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Autologous Plasma Rich in Growth Factors in the Socket Preservation after Tooth Extractions in Diabetic Patients: A Split Mouth Study

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Abstract

Background: Patients affected by type 2 Diabetes mellitus (DM) have a higher risk of developing of oral diseases than the general population. Plasma-rich growth factor (PRGF) is a technique that transforms a biological and autologous product in a platelet membrane, which can be positioned in the healing site, so that delivers platelet-derived growth factor, and stimulates soft tissue and bone regeneration. The purpose of this study is to evaluate the efficacy of PRGF in post extractive sockets in patients affected by Type 2 DM, evaluating socket reduction, VAS scores, the Healing Index (HI), and patient satisfaction based on answers to a form.

Material and methods: This is a split-mouth study in which each patient also served as the control: the study socket was treated with PRGF, whereas the control socket underwent natural healing. The outcome variables were the Healing Index, residual socket volume, VAS score, postsurgical complications, and outcome of a patient questionnaire. The investigation considered the impact of hyperglycemia, glycated hemoglobin, End Organ Disease Score and smoking habits. 4 weeks of follow-up (we had all healings at 4 weeks so we didn't continue the study beyond 4 weeks) was considered. Pairs of correlated continuous variables were analyzed with the Wilcoxon test, independent continuous variables with the Mann-Whitney test, and categorical variables with the c2 test or Fisher test.

Results: From January 2017 to December 2017, 58 patients affected by insulin-dependent diabetes mellitus (type 2 Diabetes mellitus (DM)) underwent contemporary bilateral extractions of homologous teeth. The treatment-versus-control postoperative comparison showed that PRGF resulted in significantly smaller residual socket volumes and better Healing Indices from days 3 to 21 (PRGF brings an healing improvement as an increase in wound closure speed statistically significant in all 4 follow ups ($p < 0.0001$ at 3 days, $p < 0.0001$ at 7 days, $p = 0.0002$ at 14 days, $p = 0.005$ at 21 days)). The patients' questionnaire outcomes were unanimously in favor of PRGF treatment.

Discussion: PRGF application after extraction improved the healing process in diabetic patients by accelerating socket closure (epithelialization) and tissue maturation, proving the association between PRGF use and improved wound healing in diabetic patients.

Keywords: Diabetes mellitus, Diabetic, Tooth extraction, Socket Preservation, Platelet, Plasma, PRGF

Introduction

Patients affected by type 2 Diabetes mellitus (DM) have a higher risk of developing of oral diseases than the general population. DM is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period; it is a disorder that affects millions of people worldwide.

Many oral diseases and disorders have been associated with DM, and periodontitis has been identified as a possible risk owing to poor metabolic control in patients with diabetes [1]. According to the American Diabetes Association the presence of oral diseases can exacerbate the systemic parameters of DM, worsen cardiovascular outcomes, and increase mortality [2]. During oral surgery procedures or tooth extractions, there is a higher risk of postoperative complications than in general population, due to impaired wound healing and thus the necessity to find procedures that can accelerate the healing process to avoid infectious complications [3-6].

The risks of complications increase with the duration of hyperglycemia because the production of advanced glycation end products causes micro- and macrovascular complications and increases susceptibility to infection, vascular changes, and impaired healing [7].

It has been well established that hyperglycemia causes impaired cellular immune responses, inflammatory cytokine profiles, and microcirculation during healing processes. Abnormalities of collagen metabolism, impaired proliferation of osteoblasts, and weakened mechanical properties of newly formed bone have been documented in hyperglycemic patients [8].

Platelet gels have been studied in the last years, they play a central role during the physiologic healing process, as haemostatic agents and to release secretory proteins of the healing cascade [9].

Platelet-rich preparations have been used in different medical fields; the use of platelet gels accelerate epithelialization and vascularization of connective tissue in wound healing sites, and it is used especially for the treatment of diabetic ulcers [10]. Specifically plasma-rich growth factor (PRGF) is a technique that transforms a biological and autologous product in a platelet membrane, which can be positioned in the healing site, so that delivers platelet-derived growth factor, and stimulates soft tissue and bone regeneration [11].

