately after insertion and after one week. This was consistent with the results of a clinical trial by Pirpir et al. In which it was observed that the CGF had positive effects on implant stability. The ISQ measurements at week one and at one month were significantly higher in the study group than in the control group that did not receive any addition to the implant osteotomy (21).

In another study by Mohamed AE et al to evaluate the effect of CGF on implant stability, immediate implant placement with CGF membrane/ CGF sticky bone showed a significant increase in secondary stability after six months which was also consistent with results of this study (22).

Bone density analysis showed a significant increase in mean bone density values for both groups. While bone thickness when measured horizontally buccal and lingual to the implant on the CBCT it showed no significant change after three months indicating no major bone loss happening around the implant site.

This comparison was previously done in a study on animals by Kim TH et al, CGF, PRF, and PRP were placed separately in the rabbit skull defects created in the study group; in the control group, the defects remained empty. Histologic examination revealed statistically significant differences in the growth of new bone between the study and control groups. The CGF-treated group formed the most bone in this study, as it showed in the radiographic bone density analysis but comparing the increase in bone density between the two groups did not show a statistically significant change (23).Takeda et al. performed a study on rats in which it was observed that osteoblast differentiation was significantly greater in the CGF-treated group than in the other groups (24). The results of the latter two examples concur with the statistically significant increase in bone density and the relative stability in the horizontal bone dimension around the implants observed in this study in both the study and control groups and also the statistically insignificant superiority of CGF over PRF when used under similar circumstances.

In conclusion, results have shown that both PRF and CGF enhance osseointegration around immediate implants with better implant stability and radiographic results with CGF but with no statistical significance.

LIMITATIONS

1. Availability of patients with mandibular premolars fit for immediate implantation after extraction.
2. Lack of long term follow up of evaluation parameters past four months.

RECOMMENDATIONS

1. Future research including the use of CGF membranes in different oral surgeries e.g. tumor and cyst surgeries.
2. Further studies on the implementation of CGF in implant surgery with larger sample sizes and different surgical approaches.

CONFLICT OF INTEREST

No conflicts of interest were declared by the authors.

FUNDING

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