Effect of concentrated growth factors on quality of life of patients undergoing implant therapy: a cohort study

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Pain, bad taste, and impaired daily activity after implant therapy are common sequelae. Concentrated growth factors (CGF) are a platelet concentrate with a favourable effect on wound healing, but there is still no evidence regarding its potential benefits for reducing postoperative pain and symptoms. Therefore, aim of this prospective comparative study was to determine the effect of CGF on quality of life (QoL) of patients after implant therapy. Fifty-two consecutive patients with one missing mandibular molar were included in the study and alternatively assigned to two groups. Control group received standard implant treatment, and test group received CGF associated with implants. Standard periapical radiographs were taken before and after procedure. Post-operative care consisted of 0.2% chlorhexidine digluconate solution twice daily for 10 days. A QoL questionnaire (OHIP-14) for bad taste, pain and limitation in daily activities was filled and returned one week post-operatively. Daily pain was also assessed through Visual Analogue Scale (VAS) on a 1-100 scale. Parametric test (chi-square) was performed to compare the results of the questionnaire between the two groups using STATA statistical software. All patients correctly filled and returned the questionnaire. Significantly higher proportions of patients of test group reported no bad taste, pain, and limited activity, (24/26, 13/26, and 25/26, respectively) respect to control. Postoperative pain with VAS score was significantly lower in the test group on day 1, 2, and 3 as compared to control. CGF positively influenced QoL when associated with implant rehabilitation of mandibular molars, minimizing post-operative discomfort.

Oral health is considered as an important indicator of overall health, well-being and QoL. The disease of oral cavity has become a global burden and is considered as one of the most common non-communicable diseases (NCDs) that affect people throughout their lifetime, causing pain, discomfort, disfigurement and even death. According to the 2016 WHO survey, oral diseases affected at least 3.58 billion people worldwide, with caries of the permanent teeth being the most prevalent of all conditions assessed (1). Globally, it is estimated that 2.4 billion people suffer from caries of permanent teeth and 486 million children suffer from caries of primary teeth 1. Dental caries and periodontal diseases are major causes of tooth loss. Severe tooth loss and edentulous is one of the leading ten causes of Years Lived with Disability (YLD) in some high-income countries due to their aging populations (2).

Key words: pain, bad taste, ageusia, dysgeusia, Concentrated Growth Factor, CGF, quality of life, QoL, Patient Reported Outcome Measures, PROM

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One of the common ways to tackle tooth loss by the dentists and by the patients is through the placement of dental implants. According to a cross-sectional study among 425 partially edentulous patients attending a University Dental Hospital in Peradeniya, India, between 2015 and 2016, 76.2% of participants declared that they were aware that missing teeth should be replaced by prostheses, and 32.9% were aware of the use of implant-supported prostheses (3). The success of dental implants is enhanced by using different biomaterials and/or platelet concentrates. Platelet concentrates like Platelet-rich Fibrin (PRF) and Concentrated Growth Factors (CGF) are commonly used for regenerative procedures and enhanced wound healing of hard and soft tissues (4-6). Platelet concentrates facilitate natural biologic mechanism in tissue repair that include cell proliferation, chemotaxis, differentiation and matrix synthesis (5). Previous studies have shown that platelet-derived growth factors have a modulatory role in the inflammatory process because they are found immediately few minutes after injury and in the first day after injury (6,7).

