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Effect of plasma rich in growth factors on quality of life following mandibular third molar removal: a double-blind randomized controlled trial [Au?1]

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Abstract

The objective of this study was to investigate the effect of plasma rich in growth factors (PRGF) on patient- and clinician-reported outcomes following mandibular third molar removal. Seventy-four patients requiring surgical removal of a unilateral impacted third molar under local anaesthesia were recruited into the study. PRGF was prepared for all patients irrespective of study arm allocation. Reviews were conducted 3 days (T1) and 7 days (T2) postoperatively. Primary outcome measures were pain (numerical rating scale, NRS), OHIP-14, and postoperative symptom severity scale (PoSSe) data. Secondary outcome measures including mouth opening, dry socket, socket healing, and analgesic consumption were also explored [Au?2]. The statistical

analysis was performed using analysis of covariance and the χ^2 test. NRS pain scores were higher in the PRGF group at T1, demonstrating borderline significance (MD 1.0 [Au?3]; $P = 0.06$), with no difference at T2. PoSSe scores did not differ between the groups, with the exception of the 'interference with daily activities' subscale at T1, where PRGF group patients scored 1.2 units higher ($P = 0.02$). OHIP-14 scores demonstrated a 25% increased likelihood [Au?4] of PRGF patients reporting discomfort on eating at T1 ($P = 0.02$), with no statistical significance at T2. Secondary outcomes did not differ between the groups. No difference in clinical or quality of life outcomes was observed for patients receiving adjunctive PRGF in third molar sockets.

Keywords: third molar, wisdom teeth, platelet-rich plasma, quality of life, platelet-rich fibrin, ~~blood concentrates~~ plasma [Au?5], randomized controlled trial

Introduction

Third molar surgery accounts for the vast majority of oral surgery procedures performed worldwide[1], and is one of the most popular research models for testing novel analgesics and various other interventions[2]. The impact of third molar surgery on quality of life (QoL) is well documented, with many patients experiencing deterioration in QoL for up to 1 week postoperatively[3,4].

There has been a surge in interest in the regenerative properties of autologous platelet concentrates (APCs) in recent years, with a huge body of evidence available in support of their capacity to promote osseous and soft tissue regeneration through

the physiological processes of platelet activation and subsequent growth factor release. In fact, APCs have transformed many areas of healthcare and are now considered an essential component of the surgical milieu. Authors of a recent Cochrane review included adjunctive APC use in third molar surgery as a distinct surgical technique for the first time, with equivocal results[5]. Despite the considerable volume of published studies investigating the adjunctive use of APCs in third molar sockets, it appears that no study has yet explored QoL outcomes in this cohort.

Identifying this knowledge gap in the literature, a randomized controlled trial (RCT) was designed with two aims in mind: (1) to determine whether the adjunctive use of plasma rich in growth factors (PRGF) in mandibular third molar sockets influences QoL during the immediate postoperative week; (2) to determine whether the adjunctive use of PRGF in mandibular third molar sockets influences postoperative clinical outcomes.

Materials and methods

[Au?6]

Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals. Informed consent was given by all participants. The study was conducted at Cork University Dental School and Hospital, Republic of Ireland.

This study took the form of a prospective, double-blind randomized controlled clinical trial using a parallel-group design, and was conducted during the period

November 2019 to November 2020 inclusive. The 2010 CONSORT statement was applied in the reporting of this study.

The outcome of pain was selected for the purpose of sample size calculation, as pain is one of the most common patient complaints following third molar surgery, with a significant impact on QoL[1]. A sample size of 33 patients in both study arms was calculated to have 80% power to detect a mean difference in the pain numerical rating scale (NRS) score of 1.5 ± 2 using a Wilcoxon (Mann–Whitney) rank-sum test with a 0.05 two-sided significance level. To account for anticipated attrition of 12%, a target sample size of 74 patients was agreed.

Eligibility to participate in the study was based on the following inclusion criteria: age 18–40 years, American Society of Anaesthesiologists (ASA) class 1 or 2, impacted mandibular third molar requiring surgical removal, no pre-existing temporomandibular joint disorder or other chronic pain condition, and willing to travel for follow-up at 1 week postoperatively. Patients were excluded in the following circumstances: pregnant or breastfeeding, immunosuppression, known haematological disorder/coagulopathy, current or previous bisphosphonate therapy, or history of radiotherapy to the jaws.

