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Efficacy of Ultra-Micronized Palmitoylethanolamide 600 MG (UM-PEA) for Sub-Lingual Use on Postoperative Course after Dental Implant Surgery: Multicentric Randomized Trial

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Abstract

The fatty acid amide Palmitoylethanolamide (PEA) has been studied extensively for its anti-inflammatory and neuroprotective actions. The lipidic nature and large particle size of PEA in the native state may limit its solubility and bioavailability when given orally, however. Micronized formulations of a drug enhance its rate of dissolution and reduce variability of absorption when orally administered. The present study was thus designed to evaluate the oral anti-inflammatory efficacy of ultra-micronized-PEA. All cases were performed in Department of Oral-Maxillofacial Surgery of the University of Rome "Tor Vergata". A randomized, multicenter, single-blind, split-mouth trial, was carried out on 70 patients in whom 160 dental implants were placed. Participants were selected between September 2020 and October 2022. Patients showed symmetrical and bilateral edentulism's in the posterior region of the jaw. Each of 70 patients was scheduled to undergo implants placement bilaterally; two surgical sessions were performed, the second sessions three months later from the first ones. Pharmacological protocol applied for each side of the same patient was based on ultra-micronized PEA 600 mg for sub-lingual use; in the test group patients assumed um-PEA 600 mg for sub-lingual use two times a day for a period of 30 days postoperatively. From the clinical research carried out by us, the preliminary results are very encouraging um-PEA was able to reduce significantly postoperative swelling and trismus. Additionally, this research showed that efficacy of um-PEA in decreasing pain and trismus after oral surgical procedures and this treatment did not show any serious side effect. Although the results we obtained were particularly encouraging, larger studies are needed to support the use of um-PEA in implant therapy and to evaluate its possible influence on the reduction of complications. In our opinion um-PEA administered sublingually, is useful in improving the postoperative comfort of the patient undergoing implant surgery.

Keywords: UM-PEA; Dentistry; Implant surgery

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Introduction

Implant surgical procedures represent a common strategy to rehabilitate partial or total edentulism's [1]. According to some authors, following implant placement, pain, trismus and swelling tend to be low and reduced to near zero over a week postoperatively [2]. Most patients who experienced pain, reported a peak intensity 6 h after the operation in 41.5% of cases while the maximum level of swelling is experienced after 48 h in 48.8% of cases. However, postoperative discomfort, even if it is reported to be mild, tends to adversely affect patients' judgment on dental implant surgery [2,3]. Many authors prescribe NSAIDs (Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in order to control postoperative course [4-6]. Nevertheless, the use of these drugs is associated to numerous side effects or health-related contraindications. Other authors proposed the addiction of Symphytum 5 CH (non-opioid anti-inflammatory) to conventional analgesia to reduce pain and swelling following dental implant procedures [5-7]. The study of the endogenous

lipid Palmitoylethanolamide dates back to 1970, but researchers' interest in this molecule increased significantly in 1990 when a group of researchers led by the Nobel Prize for Medicine Prof. Rita Levi Montalcini, came to understand the great importance of modulatory intervention of non-neuronal cells such as Mast Cells, Microglia and Astrocytes, in attenuating the neuroinflammation, pain and degeneration of the nervous tissue, at the base of many pathologies. Prof. Montalcini herself intuited, and confirmed, the biological mechanism of regulation of non-neuronal cells, which she herself called Autacoid Local Injury Antagonism, following this intuition and continuing the research, the potentialities of the regulatory function of Palmitoylethanolamide were discovered, first on mast cells and subsequently on Microglia and Astrocytes. Therefore, the need arose to make Palmitoylethanolamide, a lipophilic substance, active and absorbable, which in its natural physical state has too large molecular dimensions (from 2000 μm to 50 μm) to guarantee its physiological gastro-intestinal absorption and therefore the biomodulation activity. The reduction of the particle diameter of Palmitoylethanolamide, has allowed the production of two pharmacologically bioactive forms of PEA: 1. Micronized PEA with the dimensions of about 4 μm to 8 μm ideal for being absorbed at the enteric level, reaching the hyper reactive Mast cells and 2. Ultra-micronized PEA, with a size of 0.8 μm to 2 μm, able to cross the blood-brain barrier to reach effectively Microglia and Astrocytes where it acts as a neuromodulator in different situations. The fatty acid amide Palmitoylethanolamide (PEA) has been extensively studied over the years for its anti-inflammatory and neuroprotective actions. However, the lipid nature and large particle size of PEA in its original state may limit its solubility and blood bioavailability when administered orally. The micronized formulations of the molecule increase its dissolution rate and reduce the variability of absorption when administered orally. Using an experimental program performed on 70 patients scheduled for the insertion of dental implants in the OU. of Maxillofacial Surgery of the University of Rome "Tor Vergata" (Director and Chief: Prof. Leonardo Calabrese), taking into consideration all the factors that influence the course of the intervention, we decided to evaluate the effectiveness of the ultra-micronized Palmitoylethanolamide intake, in the reduction of post-surgical complications. This case control study sought to evaluate the effects on pain, trismus and swelling after dental implant surgery [5,8] comparing Ultra-Micronized Palmitoylethanolamide (UM-PEA) 600 mg for sub-lingual use versus Ibuprofen 600 mg for o.s. [8].