Such modulation of inflammation may positively affect postoperative pain and symptoms, which often cause discomfort to patients, and lead to a better acceptance of the treatment and improved satisfaction. Patient reported outcome measures (PROMs) assess the impact of oral health on patients and measures the satisfaction with the oral health status (OHRQoL) (8-10). In 21st century, dentistry has advanced and consideration of such factors that influences the QoL should be routinely measured. Leao and Sheiham (1996) developed a measure that determine the dental Impact on daily living (11) and Adulyanon and Sheiham (1997) developed oral impacts on daily performances (12). The outcome measure of CGF on patient's QoL after implant therapy is rare, as there were no reliable tools that have passed acceptability, feasibility, validity, reliability, precision, sensitivity and responsiveness. CGF has been used for hard and soft tissue regeneration in socket preservation, wound healing and implant therapy. A recent pain research on PDGF-BB mediated nociceptive hyper-excitability and elevates pain (13), but how this is clinically significant is questionable. Therefore, the objective of this study was to determine the post-operative effect of CGF on patients' QoL (pain, daily activity, and taste) after implant therapy.

MATERIALS AND METHODS

Study Design and Patient Selection

The study protocol was approved by the Institutional Review Board of the IRCCS Orthopedic Institute Galeazzi in Milan, Italy. All patients signed an informed consent form before the procedure and agreed to be part of the study performed in accordance with the Good Clinical Practice and the Declaration of Helsinki. The QoL questionnaire was administered routinely, following the guidelines of the department. A Visual Analogue Scale (VAS) and OHIP-14 questionnaire was used. The recruitment of patients started in December 2018 and ended in December 2019. Patients who met the inclusion criteria and were willing to attend scheduled follow-up controls and answer the questionnaire for following weeks were included were consecutively enrolled and alternatively assigned to two groups, i.e., Control Group: Implants only and Test Group: Implants with the adjunct of CGF.

Inclusion criteria

Patients ASA-1 or ASA-2, following the classification proposed by the American Association of anaesthesiologists. Patients with one tooth edentulism in the posterior area of the mandible (molars), no previous regenerative procedures in the site of intervention, non-smokers, former smokers, or smoking less than five cigarettes a day.

Exclusion criteria

The patients suffering from systemic diseases that affect bone healing, such as uncontrolled diabetes, osteoporosis, HIV, etc., patients who are pregnant and have lactation, and those having previous or current radiation or immunosuppressive therapy were excluded from the study.

Pre-operative treatment

Each patient received an oral hygiene session the day before surgery and instructions on food and oral hygiene at home. Each patient underwent pre-operative CBCT scanning for diagnostic purpose: the distance from the

crest to the alveolar nerve canal and the width of the ridge was measured.

Autologous CGF was prepared from fresh venous blood of patients. The venous blood samples were taken into 2 sterile 10 ml tubes without anticoagulants. The samples were immediately centrifuged with CGF centrifuge machine (Medifuge, Silfradent, Italy) using the manufacturer's instruction: 30 sec acceleration, 2' /2700 rpm, 4' /2400 rpm, 4' /2700 rpm, 3' /3000 rpm, 36" sec deceleration and stop (14). The CGF layers were mechanically separated using sterile scissors.

Surgical procedure

One experienced surgeon (S.T.) performed all interventions. The day of surgery 2g of amoxicillin (1g azithromycin in case of patients allergic to penicillin) was given prior to implant placement. Standard local anesthesia was provided (4% articaine with 1:100,000 adrenaline). Dental implants (Alpha-Bio Tec, Kiryat Arye, Petach Tikva, Israel) were positioned using the technique recommended by the manufacturer. The length of the implant was between 10 to 11.5mm, maintaining a safe distance of 2.5/3mm from the alveolar nerve and the diameter was 4.2. In Group 2, the implant surface was embedded with CGF liquid component and a clot of CGF was positioned over the surgical screw before suturing (14). A periapical radiograph was done soon after surgery in order to verify the correct positioning of the implant, and the flap was sutured with interrupted sutures 5.0 (ETHILON®, Ethicon, Inc, Johnson & Johnson, Piscataway, NJ, United States).

Post-operative care

Post-operative care consisted of 0.2% chlorhexidine digluconate solution twice a day for 10 days, and antibiotic therapy (15). After one week the suture was removed and the questionnaire was withdrawn.