The research questions were investigated using the following primary outcomes: NRS pain score (from no pain '0' to worst possible pain '10'), 14-item Oral Health Impact Profile (OHIP-14) score, and postoperative symptom severity (PoSSe) score [Au?7]. OHIP-14 total scores range from 0-56, with higher scores implying a negative impact on QoL. Each of the fifteen questions in the PoSSe questionnaire attracts a score ranging from 0 to a value that varies with each question. By adding the scores for all questions together, a total score ranging from 0 (no impact on QoL) to 100 (maximum impact on QoL) is reached. Secondary outcomes

included mouth opening in millimetres (maximum inter-incisal opening, MIO), dry socket (alveolar osteitis), socket healing (soft tissue healing assessed using a modification of the Landry healing index[6]), and analgesic consumption [Au?7].

All patients enrolled into the study presented to the oral surgery outpatient department at Cork University Dental School and Hospital on the day of treatment (T0), where informed consent was obtained. Each patient was asked to complete preoperative OHIP-14 and PoSSe questionnaires. The baseline NRS pain score and MIO, measured using a disposable plastic ruler, were recorded by a single clinician.

Patient blinding was achieved by obtaining blood from all participants irrespective of study arm allocation. For each patient, blood was collected into four 9-ml tubes containing 3.8% sodium citrate and centrifuged at 580 *g* for 8 minutes, according to the Endoret (BTI Biotechnology Institute, Vitoria, Álava, Spain) protocol ([Au?8]). Platelet-rich fraction 2 was selectively extracted using the plasma transfer device and transferred to a glass dish, where calcium chloride activator was added (2 units per millilitre of fraction 2). The dish was placed immediately in the Plasmaterm H oven (BTI Biotechnology Institute, Vitoria, Álava, Spain) ([Au?9]) and heated at 37°C for 8–10 minutes until a jelly-like 'clot' was formed.

All 74 patients underwent surgical removal of a single impacted mandibular third molar performed by one of two experienced oral surgeons. Local anaesthesia was administered using 2% lidocaine [Au?10] with 1:80,000 adrenaline via inferior alveolar nerve block and long buccal infiltration. Access to the tooth was achieved by raising a buccal envelope-type full-thickness mucoperiosteal flap. Bone removal and/or tooth/root sectioning were performed where indicated, using a bur in a surgical hand-piece with copious saline irrigation, and the tooth was delivered using elevators. Curettage of the socket was performed to remove debris, and the socket was flushed

with saline before wound closure using 4–0 Vicryl Rapide simple interrupted sutures. In all cases, details of the procedure were recorded by the operating surgeon on a data collection sheet: bone removal (yes/no), tooth sectioning (yes/no), and surgical duration (time from the first incision to the final suture), which was measured by a registered dental nurse using a stopwatch device.

The patients were allocated to one of the two study arms via computer-generated randomization. To cater for an anticipated female predominance, both study groups were stratified for gender. The surgeon caseload was also considered during randomization, with the expectation that the majority of third molar surgeries would be performed by surgeon 1. Patients were assigned to the experimental and control groups in a 1:1 ratio, using randomly permuted blocks of size 4. All patients allocated to the experimental group received the PRGF 'clot' in the third molar extraction socket prior to wound closure. Those allocated to the control group underwent surgical third molar removal in line with the study protocol but did not receive the PRGF clot or any other socket medicament prior to wound closure. [Au?11]

Study arm allocation was made available only to the operating surgeon via concealed allocation. Brown and white sealed opaque envelopes were used for male and female participants, respectively, with each envelope containing a card with written instructions for the operating surgeon: 'PRGF – Yes' or 'PRGF – No'. Each envelope was labelled with the surgeon's initials, patient sex, and study code number. To mitigate any potential for human error, a sticker was also placed on each card using a traffic light system, where a green sticker indicated 'PRGF – Yes' and a red sticker indicated 'PRGF – No'. After reviewing the instructions within each envelope, the card was discarded immediately in the confidential waste bin by the operating

surgeon. The principal study investigator and all study participants were blinded to the study arm allocation. [Au?11]

All patients received standard postoperative instructions and a 7-day prescription for paracetamol 1 g four times daily, ibuprofen 400 mg three times daily, codeine phosphate 30–60 mg four times daily, and a 2-week course of chlorhexidine gluconate 0.2% twice daily antiseptic mouthwash. The patients were asked to record the quantity and frequency of analgesic consumption during the immediate postoperative week.