In a previous study of our department, 34 patients affected by insulin-dependent diabetes mellitus underwent contemporary bilateral extractions of homologous teeth. The treatment-versus-control postoperative comparison showed that PRGF resulted in significantly smaller residual socket volume sand better Healing Indices from days 3 to 14. The patients' questionnaire outcomes were unanimously in favor of PRGF treatment. The small sample of patients with glycemia values of at least 240 mg/dL showed worse Healing Index and minor socket decreases [12].

The purpose of this study is to evaluate the efficacy of PRGF in post extractive sockets in patients affected by Type 2 DM, evaluating socket reduction, visual analog scale (VAS) scores, the Healing Index (HI), and patient satisfaction based on answers to a form. Compared to the previous study we have kept the same study type, they are both split-mouth but we have increased the sample to have a greater scientific validity and reduce the bias.

Also, the study is designed to assess whether certain patient baseline characteristics, such as glycated haemoglobin (HA1C), End Organ Disease Score (EODS), smoking habits, and glycemia values, had an impact on the healing process.

Finally authors want to evaluated (wanted to evaluate) in PRGF can be used by experts and less experts surgeons with the same results. (we randomized the interventions between an expert operator with more than 20 years of experience and a recent graduate dentist and we compared the values seeing that there were no statistically significant differences).

Materials and Methods

This is a split-mouth study: a post extractive socket was treated with PRGF application (study socket), whereas the other (control socket) had to undergo natural healing by clot formation.

The choice of the socket was treated with PRGF was randomized through standard software. All patients were referred by the Diabetic Center, AOU Città della Salute e della Scienza of Turin to the Oral Surgery Departement, Dental School, University of Turin and were all affected by type 2 DM for extraction of untreatable teeth from January to December 2017.

Criteria for inclusion were as follow: i) age> 18 years, ii) HAIC level of at least 8%, iii) insulin therapy, iv) evidence of systemic complications from DM (heart and vascular disease, nephropathy, neuropathy, or retinopathy), v) need for bilateral extractions of homologous teeth, vi) informed

consent and ability/will to complete the trial.

Exclusion criteria include: i) platelet dysfunction, ii) thrombocytopenia, iii) treatment with corticosteroids, iv) not been able/willing to give informed consent.

All patients were informed about the nature of the study and had to explicitly express willingness to cooperate with the study protocol and follow-up programme and sign an informed consent form. The patient data were anonymized before analysis. None of them refused the PRGF approach and afterwards all expressed satisfaction with the procedure and its outcome. The analysis was performed in accordance with the local institutional review board standards and conformed to the Declaration of Helsinki of 1975 and subsequent modifications.

Surgical protocol

Before surgical treatment, each patient attended a program of professional dental hygiene to have no differences in pre-operative hygiene conditions.

When included in the trial, patients were registered in a computerized clinical file, in order to record information on age, gender, smoking habits, alcohol consumption, systemic pathologies, and the use of any drugs. Also clinical and radiologic evaluation were recorded, with oral and dental parameters: periodontal screening and recording code; conditions of untreatable teeth undergoing extraction (presence of infections, carious processes, or periodontal affection); difficulty of extraction (based on crown integrity, root morphology, space, and patient compliance); and symptoms.

Systemic conditions of diabetic patients were evaluated: usual blood glucose levels and the frequency of glycemic controls; HA1C level; usual blood pressure; pharmacologic therapy; number of years since the initial diagnosis of DM; and prior hospitalization for DM complications.

Two different operators performed the surgery, an experienced surgeon (operator 1) and a less expert surgeon (operator 2) (we randomized the interventions between an expert operator with more than 20 years of experience and a recent graduate dentist and we compared the values seeing that there were no statistically significant differences). The post operative follow ups were carried out by a blind operator who did not know who had performed the extractions and even which side was treated with PRGF and which was not.

Before the surgery, a blood sample of 20 mL was obtained from each patient and prepared as described and standardized according to the technique of Anitua et al [13]. Each 5 mL test tube, containing sodium citrate as an anticoagulant, was centrifuged for 8 minutes at 460 g. After centrifugation, the plasma separated into 2 similar fractions: the upper one containing the superficial fractions from which it was possible to obtain the fibrin membrane and the lower one containing larger numbers of platelets and growth factors. Then, each fraction (PRGF was divided as protocol in two fractions which are two parts of the concentrate) was activated with calcium chloride at a specific and constant ratio of 50 mL for each 1,000 mL of plasma and incubated at 37°C until it coagulated and was ready to be applied.