The patients were followed-up for 6 months after implant placement. Supragingival/mucosal mechanical debridement and reinforcement of oral hygiene were performed professionally during postoperative period. When necessary, localized subgingival/mucosal instrumentation was done, except for the area of surgery.

Patient-reported outcome measures (PROMs)

Pain, bad taste and limited activity were the primary outcomes. Postoperative limitations in function (mouth opening, chewing, speaking, sleeping, daily routine, and work) as well as pain and the presence of other symptoms like bad taste/breath, nausea, swelling, bleeding, were evaluated by means of a questionnaire, previously adopted in other studies. Pain was specifically self-assessed daily through a 0-100 VAS scale, where 0=no pain and 100=the worst conceivable pain. For other symptoms and functional activities, the answers were based on a 5-point Likert-type scale, ranging from 0 (none, not at all) to 4 (very much, very often).

Statistical analysis

A descriptive statistics and significance for pain, bad taste and limited activity was undertaken for the first 7 days postoperatively. Statistical analysis was carried out using STATA IC (USA 2020 INC). Fisher's exact test was used to statistically assess the between-group difference for the questionnaire results. Variables related to function, pain and symptoms on each postoperative day were compared. Regarding the patient's experience of pain, the D'Agostino and Pearsons omnibus test was done to evaluate normality of the distribution of VAS scores. The Friedman test was used to evaluate within-group differences in pain scores in the first 7 days. The between-group difference for pain on each postoperative day was evaluated with the Mann-Whitney test. The patient was considered as the unit of analysis. Significance level was set at P=0.05.

RESULTS

The mean age was 55 (range 45-65) years, with equal number of males and females (n=26). Twenty-six patients were included in each group. In all patients, the distance from the crest to the alveolar nerve canal varied between 12.5 mm and 15 mm and the diameter of the ridge was between 5.5 to 6 mm.

Table I reports the post-operative data for control (implants) and test group (implants with CGF).

Among test group, 92.3% patients had better experience for bad taste on the first day in comparison to control group ($P<0.001$). The samples who responded "Not at all" among test group were 24/26 and in the control group were 4/26. The significance continued in the following Day 2, Day 3 and Day 4 ($p<0.001$). The pain experienced by patients of

the test group was significantly less in comparison to control on the first day and continued up to day 4 ($p<0.001$). Group using CGF experienced less activity limitations than control group ($p<0.001$).

Fig. 1 shows the post-operative VAS score for self-assessed pain between Group I (Implants) and Group II (Implants with CGF). The post-operative level of pain on day 1 was significantly less in the test group compared to control ($p<0.001$). The pain decreased in both groups during the first week and the difference in favour of the CGF group was significant till day 4.

DISCUSSION

Wound healing after implant surgery is related to soft tissue attachment and hard tissue/implant osseointegration (16,17). The factors like implant surface preparations, designs and mechanics influences tissues and cells while healing. The healing experiences for the first two post-surgical weeks considered to have minor differences. Previous studies have demonstrated significant differences of healing during first 3 days (18). Healing following implant installation has different response from the bone as compared to normal extraction histologically but clinically there was difference found in post-operative wound healing among patients with implant therapy. This suggests the impact of clinical outcomes i.e. after surgery on QoL. Therefore, it becomes prudent to rule out the impact of CGF on PROM's/QoL. The early phase of healing involves changes in the marginal bone level around implants (19). Initially, there is marginal soft tissue adaptation that enables physical seal between oral environment and the bone surrounding implants (16,17). Since, CGF is thought to have very good soft tissue healing properties, it facilitates marginal soft tissue adaptation at faster rate as compared to traditional approach (20). It prevents peri-implantitis and implant failure, thereby avoiding post-operative complications and symptoms (21).