The benefits of administering enzymes after surgical procedure demonstrated both *in-vitro* and *in-vivo* are anti-inflammatory, antithrombotic, and fibrinolytic, however minimizing postoperative complications [9,10]. The endogenous fatty acid Palmitoylethanolamide (PEA) is one of the members of N-acyl-ethanolamine's family. PEA was identified more than five decades ago and was shown to reduce allergic reactions and inflammation in animals along with influenza symptoms in humans. Interest in this compound faded, however, until the discovery that one of its structural analogs, anandamide (arachidonoylethanolamide), serves as an endogenous ligand for cannabinoid receptors, the molecular target of Δ9-tetrahydrocannabinol in marijuana. Since this finding, PEA has been shown to inhibit peripheral inflammation and mast-cell degranulation, as well as to exert neuroprotective and antinociceptive effects in rats and mice [10]. PEA is an endogenous fatty acid amide signaling molecule which is synthesized in consequence of a tissue stress or damage, so PEA can maintain and re-establish homeostasis with anti-inflammatory and neuroprotective actions. Micronized/ultra-micronized PEA was produced by the air-jet milling technique, and the various PEA preparations were subjected to physicochemical characterization to determine particle size distribution and purity. Each PEA formulation was then assessed for its anti-inflammatory effects when given orally in the carrageenan-induced rat paw model of inflammation, a well-established paradigm of edema formation and thermal hyperalgesia [11]. Ultra-micronization of PEA improve the bioavailability and efficacy of this very low water-soluble molecule [9,11,12-14].

Results

A total of 70 patients who required dental implant placements were included in this randomized split-mouth clinical investigation. In control group, the mean surgery duration was 20.55 ± 4.23 minutes for the placement of one dental implant and 30.40 ± 7.02 minutes for the installation of two implants. In test group, the mean time for implant placement was 22.22 ± 5.63 and 33.12 ± 5.54 minutes respectively for the placement of one and two dental implants. The difference between the groups was not statistically significant (Table 1).

Pain value (as evaluated on the VAS) at baseline was 0 in both groups. The level of pain felt by the patients of both group at T1 was not statistical different among them. However, at T2, patients belonging to test group experienced a significantly lower pain (VAS = 1.0 ± 1.01) than the controls (VAS = 1.8 ± 0.75).

In all cases the reported pain evaluated was higher the first day post-surgery, subsequently decreasing steadily daily until days 7 post surgery (Table 2).

Trismus, evaluated in terms of millimeters of mouth opening, was the same at T0 for both groups. At 1 day after surgery, the comparison

Table 1: Mean time and standard deviation of each surgery.

	1 Implant Placement	2 Implants Placement
Control Group	20.55 ± 4.23	30.40 ± 7.02
Test Group	22.22 ± 5.63	33.12 ± 5.54
P-value	>0.05	>0.05

Table 2: Pain score (M ± SD) on visual analog scale for control and test groups.