Alveolar nerve block infiltration was administered with local anesthesia, using 2% mepivacaine, since that molecule does not contain epinephrine; therefore, it was used to prevent restriction of the blood supply. No intraligamentous or intrapapillary infiltrations were performed to prevent interference with the healing process.

Atraumatic bilateral extractions were accomplished without flaps elevation to preserve bone ridges and soft tissue. Surgery was performed on the treatment and control sides at the same time. After extraction the surgeon curetted the socket to remove granulation tissue. Then, a millimeter probe was used to measure the socket diameters (Maximum Mesiodistal [MD] and Buccolingual Extensions [BL]) and the deepest Probing Depth (PD) without forcing of the probe.

PRGF was applied in the socket chosen as the study site, and the membrane was laid above the socket walls. (PRGF membrane: the poor-platelets fraction of the PRGF protocol is commonly known as membrane). After 5 minutes of compression with sterile cotton, bleeding was evaluated as spontaneous, induced by palpation, or absent (we wanted to check for bleeding episodes).

Postoperative recommendations were provided to patients, and no pharmacologic therapy was prescribed. Recourse to antibiotics was considered a negative postoperative parameter, a sign of postoperative complications from infection. Also, use of nonsteroidal anti-inflammatory drugs (NSAIDs) was forbidden to avoid any influence on the healing process that might prevent a fair evaluation of the anti-inflammatory effects of PRGF; 5 patients who reported having taken NSAIDs were excluded from the study.

After the extractions, each patient underwent a precise follow-up program: 4 sessions conducted at 3, 7, 14, and 21 days or until socket closure. Each session included measurements of the 3 variables (MD, BL, and PD) in the study and control sites (with a millimeter probe we measured the PD immediately after extraction to obtain the depth of the post-extraction alveolus and in the subsequent checks for comparisons. The probe was stopped when there was solid gingival tissue).

Because the socket volume (SV) is proportional to the product of the 3 variables (MD, BL, and PD), the residual SV (RSV), ie, the fraction of the post-extraction original cavity still open at each follow-up session (t = 3, 7, 14, and 21 days), was computed as the ratio of (MD _ BL _ SD)t to the value (MD _ BL _ SD)t = 0 , measured after extraction (perfect closure corresponds to RSV = 0.00).

The maturation and quality of regenerating tissues were evaluated using a modified version of the HI of Masse [14]. The modified HI, adapted to estimate socket healing without primary closure, involved 3 scoring levels for each of the 4 parameters considered: tissue color (1 = 100% of gingiva pink; 2 =< 50% of gingiva red, hyperemic, movable; 3 => 50% of gingiva red, hyperemic, movable), color and consistency of the healing tissue (1 = close grained, pink; 2 = soft, red; 3 = fragile, greenish or grayish), suppuration (1 = absent; 2 = absent but pronounced amount of plaque around socket walls; 3 = pronounced), and bleeding (1 = absent; 2 = induced by palpation; 3 = spontaneous). Thus, the scoring scale ranged from 4, corresponding to excellent healing, to 12, indicating severely impaired healing.

Pain was evaluated by the patients using a VAS, which distinguished the study and control sockets, for 7 consecutive days, with day 0 considered the day of extraction, after resolution of the effects of the anesthesia. The patients' general satisfaction was evaluated with a questionnaire administered after extraction. Patients were asked to state any differences noticed in bleeding or pain between the 2 sites and to state which technique they would choose for a future extraction.

Additional control sessions after postoperative day 21 until the achievement of socket epithelialization and the need for antibiotic administration or for surgical re-intervention in cases of alveolitis were considered possible negative postoperative parameters.

Study variables

The primary predictor variable in the trial was treatment group status (study or control socket). The primary outcome variables were socket volume, pain, HI, and postsurgical complications (mainly the need for late follow-up and reoperations). The secondary outcome variables were patient satisfaction, effects of smoking habits and of different value ranges for HAIC, EODS, and glycemia (chronic and preoperative) on socket reduction, and HI. A third category of variables described the anamnesis of the sample (age, gender, smoking habits, HAIC, EODS, chronic and preoperative glycemia, and systemic risk) and the dental characteristics (tooth vitality, caries, periodontal diseases, granuloma, and pain).