Our study results have found that, the significant differences during first 4 days for pain. The patient reported outcome measures (PROM's) variables like bad taste, pain and limited activity was better

Table I. *Post-operative data for Implants and Implants with CGF.*

Symptom	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
	Implant	Implant + CGF	Implant	Implant + CGF	Implant	Implant + CGF	Implant	Implant + CGF	Implant	Implant + CGF	Implants	Implants + CGF	Implants	Implants + CGF
Bad Taste														
Not at all	4(15.38)	24 (92.30)	10(38.46)	26 (100)	14(53.84)	26 (100)	18(69.23)	26 (100)	20(76.92)	26 (100)	20(76.92)	26 (100)	20(76.92)	26 (100)
Almost No	12(46.15)	1 (3.84)	14(53.84)	0 (0.0)	9(34.61)	0 (0.0)	6(23.07)	0 (0.0)	4(15.38)	0 (0.0)	4(15.38)	0 (0.0)	4(15.38)	0 (0.0)
Sometimes	6(23.07)	0 (0.0)	-	-	1(3.84)	0 (0.0)	-	-	-	-	-	-	2(7.69)	0 (0.0)
Quite Often	4(15.38)	0 (0.0)	2(7.69)	0 (0.0)	-	-	2(7.69)	0 (0.0)	-	-	2(7.69)	0 (0.0)	-	-
Very Often	0(0.0)	1 (3.84)	-	-	2 (7.69)	0 (0.0)	-	-	2(7.69)	-	-	-	-	-
Pain														
Not at all	5(19.23)	13 (50.0)	10 (38.46)	21 (80.76)	14 (53.84)	24 (92.30)	19 (73.07)	25 (96.15)	23 (88.46)	26 (100.0)	23 (88.46)	26 (100.0)	23 (88.46)	26 (100.0)
Almost No	3 (11.53)	9 (34.61)	3 (11.53)	4 (15.38)	4 (15.38)	2 (7.69)	5 (19.23)	1 (3.84)	2 (7.69)	0 (0.0)	2 (7.69)	0 (0.0)	2 (7.69)	0 (0.0)
Sometimes	8 (30.76)	4 (15.38)	6 (23.07)	1 (3.84)	6 (23.07)	0 (0.0)	-	-	-	-	-	-	1(3.84)	0 (0.0)
Quite Often	4 (15.38)	0 (0.0)	3 (11.53)	0 (0.0)	1 (3.84)	0 (0.0)	1 (3.84)	0 (0.0)	-	-	1 (3.84)	0 (0.0)	-	-
Very Often	6 (23.07)	0 (0.0)	4 (15.38)	0 (0.0)	1 (3.84)	0 (0.0)	1 (3.84)	0 (0.0)	1 (3.84)	0 (0.0)	-	-	-	-
Limited Activity														
Not at all	9 (34.61)	25 (96.51)	14 (53.84)	26 (100)	18 (69.23)	26 (100)	22 (84.61)	26 (100)	23 (88.46)	26 (100)	23 (88.46)	26 (100)	23 (88.46)	26 (100)
Almost No	6 (23.07)	1 (3.84)	7 (26.92)	0 (0.0)	6 (23.07)	0 (0.0)	3 (11.53)	0 (0.0)	2 (7.69)	0 (0.0)	2 (7.69)	0 (0.0)	2 (7.69)	0 (0.0)
Sometimes	6 (23.07)	0 (0.0)	4 (15.38)	0 (0.0)	1 (3.84)	0 (0.0)	-	-	-	-	-	-	1 (3.84)	0 (0.0)
Quite Often	3 (11.53)	0 (0.0)	-	-	-	-	-	-	-	-	1 (3.84)	0 (0.0)	-	-
Very Often	2 (7.69)	0 (0.0)	1 (3.84)	0 (0.0)	1 (3.84)	0 (0.0)	1 (3.84)	0 (0.0)	1 (3.84)	0 (0.0)	-	-	-	-

Data are reported as frequency, and percentages are between parentheses. Significant differences between groups are represented by shaded cells (first 4 days postsurgery).