All patients received a telephone call on day 3 postoperative (T1), and the primary outcome variables were documented for all patients by a single clinician.

The patients were asked to return to the clinic for review on day 7 postoperative (T2). A clinical inspection was performed by a single clinician and any complications such as dry socket were documented and managed with local measures. The presence of dry socket was documented where signs and symptoms of the Blum criteria were observed[7] [Au?12]. [Au?12] Socket healing was assessed and graded using a modified version of the seven-point index devised by Landry et al., with '0' and '7' indicating the worst and best outcomes, respectively [Au?7]. The NRS pain score, OHIP-14 and PoSSe scores, MIO and analgesic consumption were also documented [Au?13].

Statistical analysis

The data analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) and Stata version 15.1 (StataCorp LLC, College Station, TX, USA). Analysis of covariance (ANCOVA) was used for the analysis of the NRS pain,

OHIP-14 and PoSSe total scores, and MIO outcomes. T1 and T2 scores were considered as the outcome variables, with the equivalent scores at baseline (T0) used as covariates. When the assumptions of this method were met, the analyses were performed with the outcome on the original scale of measurement. However, when the assumptions were not met (for example if the residuals were not normally distributed) the analyses were performed on the log scale. Equivalent statistical methods were used for the secondary outcomes measured on a continuous scale, where there was a measurement at baseline to allow for. OHIP-14 subscale data were collected in a binary format, and a general linear model (GLM) was used for analysis assuming a binomial outcome and a log link function. Group differences were expressed as risk ratios (RR). Categorical variables with no baseline value were analysed using the χ^2 test.

Results

A convenience sample of 74 patients was recruited into the study; mean age was 28.1 ± 5.8 years (range 19–39 years) [Au?7]. The majority of the patients were female (57/74 [Au?14], 77.0%). Thirty-eight patients were allocated to the control group and 36 to the experimental (PRGF) group. Table 1 summarizes the baseline demographics of both study groups. Fifty-two patients (70.3% [Au?15]) were treated by surgeon 1 and 22 (29.7% [Au?15]) by surgeon 2. The mean surgical time for the entire study population was 13.59 ± 6.52 minutes (range 3.93–30.67 minutes), with similar values observed in the control group (13.69 minutes) and PRGF group (13.49 minutes). Eleven patients failed to return for follow-up at 1 week postoperatively: six from the

control group and five from the PRGF group. Of these, three patients were contactable via telephone, and T2 PoSSe, OHIP-14, and NRS pain data were collected virtually.

[Table 1 here]

The mean NRS pain score at T1 was higher in the PRGF group (4.1 ± 2.4) than in the control group (3.2 ± 2.3), demonstrating borderline significance only (MD 1.0; $P = 0.06$) (Fig. 1). No significant difference in mean NRS pain score at T2 was observed between the PRGF group (2.7 ± 2.2) and control group (3.2 ± 2.6) ($P = 0.44$).

[Figure 1 here]

Regarding the seven PoSSe subscales, no significant differences were observed between the two groups at T1, with the exception of the 'interference with daily activities' subscale (Table 2), where PRGF patients scored on average 1.2 units higher ($P = 0.02$). The 'eating' and 'pain' subscales had the highest scores in both study groups at 1 week postoperative (Table 3). At T2, the mean total PoSSe score was 33.2 ± 15.5 (range 7.4–61.3) for the control group and 35.1 ± 15.0 (range 2.4–61.4) for the PRGF group. There were no statistically significant differences in PoSSe subscale and total scores between the two groups at T2 [Au?7].