Statistical methods

The results included continuous and categorical variables. The former are reported as mean and standard deviation. Nonparametric tests were used: the Wilcoxon signed-rank test for comparisons of 2 correlated samples involving matched pairs and the Mann- Whitney test for comparisons of 2 independent distributions. Categorical variables, reported as count and percentage, were arranged in cross-correlation tables and compared using the c2 test with the Yates correction when all expected values were higher than 5 or the Fisher test. Statistical significance corresponded to a probability less than .05 that differences could be ascribed to chance.

Results

The baseline data of the 58 patients (116 extractions) who met all the inclusion criteria and satisfied all the requirements are listed in Table 1.

Table 2 presents the results of their preoperative evaluations. The statistical analysis of the preoperative evaluations show comparable conditions in treated and control sides, so that healing of the sites belonging to the two groups occurred independently from preoperative conditions.

Important general result, for both study and control sites was the complete absence of any complications from surgery, such as excessive bleeding, infection, or alveolar osteitis; a consistently observed HI of at least 8; and complete socket closure at the 21-day checkup for most of patients.

Results concerning the healing of the sockets and their progressive decreases in volume are presented in Tables 3 and Table 4.

Table 1: Patients' baseline characteristics.

Baseline characteristics	Patients n = 58
Female %	58%
Age (yr)	67.2 ±12.8
Years since diagnosis	19.8 ±7.76
Body mass index (kg/m2)	29.3 ±4.7
Smoking (%)	62.50%
Glycemia preoperative: 1=<180 mg/dL 2=180-240 mg/dL 3=>240 mg/dL	57%=1 36%=2 7%=3
Glycated hemoglobin (%)	8.4 ±1.6
Retinopathy %	71%
Neuropathy, %	50%
Nephropathy %	29%
Vasculopathy %	55%
Cardiopathy, %	72%
End Organ Disease : low medium hi	7% 22% 71%

Table 2: Preoperative evaluation.

	PRGF	CTRL	P value
Tooth vitality			
Necrotic	31.60%	31.60%	0.99
Devitalized	21%	15.80%	
Vital	47.40%	52.60%	
Caries	36.80%	26.30%	0.49
Periodontal disease	63.20%	84.20%	0.27
Apical granuloma with abscesses	78.90%	42.10%	0.045
Difficulty of extraction			
Low	63.20%	84.20%	0.27
Medium	36.80%	15.80%	

Abbreviations: CTRL = Control; PRGF = Plasma-rich growth factor.

Table 3: Results for healing index.

	Day 3		Day 7		Day 14		Day 21	
	PRGF	CTRL	PRGF	CTRL	PRGF	CTRL	PRGF	CTRL
Healing Index Score (4-12)	5.0 ±1.2 (4-9)	5.9± 1.5 (4-11)	4.3± 0.5 (4-6)	5.0± 1.1 (4-9)	4.1± 0.4 (4-6)	4.4± 0.8 (4-8)	4.0±0.1 (4-5)	4.1±0.3 (4-6)
p	<0.0001*		<0.0001*		<0.002*		<0.16	
Scores=4, %	30 (51.7%)	10 (17.2%)	46 (79.3%)	24 (41.4%)	52 (89.7%)	43 (74.1%)	57 (98.3%)	56 (96.6%)
p	0.0002*		<0.0001*		0.05*		>0.99	

Abbreviations: CTRL = Control; PRGF = Plasma-rich growth factor; * = Statistically significant (P < .05)

Table 4: Results for residual socket volume.

	Day 3		Day 7		Day 14		Day 21	
	PRGF	**CTRL**	**PRGF**	**CTRL**	**PRGF**	**CTRL**	**PRGF**	**CTRL**
Residual Socket Volume (0.00-1.00)	0.23± (0.18)	0.35 ±(0.2)	0.08 ±(0.08)	0.14 ±(0.12)	0.02 ±(0.03)	0.05 ±(0.07)	0.005 ±(0.01)	0.01 ±(0.03)
p	<0.0001*		<0.0001*		0.0002*		0.005*	
Socket Closure, %	3 (5.2%)	0.00%	17.20%	13.80%	46.60%	39.70%	86.20%	77.60%
p	0.24		0.8		0.57		0.33	

Abbreviations: CTRL = Control; PRGF = Plasma-rich growth factor. * = Statistically significant (P < .05).