	T0	T1	T2
Control Group	0.00 ± 0.00	2.8 ± 0.92	1.8 ± 0.75
Test Group	0.00 ± 0.00	2.6 ± 0.76	1.0 ± 1.01
P-value	>0.05	>0.05	*<0.05

*Statistically significant difference between the 2 groups

Table 3: Mean mouth opening values for control and test groups.

	T0	T1	T2
Control Group	46.0 ± 0.97	28.5 ± 1.34	40.88 ± 0.85
Test Group	46.0 ± 0.97	35.3 ± 0.99	43.02 ± 1.31
P-value	>0.05	<0.05*	>0.05

*Statistically significant difference between the 2 groups

Table 4: Mean difference in cheek swelling between control and test groups.

	T0	T1	T2
Control Group	50.6 ± 6.37	79.6 ± 5.34	59.8 ± 3.91
Test Group	50.6 ± 6.37	64.4 ± 4.59	60.1 ± 4.92
P-value	>0.05	<0.05*	>0.05

*Statistically significant difference between the 2 groups

between the control and the test groups showed no significant difference. At the seventh-day visit, the inter-incisal distance was greater in the test group than in the control group, even though a level of significant difference was not reached. In all cases the trismus (reduction of degree of mouth opening) was higher on the day of surgery, subsequently decreasing daily until T2 (Table 3).

Postoperative swelling was present in both groups at T1. However, the measurements were significantly higher in the control group (Table 4). At T2 swelling was no significantly different among group tested.

There was no incidence of alveolar osteitis (checked on postoperative day 3 onwards), paresthesia, or altered nerve sensation for any patient in either group postoperatively.

Discussion

Our study design, because it is a split-mouth investigation, has the statistical power to rule out the possibility of a difference between the 2 groups, including age, sex and general health condition. Because some authors have reported a statistically significant difference in pain evaluations depending on the duration of surgery [15,16], in our study all the procedures were performed by the same trained oral surgeon, resulting in no significant different in terms of mean surgery time [15]. This should be taken into account in our assessment of the relationship between the duration of the intervention and postoperative pain [6,15,17,18]. No periosteal releasing incision were done, so there were minimal postoperative pain and discomfort [19-21]. Palmitoylethanolamide (PEA), a special food for medical purposes, has anti-inflammatory and neuroprotective effects. Nevertheless, PEA lacks direct ability to prevent free radical formation. The combination of PEA and Polydatin PLD could have beneficial effects on oxidative stress induced by inflammatory processes [22]. In all cases the reported pain evaluated was higher the first day post-surgery, subsequently decreasing steadily daily until days 7 post-surgery with no difference of anti-dolorific effect between um-PEA and NSAIDs [13,22,23]. Inflammation is basically a protective cellular response aimed at removing harmful stimuli and initiating the healing process. However, if prolonged, it can override the boundaries of physiological control and become destructive [13]. Inflammation is a key element in the pathogenesis of acute and chronic pain, and also intervenes in cases of surgical trauma such as the insertion of dental implants. T0 was the same in both groups because, as a split-mouth study design, patients were the same, clearly the only difference was the surgical time that was different from test and control. As clearly visible at table 4 um-PEA was able to reduce significantly postoperative swelling and trismus [24,25]. Ultra-Micronized Palmitoylethanolamide (UM-PEA) represents an attractive option for postoperative pain control in complex patients at increased risk of adverse effects with traditional analgesics and can be administered as an adjunct to conventional therapies. From the data in our possession, we can confirm the efficacy of um-PEA administered sublingually in the reduction of pain, swelling and trismus after oral and implant surgery. In accordance with recent discoveries in international literature, in consideration of the association between surgical experience and the duration of the intervention, we would expect a lower duration than in a study with a sample composed of a mixture of providers with varied levels of training and experience [8,9,11,26,27].