[Tables 2 and 3 here]

OHIP-14 outcomes data revealed that patients in the PRGF group were 25% more likely to give a negative response to Question 4 “Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth or dentures?” at T1 ($P = 0.02$). However, there were no statistically significant differences in any of the seven subscale scores between the groups at T1 (Table 4) or T2 (Table 5) [Au?7].

[Tables 4 and 5 here]

Reduced MIO was observed at T2 in the control group (35.7 ± 8.2 mm) and PRGF group (35.4 ± 8.5 mm), with no difference observed between the groups ($P = 0.67$), compared to baseline (T0) measurements of 41.8 ± 7.0 mm and 43.1 ± 7.2mm in the control and PRGF groups, respectively [Au?16]. Four patients in total developed dry socket postoperatively, one in the control group (3%) and three in the PRGF group (9%). This outcome was not found to be of statistical significance ($P = 0.30$). Socket healing, graded using a modified Landry healing index[6], did not differ significantly between the groups (control 4.0 ± 1.2; PRGF 3.6 ± 1.2; $P = 0.21$), nor did analgesic consumption (Table 6).

[Table 6 here]

Discussion

There is a paucity of published literature on the topic of PRGF use in third molar surgery. A literature search using relevant medical subject heading (MeSH) terms

generated only five articles, three of which report RCTs of uncertain quality[8–10]. Furthermore, PRGF is the only APC not included in the 2020 Cochrane Review on surgical techniques in third molar surgery[5]. The reasons for the low uptake of PRGF among researchers is unclear, but it is likely a consequence of the commercial drive behind the procurement of APC systems with little guidance available to clinicians in deciding which system is best suited to their individual needs[11]. Ultimately, all APCs achieve the same end goal of regeneration, with relatively minor differences in preparation protocols and composition. PRGF differs from its main rival products of platelet-rich plasma (PRP) and leucocyte and platelet-rich fibrin (L-PRF) through the selective exclusion of leucocytes during product preparation. This remains a contentious issue with no agreed consensus on the subject. One argument in favour of exclusion is the production of a more homogeneous and reproducible platelet product[12]. No superiority has yet been conclusively demonstrated by any one product in terms of physical properties, physiological performance, or regenerative capacity, and some experts suggest that to distinguish between them is potentially "disingenuous" and that "PRP is PRP, whatever way you look at it"[13]. It is hoped this study will alert interested clinicians and researchers to the availability of alternatives to PRP and L-PRF, which appear to be more ubiquitous in the literature.

The proportion of female patients in the study population was high (77.0%). This was managed by successfully stratifying for sex at the outset. It has long been reported that the pain experience is influenced by sex, with female patients tending to report higher levels of postoperative pain. In a cohort of 255 patients undergoing surgical removal of a unilateral mandibular third molar under local anaesthesia, Grossi et al.[14] found that female patients were twice as likely as male patients to experience severe postoperative discomfort. Other factors shown to influence

postoperative morbidity include impaction type and smoking status, with distoangular and horizontal impaction types, as well as current smoking habit, increasing postoperative morbidity[15] [Au?7]. In this study, an almost equal proportion of distoangular impactions (control group 16%, PRGF group 17%) was observed in the two study groups, whereas the proportion of horizontal impactions was higher in the PRGF group (25%) than in the control group (16%) [Au?7]. It is unclear whether this marginal imbalance had any tangible influence on postoperative outcomes in the PRGF group. Meanwhile, the two groups were balanced with respect to smoking status, with 29% (11/38) in the control group and 33% (12/36) in the PRGF group being current smokers [Au?7].

The results of this study corroborate previous reports of a notable deterioration in QoL for patients up to 1 week following third molar removal[16]. Median OHIP-14 scores in this cohort were highest at T2 in both study groups. In the control group, the total OHIP-14 score increased from a median of 15 (IQR 8–20) at baseline, to 16 (IQR 5–20) at T1 and 20 (IQR 8–28) at T2 [Au?7]. A similar trend was observed in the PRGF group: 8 (IQR 4–15) at baseline, 15 (IQR 8–28) at T1, and 17 (IQR 5-29) at T2 [Au?7] [Au?17] [Au?18]. An earlier study evaluating QoL outcomes in 100 patients undergoing mandibular third molar removal under local anaesthesia using the OHIP-14 instrument found that QoL outcomes deteriorated for 5 days postoperatively, with scores returning to baseline levels by day 7[17]. The reasons for this disparity are unclear, but may be due to the lower mean age of the study population in the previous study of 26 ± 8 years compared to the mean age of 28.1 ± 5.8 years in the present study population. Moreover, there are racial differences between the study populations: 89% of the present study population were White Irish, while McGrath et al. conducted their study in an Asian population in Hong Kong [Au?19]. Further