Comparisons between values relative to the study and control sides showed better healing and faster socket closure for the side treated with PRGF. At 3, 7 and 14 days was statistically significant the difference between the healing site PRGF and control, with a much higher quality healing for the PRGF group.

Table 4 shows that PRGF brings an healing improvement as an increase in wound closure speed statistically significant in all 4 follow ups ($p < 0.0001$ at 3 days, $p < 0.0001$ at 7 days, $p = 0.0002$ at 14 days, $p = 0.005$ at 21 days).

Figure 1 highlights the progressive evolution of wound healing toward complete recovery (RSV = 0), which was almost entirely achieved for the study and control sides by the end of the third week after extraction; at the same time, the graph enhances the statistically significantly better performance of the side treated with PRGF in the 14 days after the extraction.

The VAS score was nearly equal for the 2 sides, decreasing to 0 after 4 days for the side treated with PRGF and after 6 days for the control side.

The next step of the investigation was to evaluate if there are influences of patient characteristics on outcomes; for every parameter, the sample was subdivided into 2 subgroups, corresponding to opposite conditions. Socket reduction and HI were similar for an EODS lower than 3 versus higher than 3, for smokers versus nonsmokers, and for the percentage of HAIC lower than 8% versus higher than 8%, with the PRGF side consistently leading the control side.

Glycemia values higher than 240 mg/dL were associated with a consistent increase in HI and RSV, which was slightly quenched by PRGF treatment on the study side. The results of the questionnaire on patient satisfaction were 100% in favor of treatment with PRGF.

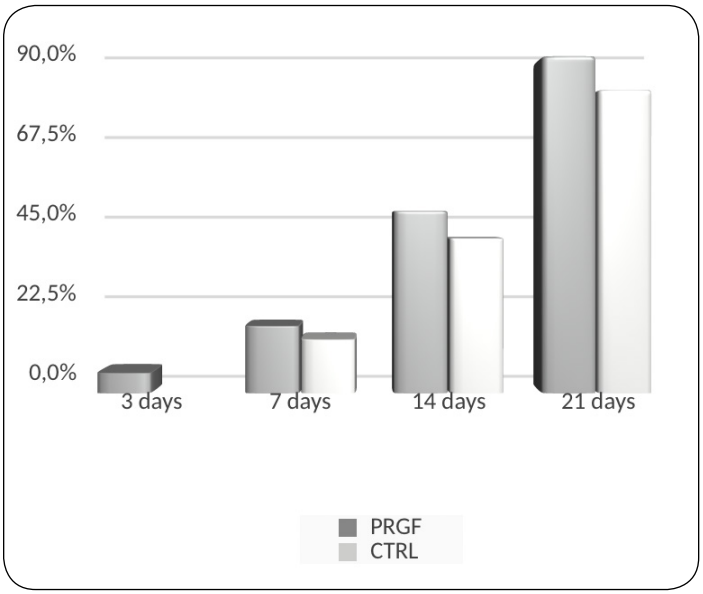

Figure 1: % of RSV=0 (i.e. complete socket closure)
Abbreviations: CTRL, control; PRGF, plasma-rich growth factor. * Statistically significant (P < .05).

From the data shown on Figure 2 there are no statistically significant differences between the 2 operators both as regards the monoradicular ($p = 0.89$) and the multi-rooted teeth ($p = 12.48$), showing that use of PRGF is independent of the operational capacity of the individual operator.

Discussion

PRGF has been used in oral surgery [15], also with other biomaterials, and it has been seen to have among the others antibacterial effects, decrease postoperative aedema, pain and swelling, and decrease postoperative complications [16,17]. It has been used also in patients with bleeding disorders, proving that PRGF works as well as fibrin glue as a local haemostatic [18].

In fact, the growth factors in PRGF constitute a supplementary source of stimulation for physiologic deficits typical in diabetic patients and promote angiogenesis and bone and mucosal wound healing [19,20].