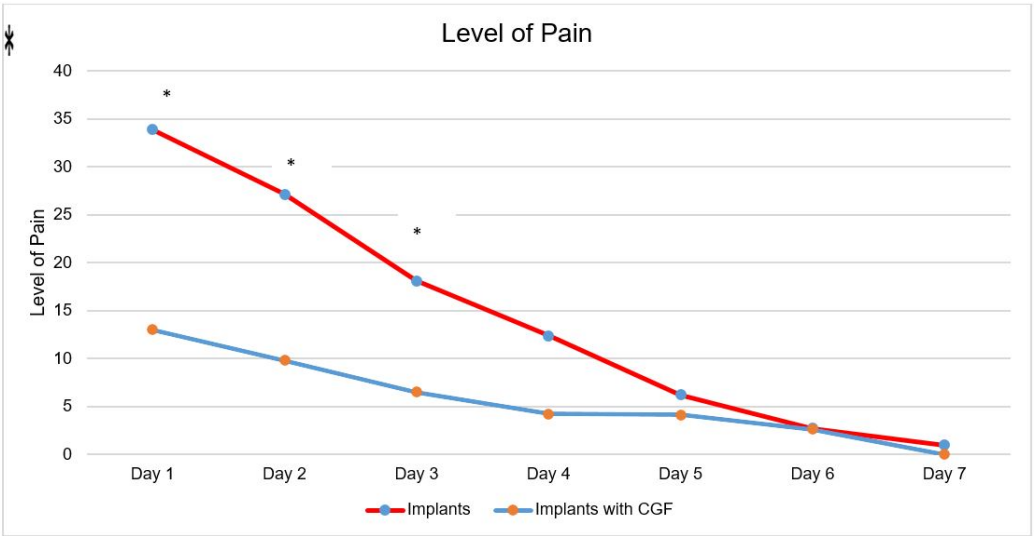

Fig. 1. *Post-operative level of pain between control and test group.*

in patients who had implants along with CGF (Table 1). The pain (NRS scale = 0-100) was less among implants with CGF group as compared to control group (Figure 1). The immediate implant placement with CGF has proven benefits and facilitates wound healing, lesser pain experience and improved QoL. This was evidenced from the previous studies (20,22). The possible reason because application of CGF to implant surfaces enables faster healing of the bone surrounding the implant and enhancement of bone-implant contact (BIC). Mohamed et.al (2019) reported better bone-implant contact (BIC) with CGF (23,24). Another possible explanation of relieving pain by CGF is that, nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), substance P (SP) and glutamate are better neutralised by the growth factors present in CGF (25). But evidence for this can be added with further well designed molecular and clinical studies.

Fuerst et al. in 2003 determined the effects of platelet-released growth factors on bone-to-implant contact (BIC) in minipig cortical bone. The authors concluded that, Growth factors and other molecules released upon activation of platelet-rich plasma cells can enhance implant anchorage in cortical bone (26). Poor bone-to-implant contact can occur when fibrous tissue encapsulates the body of the implant, which is then layered with bone. Radiographically the implant appears as if the bone levels are normal, and clinically the implant may exhibit no signs of mobility; however, the patient still experiences dental pain. This can be evident especially when the implant is put into function with a healing abutment or loaded with a crown (27).

Previous study is limited to CGF role in pain among third molar extractions. Torul D (2020) in a single centre prospective randomised trial aimed to investigate the effects of CGF and PRF on pain, edema and trismus among third molar extraction (28). Surprisingly, no positive effects were found in A-PRF and CGF on pain, edema, and trismus after third molar surgery. During interpretation of results, caution should be followed while concluding because it is best practice to assess internal and external validity of the therapy studies.