research is merited to fully evaluate potential geographic variations in perceived QoL outcomes following third molar surgery.

Dichotomization of OHIP-14 data was performed in this study for ease of analysis. This decision was made following the observation that in many instances, multiple choices were selected by patients when completing the OHIP-14 questionnaire. As a consequence, it was decided to merge the negative responses 'never' and 'hardly ever' together as 'no', and the responses 'occasionally', 'fairly often', and 'very often' together as 'yes'. Ideally, an analysis would have been performed on a continuous rather than ordinal dataset to permit more accurate detection of group differences. However, despite this limitation, it was possible to infer commonality between PoSSe data and clinician-reported outcome data with respect to MIO measurements in both groups, and it is unlikely that dichotomization of the OHIP-14 data had any demonstrable impact on the overall results [Au?20].

The total PoSSe scores followed a similar trend at each time-point. The mean total PoSSe score in the control group increased from 9.6 ± 10.9 at baseline to 26.2 ± 10.9 at T1 and to 33.2 ± 15.5 at T2, while in the PRGF group, the mean total score similarly increased from 11.4 ± 12.2 at baseline to 30.3 ± 10.0 at T1 and to 35.1 ± 15.0 at T2. The total PoSSe scores at T2 in the present cohort are similar to that cited in a similar study investigating QoL outcomes in patients undergoing the surgical removal of mandibular third molars under local anaesthesia, with the authors reporting a mean PoSSe score of 35.7 ± 13.5[14]. [Au?21]

The researchers responsible for the development of the PoSSe instrument have previously cited the 'pain' subscale and the total PoSSe score as being most responsive to change[18]. The present study demonstrated greatest responsiveness to the 'pain' and 'eating' subscales, with the latter having the highest scores of all subscales

at T1 and T2 in both study groups (Tables 2 and 3). Agreement may be inferred with the equivalent 'physical pain' and 'physical disability' domains of the OHIP-14 instrument (Tables 4 and 5) [Au?22]. Furthermore, the 19% reduction in MIO observed in both study groups is in keeping with the increase in equivalent domain/subscale scores in the OHIP-14 and PoSSe instruments, respectively [Au?23].

A lack of baseline data is identified as a weakness of many QoL studies[19], and although the PoSSe instrument is not validated for use as a preoperative tool[18], T0 and T1 data were collected in this instance to permit full evaluation of the trends in QoL arising as a result of the intervention. It is the authors' opinion that the collection of PoSSe data at multiple time-points serves to strengthen rather than detract from the overall results.

In conclusion, no difference in QoL outcomes was detected in this study in patients undergoing conventional third molar surgery versus surgery with adjunctive PRGF. This study is novel in investigating APC use in third molar surgery to explore clinician- and patient-reported outcome measures using psychometrically tested instruments [Au?7]. The evaluation of QoL in the third molar surgery population has transcended its original brief of application in research studies and has helped shape the course of discussion with patients considering third molar surgery. It should be borne in mind that 'cure' is often worse than 'disease', and it is imperative that patients are appropriately and adequately informed during the decision-making process[17]. The authors believe that the robust methodology employed and broad scope of outcome measures selected are two of the major strengths of this study, and the study design would form a useful template for researchers hoping to conduct a third molar interventional RCT. The collection of QoL data at daily intervals during the immediate postoperative period would permit a more in-depth analysis of QoL trends

in this cohort, similar to that seen in the observational study by McGrath et al.[3], and is a recommendation for future research.

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Competing interests

None.

Ethical approval

Ethical approval to conduct this study was granted by the Clinical Research Ethics Committee (CREC) of the Cork Teaching Hospitals.