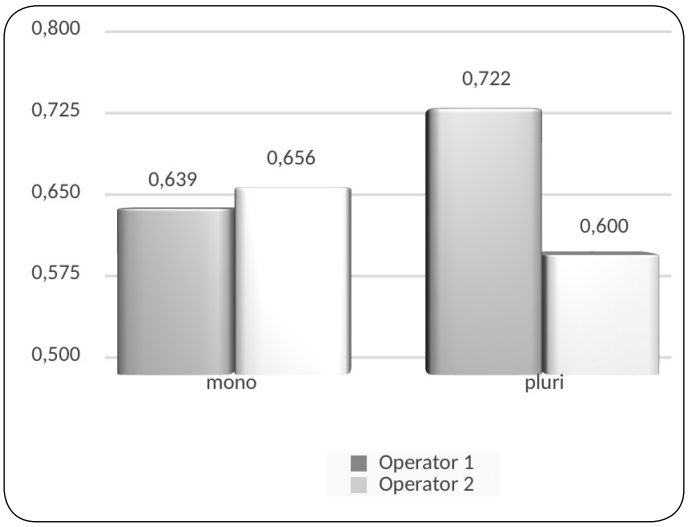

Figure 2: Comparison between the operator 1 and operator 2 of RSV in PRGF site and control site after 3 days.

The present study was designed to confirm the validity of PRGF treatment for patients affected by DM: a split-mouth trial to monitor outcomes and possible discriminant factors. This study demonstrate that the application of PRGF after tooth extraction in diabetic persons can results in healthier and earlier recovery by accelerating healing and sockets closure; also can generally improve clinical conditions.

The adjusted HI showed statistically significantly better hemostasis and epithelialization for the PRGF treated side compared with the control side from extraction with a simultaneously greater decrease in the remaining socket cavity.

Poor wound healing is typical in diabetic patients and is characterized by a decrease in the amount of wound collagen and lowered tensile strength. The molecular mechanisms involved in chronic wounds are under study.

Biology attempts to explain the mechanism involved in chronic wound healing through cellular injury. Keratinocytes are the first cells to respond to injury; they are programmed to maintain skin integrity based on their specific attachment to extracellular matrix and vice versa. The absence of normal migration and proliferation of cells caused by failure of Keratinocytes activation during wound healing results in non-healing [21].

Platelet-rich fibrin membrane releases various growth factors such as PDGF, TGF-β, and VEGF slowly and its supportive fibrin matrix plays an important role in its therapeutic effects. The potential of platelet-rich membrane in accelerating regeneration has led to its application in various regenerative treatments like sinus floor elevation, ridge augmentation, socket preservation, root coverage, intrabony defects, and furcation defects. It has been shown that fibrin membranes could be better scaffolds for proliferation of periosteal and osseous cells than collagen membranes in vitro. The membranes that are used in regenerative procedures should have strong mechanical properties to protect blood clot and healing process. As a scaffold, they provide better support against forces from infiltrating cells and adjacent tissues [22].

The rapid epithelialization triggered by the PRGF avoided the occurrence of alveolitis, which is a typical complication after tooth extraction in patients with diabetes.

Also, all patients were very satisfied with the results of the PRGF treatment; all declared their intention to repeat the treatment for any future dental interventions.

Different values for EODS, HAIC, and smoking habits did not have any effects on the post-extraction evolution: in all cases, the PRGF side recovered better than the control side. As expected, there was an indication that glycemia values of at least 240 mg/dL resulted in a less satisfactory post-extraction evolution in both sites and that this situation was improved to some extent by the application of PRGF. As regards smoking we had no statistically significant difference in healing between smokers and non-smokers; this could be due to a protective factor of the PRGF but further studies are needed to confirm it.

As a practice in our hospital, antibiotic therapy is not administered to diabetic patients unless there are concomitant pathologies that require antibiotic therapy or prophylaxis. We had no need to give antibiotic therapy for PRGF-treated or untreated sites. We did not prescribe NSAID because it could affect the results but we recommended paracetamol therapy as needed.

Conclusions

PRGF application after extraction improved the healing process in diabetic patients by accelerating socket closure (epithelialization) and tissue maturation, proving the association between PRGF use and improved wound healing in diabetic patients.

Declaration

Authorship Contribution

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before.

Disclosure of Conflict of Interest

No conflict of interest was declared by the authors.

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Gratis

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