Material and Methods

A randomized, multicenter, single-blind, split-mouth study was carried out on 70 patients in whom 160 dental implants were placed. Participants were selected between September 2021 and October 2022). Patients showed symmetrical and bilateral edentulism's in the posterior region of the jaw. Sixty patients received 1 implant per hemiarch (2 implants per patient) for a total of 120 implants. Ten patients were treated with 2 implants per hemiarch (4 implants per patient) for a total of 40 implants. All patients, aged between 18 and 50 years with a mean age of 35.5 ± 9.8 years, were in good health conditions (ASA 1 or 2) and exhibited a good level of oral hygiene (FMPS lower that 20%). None was a smoker. Patients with known allergies to NSAIDs and those who could not take such medication for gastric disorders were excluded. The study was conducted according to the ethical principles for medical research on human beings established by the 1964 Helsinki protocol. Preoperatively, the protocol of the study was explained to the patients and the relative informed consent was obtained.

Inclusion criteria

- Patients in the age group of 18 years to 50 years
- Patients with unilateral and bilateral symmetrical and bilateral edentulism's in the posterior region of the jaw.

Exclusion criteria

- Patients with known severe systemic diseases contraindicating tooth extraction
- Known mentally challenged patients, and patients who are unable to communicate
- Pregnant and lactating women
- Patients on anticoagulant therapy
- Patients allergic to Palmitoylethanolamide
- Immunocompromised patients

All patients assumed a prophylactic dose of amoxicillin with clavulanic acid (1000 mg) one hour before surgery. All of them were treated via the same surgical procedure. All operations were performed under local anesthesia consisting of 2% mepivacaine hydrochloride with 1:80,000 adrenaline bi-tartrate. In both groups the site was prepared with 5% povidone-iodine solution, and a conventional linear incision was made to reflect the flap. No periosteal releasing incisions were done. A mucoperiosteal flap was raised with a periosteal (Molt's No. 9) elevator to expose the implant site. All implants had a length between 10 mm and 13.5 mm and diameter between 3.75 mm and 4.5 mm. Implants were placed submerged on the basis of a CT-Dental Scan and a surgical guide. Primary suture was carried out with a combination of single and horizontal mattress stitches by means of a 4-0 absorbable suture thread. The length of surgery was noted in each case.

Each of 70 patients was scheduled to undergo implants placement bilaterally; two surgical sessions were performed, the second sessions three months later from the first ones. Pharmacological protocol applied for each side of the same patient was based on ultra-micronized PEA 600 mg for sub-lingual use. In the test group patients assumed um-PEA 600 mg for sub-lingual use two times a day for a period of 30 days postoperatively. Each patient of the control group had to take Ibuprofen 600 mg one hour preoperatively. Furthermore, patients

were recommended to use a rescue analgesic (paracetamol 1000 mg) if the pain score was higher than 3. The order of the two pharmacological protocols was randomly assigned. The same postoperative instructions were given to all patients: soft and cold diet for 24 h and chlorhexidine mouthwash for 14 days. Postoperatively, patients were instructed to take amoxicillin with clavulanic acid 1000 mg, two times daily for 5 days. Pain, trismus, swelling (thickness of the cheek) were evaluated before surgery (T0) and then again on postoperative days 1 (T1) and 7 (T2). Peri-implants tissues damages were checked at the same time. Both groups were evaluated by the same team, who were unaware of pharmacological therapies and surgical procedure for each individual case, in order to avoid investigator bias. Postoperative pain was assessed with a visual analogue scale (VAS) of 10 units: The leftmost end represented absence of pain (score of 0) and the rightmost end indicated the most severe pain (score of 10). Trismus was evaluated by measuring the distance between the mesial incisal corners of the upper and lower right central incisors at the maximum mouth opening in millimeters, as described by Ustun et al. [18]. Postoperative swelling was considered the difference of the distances between two landmarks measured after and before surgery. The first landmark was situated on the lingual side of distal trigon region (5 mm from the distal cusps of second molar, if present), whereas the second landmark was located in the cutaneous region (2 cm medially to the mandibular angle) and marked with a dermographic pencil to allow postoperatively repetition of the measurement in the same cutaneous region. The distance between the 2 landmarks measured in degrees by a pair of compasses was converted in millimeters by means of superimposition on a millimeter ruler. The method chosen for swelling assessment was the same reported by Sortino et al. [5], this method was preferred to others reported in literature because it was easily and rapidly reproducible. Moreover, this method provides a volumetric measurement rather than a sum of linear measurements used by other methods. The preoperative measurement was the baseline value. The difference between each postoperative evaluation and baseline indicated the swelling for that day. Patients were further evaluated for paresthesia using the cotton wool test. Postoperative alveolar osteitis was checked for and documented if present [28,29].