Patient consent

Informed consent was obtained from all participants. [Au?7]

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Figure caption

Fig. 1. Mean NRS pain scores in the PRGF and control groups, showing a slightly higher peak pain score in the PRGF group at T1. (NRS, numerical rating scale; PRGF, plasma rich in growth factors; T0, day of treatment; T1, 3 days postoperative; T2, 7 days postoperative.)

Table 1. Demographic and surgical characteristics.

Variable		Control group (n = 38)	PRGF group (n = 36)
Age (years), mean ± SD		29.4 ± 6.5	26.8 ± 4.5
Sex	Female	29 (76%)	28 (78%)
	Male	9 (24%)	8 (22%)
Race [Au?19]	White Irish [Au?19]	34 (89%)	32 (89%)
	Other	4 (11%)	4 (11%)
Current smoker	No	27 (71%)	24 (67%)
	Yes	11 (29%)	12 (33%)
Surgical time (min), median (IQR)		13.4 (7.6–19.7)	12.9 (9.2–16.0)
ASA score	1	20 (53%)	21 (58%)
	2	18 (47%)	15 (42%)
Type of impaction	Distoangular	6 (16%)	6 (17%)
	Mesioangular	11 (29%)	8 (22%)
	Vertical	15 (39%)	13 (36%)
	Horizontal	6 (16%)	9 (25%)
Pederson score	4	6 (16%)	3 (8%)
	5	13 (34%)	14 (39%)
	6	10 (26%)	12 (33%)
	7	6 (16%)	6 (17%)
	8	3 (8%)	1 (3%)
Tooth sectioning	No	16 (42%)	19 (53%)
	Yes	22 (58%)	17 (47%)
Bone removal	No	15 (39%)	16 (44%)
	Yes	23 (61%)	20 (56%)

ASA, American Society of Anesthesiologists; IQR, interquartile range; PRGF, plasma rich in growth factors; SD, standard deviation. Summary statistics are number (percentage), unless stated otherwise.

Table 2. PoSSe subscales on postoperative day 3 (T1). [Au?25]

PoSSe outcome	Treatment	Number of patients	PoSSe score, mean ± SD		Group difference[a]	*P*-value
			Baseline	3 days postop.	Mean (95% CI)	
Eating	Control	38	3.3 ± 3.6	9.4 ± 4.4	0 [Au?26]	0.10
	PRGF	34	4.0 ± 4.8	11.2 ± 3.8	1.6 (−0.3 to 3.4)	
Speech	Control	38	0.3 ± 1.1	1.0 ± 1.2	0 [Au?26]	0.12
	PRGF	34	0.3 ± 1.1	1.5 ± 1.4	0.5 (−0.1 to 1.1)	
Sensation	Control	38	0.2 ± 1.3	2.0 ± 2.2	0 [Au?26]	0.59
	PRGF	34	0.2 ± 0.8	2.3 ± 1.9	0.3 (−0.7 to 1.2)	
Appearance	Control	38	0.4 ± 1.1	2.7 ± 1.5	0 [Au?26]	0.58
	PRGF	34	0.4 ± 1.2	2.1 ± 1.3	−0.2 (−0.8 to 0.5)	
Pain	Control	38	4.0 ± 5.0	7.6 ± 2.7	0 [Au?26]	0.89
	PRGF	34	5.0 ± 5.4	7.8 ± 3.2	0.1 (−1.3 to 1.5)	
Sickness	Control	38	0.3 ± 1.0	0.9 ± 1.8	0 [Au?26]	0.43
	PRGF	34	0.4 ± 1.3	1.3 ± 2.1	0.3 (−0.5 to 1.2)	
Interference with daily activities	Control	38	1.1 ± 1.8	2.5 ± 2.1	0 [Au?26]	0.02*
	PRGF	34	1.0 ± 1.7	3.7 ± 2.3	1.2 (0.2 to 2.2)	
Total score	Control	38	9.6 ± 10.9	26.2 ± 10.9	0 [Au?26]	0.13
	PRGF	34	11.4 ± 12.2	30.3 ± 10.0	3.5 (−1.1 to 8.1)	

CI, confidence interval; PoSSe, postoperative symptom severity scale; PRGF, plasma rich in growth factors; SD, standard deviation.