Osseoperception (sensation) is affected when implants are loaded mechanically. The phenomenon behind the sensation loss in osseointegrated implants and natural teeth is different. Natural teeth have periodontal mechanoreceptors that are attached to the tooth surface and these mechanoreceptors are lost when implants are placed (29). Patients usually experience severe pain within 24hours of surgery (30) and this finding was correlated with our study (Figure 1) in implant cases. Hashem et al.'s (2005) study also demonstrated similar findings (18). The

behaviour pattern of pain after implant surgery and tooth extraction was described by Yao et al in 2014 (30). It was reported; irrespective of type of procedures and techniques, pain decreases after 3rd day (30). One of the factors for post-operative pain was the duration of the surgery and Yao et al. found that there was significant differences between shorter (<60 min) and longer (>60 min) duration surgeries. Not surprisingly, procedures below 60 min yielded significantly better healing outcomes and better reported patient experience (30). Some studies have suggested, however, that a lack of keratinized tissue can lead to pain post implant placement and/or restoration (27). We found better pain perception among implant with CGF group, because CGF forms better soft tissue healing and formation of keratinised tissue around the implant (20, 31).

Pain can be nociceptive, inflammatory and neuropathic pain. Typically, pain after implant placement may be due to nociceptive and inflammatory causes (32). The inflammatory process is a complex biological response to tissue injury by normally functioning vascular and somatosensory nervous systems. It is a protective response intended to eliminate the initial cause of the injury and to foster healing and repair of the injured part. The incidence of nerve injury after dental surgical procedures, including third-molar extractions and placement of implants, is higher than that commonly believed (possibly up to 40 percent), and, for the latter, the incidence is increasing (33).

Platelet-derived components like Concentrate growth factor (CGF) have the ability to minimize the inflammatory responses after surgery, positively affecting the postoperative QoL of the patients. The suppression of IL-1, a pro-inflammatory chemokine could produce the anti-inflammatory effect. Considering these aspects, it is possible to consider that the properties of CGF had a main role in significantly reducing the most common symptoms as pain and swelling as observed in patients treated in this study. A previous study investigating QoL after implant surgery suggested that the application of microsurgical techniques for soft tissues may have an effect in improving the patients' postoperative QoL (24). But some studies did not find similar results and concluded no somatosensory alterations was seen after implant placement (13 ,34).

The functional and neurobiological properties of bad taste was demonstrated by Schier et.al in 2019 (35). Taste signals contribute to several different functions, which can be categorized into three primary domains. Firstly, sensory-discriminative, secondly Taste-guided consummatory behaviours and thirdly physiological reflexes. The taste innervation in the anterior 2/3rd of the tongue is supplied by the chorda tympani and posterior third by the lingual branch of glossopharyngeal nerve. Ageusia (Bad taste) or dysgeusia (alteration of taste), a common symptom experienced following extraction of the tooth and implant surgery. This may be due to dry socket, local anaesthetics, nerve damage, infected implant or decreased salivary flow rate (36,37). Usually, it occurs after 2 to 4 days after the oral surgical procedure (37). Our study results have found that, the taste altered during first two days after implant surgery. This altered taste or bad taste was not found among implants with CGF group (Table 1). The possible hypothesis can be explained as related to better healing stimulation with CGF. When implants get infected, they may associate with smell and bad taste. This is usually detected when the taste does not wade off after brushing or rinsing with mouthwash.

The results should be interpreted carefully as the VAS pain score is quite subjective and therefore it is suggested in future studies to include other pain scales like Mcgill Pain Score and brief pain questionnaire. The future studies with baseline parameters for PROM's would add clinical advantage. One of the confounding factors in pain assessment is the anxiety and reported to be a causative factor for post-operative pain on post implant insertion (38). Other include poor bone-implant contact, implant surface preparations, designs and mechanics influence could influence post-operative complication symptoms.

In conclusion, there was improved performance regarding post-operative discomfort among patients treated with CGF. Anti-inflammatory and antibacterial effect of CGF can modulate the healing process that enable soft and hard tissue regeneration. This may prevent pain, bad taste and limited activity during early postoperative healing.

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