Conclusion

Our study confirmed the researchers' views on the neuromodulators effect of um-PEA in the control of general complications after oral surgery. the results obtained in our sample were encouraging even if, in our opinion, confirmation should be sought in larger study groups. As the present investigation represents a pilot study, we are not able to establish whether the intake of PEA can positively influence the osseointegration of the dental implant. Furthermore, this research, in agreement with the most experienced researchers in the field, has successfully demonstrated the efficacy of um-PEA in the reduction of pain, swelling and trismus after oral surgery and the insertion of dental implants. Moreover, this treatment did not show serious side effects and was safer than the administration of conventional therapies. We can therefore conclude that PEA may be a useful treatment for pain and is generally well tolerated in research populations. Well-designed, randomized, placebo-controlled clinical trials are also needed to provide reliable estimates of its efficacy and to identify less serious adverse events associated with this compound. Obviously, to confirm what we have obtained, larger studies are needed to definitively demonstrate the advantages of use of um-PEA, as a pharmacological support in implant therapy and to evaluate its influence on the epidemiology of complications, but in our opinion the um-PEA administered sublingually is certainly useful for improving the comfort and postoperative of the patient undergoing to implant surgery.

References

1. Pjetursson BE, Heimisdottir K. Dental implants are they better than natural teeth? Eur J Oral Sci. 2018;126(Suppl 1):81-7.
2. Luciani F, Papa E, Leggeri A, Calabrese C, Coniglione F, Calabrese L. Diagnosis and treatment planning in oral surgery using Cone Beam Computed Tomography (CBCT): A narrative review. Int J Clin Dent. 2022;15(4):795-820.
3. Kotsakis GA, Romanos GE. Biological mechanisms underlying complications related to implant site preparation. Periodontol 2000. 2022;88(1):52-63.
4. Chapman PJ. Postoperative pain control for outpatient oral surgery. Int J Oral Maxillofac Surg. 1987;16(3):319-24.
5. Cecchetti F, Luciani F, Bramanti E, Bartuli FN, Ottria L, Arcuri C. Cemento-ossyfying fibroma juvenile of the oral cavity. Oral Implantol (Rome). 2010;3(1):33-7.
6. Ottria L, Luciani F, Piva P, Alagna AM, Arcuri C, Bartuli FN. The flap recovery on the impacted lower third molar surgery comparing 3 different flap designs: A clinical study. Oral Implantol. 2017;10(3):270-5.
7. Bartuli FN, Piva P, Savo A, Di Dio M, Luciani F, Arcuri C. Lower third molar germectomy: The flap recovery on the lower second molar. A clinical study. Int J Clin Dent. 2014;7(3):289-94.
8. Bailey E, Worthington HV, van Wijk A, Yates JM, Coulthard P, Afzal Z. Ibuprofen and/or paracetamol for pain relief after surgical removal of lower wisdom teeth. Cochrane Database Syst Rev. 2013;(12):CD004624.
9. Ardizzone A, Fusco R, Casili G, Lanza M, Impellizzeri D, Esposito E, et al. Effect of ultra-micronized-palmitoylethanolamide and acetyl-l-carnitine on experimental model of inflammatory pain. Int J Mol Sci. 2021;22(4):1967.
10. Esposito E, Cuzzocrea S. Palmitoylethanolamide is a new possible pharmacological treatment for the inflammation associated with trauma. Mini Rev Med Chem. 2013;13(2):237-55.
11. Impellizzeri D, Bruschetta G, Cordaro M, Crupi R, Siracusa R, Esposito E, et al. Micronized/ultramicronized palmitoylethanolamide displays superior oral efficacy compared to nonmicronized palmitoylethanolamide in a rat model of inflammatory pain. J Neuroinflammation. 2014;11:136.
12. Britti D, Crupi R, Impellizzeri D, Gugliandolo E, Fusco R, Schievano C, et al. A novel composite formulation of palmitoylethanolamide and quercetin decreases inflammation and relieves pain in inflammatory and osteoarthritic pain models. BMC Vet Res. 2017;13(1):229.
13. Skaper SD, Facci L, Barbierato M, Zusso M, Bruschetta G, Impellizzeri D, et al. N-palmitoylethanolamine and neuroinflammation: A novel therapeutic strategy of resolution. Mol Neurobiol. 2015;52(2):1034-42.
14. Micheli L, Lucarini E, Toti A, Ferrara V, Ciampi C, Parisio C, et al. Effects of ultramicronized N-palmitoylethanolamine supplementation on tramadol and oxycodone analgesia and tolerance prevention. Pharmaceutics. 2022;14(2):403.
15. Pedersen A. Interrelation of complaints after removal of impacted mandibular third molars. Int J Oral Surg. 1985;14(3):241-4.
16. Lima TC, Bagordakis E, Falci SGM, Dos Santos CRR, Pinheiro MLP. Pre-emptive effect of dexamethasone and diclofenac sodium associated with codeine on pain, swelling, and trismus after third molar surgery: A split-mouth, randomized, triple-blind, controlled clinical trial. J Oral Maxillofac Surg. 2018;76(1):60-6.
17. Laureano Filho JR, Maurette PE, Allais M, Cotinho M, Fernandes C. Clinical comparative study of the effectiveness of two dosages of dexamethasone to control postoperative swelling, trismus and pain after