[a]Calculated from analysis of covariance (ANCOVA), adjusting for baseline value. *$P < 0.05$ [Au?27].

Table 3. PoSSe subscales on postoperative day 7 (T2).

PoSSe outcome	Treatment	Number of patients	PoSSe score, mean ± SD		Group difference[a]	*P*-value
			Baseline	7 days postop.	Mean (95% CI)	
Eating	Control	33	3.3 ± 3.5	11.4 ± 5.8	0 [Au?26]	0.71
	PRGF	33	4.1 ± 4.8	12.0 ± 5.7	0.5 (−2.3 to 3.4)	
Speech	Control	33	0.3 ± 1.2	1.4 ± 1.9	0 [Au?26]	0.37
	PRGF	33	0.3 ± 1.1	1.8 ± 1.9	0.4 (−0.5 to 1.3)	
Sensation	Control	33	0.2 ± 1.3 [Au?28]	2.1 ± 2.6	0 [Au?26]	0.95
	PRGF	33	0.2 ± 0.8	2.0 ± 1.8	0.0 (−1.2 to 1.1)	
Appearance	Control	33	0.4 ± 1.2	3.1 ± 2.4	0 [Au?26]	0.70
	PRGF	33	0.4 ± 1.2	3.3 ± 2.0	0.2 (−0.9 to 1.3)	
Pain	Control	33	4.5 ± 5.2	10.9 ± 4.1	0 [Au?26]	0.93
	PRGF	33	5.2 ± 5.5	10.8 ± 4.1	−0.1 (−2.1 to 1.9)	
Sickness	Control	33	0.2 ± 0.7	1.2 ± 1.8	0 [Au?26]	0.96
	PRGF	33	0.4 ± 1.3	1.3 ± 2.0	0.0 (−0.9 to 0.8)	
Interference with daily activities	Control	33	1.1 ± 1.6	3.2 ± 2.5	0 [Au?26]	0.26
	PRGF	33	1.0 ± 1.7	3.9 ± 2.9	0.8 (−0.6 to 2.1)	
Total score	Control	33	9.8 ± 10.7	33.2 ± 15.5	0 [Au?26]	0.64
	PRGF	33	11.7 ± 12.2	35.1 ± 15.0	1.8 (−5.8 to 9.4)	

CI, confidence interval; PoSSe, postoperative symptom severity scale; PRGF, plasma rich in growth factors; SD, standard deviation.

[a]Calculated from analysis of covariance (ANCOVA), adjusting for baseline value.

Table 4. OHIP-14 subscales on postoperative day 3 (T1). [Au?29]

OHIP-14 outcome	Treatment	Number of patients	Score, median (IQR)		Group difference[a]	*P*-value
			Baseline	3 days postop.	Ratio (95% CI)	
Functional limitations	Control	29	1 (0–2)	0 (0–3)	1 [Au?26]	0.19
	PRGF	29	0 (0–0)	1 (0–3)	1.28 (0.88–1.86)	
Physical pain	Control	29	4 (3–4)	5 (3–6)	1 [Au?26]	0.16
	PRGF	29	3 (1–4)	6 (4–7)	1.20 (0.93–1.56)	
Psychological discomfort	Control	29	1 (1–4)	1 (0–2)	1 [Au?26]	0.44
	PRGF	29	1 (0–4)	2 (0–3)	1.16 (0.80–1.68)	
Physical disability	Control	29	2 (1–3)	2 (0–4)	1 [Au?26]	0.20
	PRGF	29	1 (0–2)	2 (0–6)	1.33 (0.86–2.06)	
Psychological disability	Control	29	2 (1–4)	1 (0–3)	1 [Au?26]	0.88
	PRGF	29	2 (0–2)	1 (0–3)	1.03 (0.69–1.53)	
Social disability	Control	29	1 (0–3)	1 (0–3)	1 [Au?26]	0.20
	PRGF	29	0 (0–1)	1 (0–4)	1.30 (0.86–1.97)	
Handicap	Control	29	1 (0–2)	0 (0–2)	1 [Au?26]	0.27
	PRGF	29	0 (0–2)	0 (0–3)	1.25 (0.84–1.85)	
Total score	Control	29	15 (8–20)	16 (5–20)	1 [Au?26]	0.10
	PRGF	29	8 (4–15)	15 (8–28)	1.44 (0.93–2.22)	

CI, confidence interval; IQR, interquartile range; OHIP-14, 14-item Oral Health Impact Profile; PRGF, plasma rich in growth factors.

[a]Calculated from analysis of covariance (ANCOVA), adjusting for baseline value.

Table 5. OHIP-14 subscales on postoperative day 7 (T2).

OHIP-14 outcome	Treatment	Number of patients	Score, median (IQR)		Group difference[a]	*P*-value
			Baseline [Au?17]	7 days postop. [Au?17]	Ratio (95% CI)	
Functional limitations	Control	26	1 (0–2)	2 (0–3)	1 [Au?26]	0.52
	PRGF	28	0 (0–0)	1 (0–3)	0.89 (0.61–1.28)	
Physical pain	Control	26	4 (3–4)	6 (3–7)	1 [Au?26]	0.85
	PRGF	28	3 (1–4)	5 (3–7)	1.03 (0.76–1.38)	
Psychological discomfort	Control	26	1 (1–4)	2 (0–3)	1 [Au?26]	0.43
	PRGF	28	1 (0–4)	1 (0–3)	0.87 (0.60–1.25)	
Physical disability	Control	26	2 (1–3)	3 (1–5)	1 [Au?26]	0.56
	PRGF	28	1 (0–2)	4 (0–6)	1.14 (0.73–1.78)	
Psychological disability	Control	26	2 (1–4)	2 (1–4)	1 [Au?26]	0.62
	PRGF	28	2 (0–2)	2 (0–3)	0.91 (0.63–1.33)	
Social disability	Control	26	1 (0–3)	2 (1–5)	1 [Au?26]	0.37
	PRGF	28	0 (0–1)	2.5 (0–4)	1.21 (0.80–1.82)	
Handicap	Control	26	1 (0–2)	1 (0–2)	1 [Au?26]	0.50
	PRGF	28	0 (0–2)	1 (0–3)	1.15 (0.76–1.74)	
Total score	Control	26	15 (8–20)	20 (8–28)	1 [Au?26]	0.86
	PRGF	28	8 (4–15)	17 (5–29)	1.05 (0.62–1.77)	

CI, confidence interval; IQR, interquartile range; OHIP-14, 14-item Oral Health Impact Profile; PRGF, plasma rich in growth factors.

[a]Calculated from analysis of covariance (ANCOVA), adjusting for baseline value.

Table 6. Secondary outcome variables (dry socket, socket healing, and analgesic consumption) on postoperative day 7 (T2).

Outcome	Control		PRGF		Difference[a]	*P*-value
	Patients, *n*	*n* (%)	Patients, *n*	*n* (%)	RR (95% CI)	
Dry socket	33	1 (3%)	33	3 (9%)	3.00 (0.33 to 27.4)	0.30
	Control		PRGF		Difference[b]	*P*-value
	Patients, *n*	Mean ± SD	Patients, *n*	Mean ± SD	Mean (95% CI)	
Socket healing (Landry index)	31	4.0 ± 1.2	32	3.6 ± 1.2	−0.4 (−1.0 to 0.2)	0.21
	Control		PRGF		Difference[b]	*P*-value
	Patients, *n*	Median (IQR)	Patients, *n*	Median (IQR)	Median (95% CI)	
Analgesic consumption						
Paracetamol	33	12 (0–22)	33	8 (1–22)	0 (−8 to 3)	0.63
Ibuprofen	33	6 (0–11)	32	8 (2.5–11.5)	1 (−2 to 4)	0.46
Codeine	33	2 (0–7)	33	1 (0–7)	0 (−2 to 1)	0.89

CI, confidence interval; IQR, interquartile range; PRGF, plasma rich in growth factors; RR, risk ratio; SD, standard deviation.

[a]Risk ratio calculated as PRGF divided by control.

[b]Difference calculated as PRGF minus control.