the surgical extraction of mandibular impacted third molars. Med Oral Patol Oral Cir Bucal. 2008;13(2):E129-32.

18. Ustün Y, Erdogan O, Esen E, Karsli ED. Comparison of the effects of 2 doses of methylprednisolone on pain, swelling, and trismus after third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96(5):535-9.

19. Sridharan G, Nakkeeran KP, Andavan G, Raja VBKK. Effects of flap modification on third molar extraction outcomes - A randomised split mouth study. J Oral Biol Craniofac Res. 2020;10(4):619-24.

20. Materni A, De Angelis N, Di Tullio N, Colombo E, Benedicenti S, Amaroli A. Flapless surgical approach to extract impacted inferior third molars: A retrospective clinical study. J Clin Med. 2021;10(4):593.

21. Starzyńska A, Kaczoruk-Wieremczuk M, Lopez MA, Passarelli PC, Adamska P. The growth factors in Advanced Platelet-Rich Fibrin (A-PRF) reduce postoperative complications after mandibular third molar odontectomy. Int J Environ Res Public Health. 2021;18(24):13343.

22. Esposito E, Impellizzeri D, Bruschetta G, Cordaro M, Siracusa R, Crupi R, et al. A new co-micronized composite containing palmitoylethanolamide and polydatin shows superior oral efficacy compared to their association in a rat paw model of carrageenan-induced inflammation. Eur J Pharmacol. 2016;782:107-18.

23. Hu J, Ying H, Yao J, Yang L, Jin W, Ma H, et al. Micronized palmitoylethanolamide ameliorates methionine- and choline-deficient diet-induced nonalcoholic steatohepatitis *via* inhibiting inflammation and restoring autophagy. Front Pharmacol. 2021;12:744483.

24. Del Re A, Corpetti C, Pesce M, Seguella L, Steardo L, Palenca I, et al. Ultramicronized palmitoylethanolamide inhibits NLRP3 inflammasome expression and pro-inflammatory response activated by SARS-CoV-2 spike protein in cultured murine alveolar macrophages. Metabolites. 2021;11(9):592.

25. Germini F, Coerezza A, Andreinetti L, Nobili A, Rossi PD, Mari D, et al. N-of-1 randomized trials of ultra-micronized palmitoylethanolamide in older patients with chronic pain. Drugs Aging. 2017;34(12):941-52.

26. Rankin L, Fowler CJ. The basal pharmacology of palmitoylethanolamide. Int J Mol Sci. 2020;21(21):7942.

27. Clayton P, Hill M, Bogoda N, Subah S, Venkatesh R. Palmitoylethanolamide: A natural compound for health management. Int J Mol Sci. 2021;22(10):5305.

28. Paladini A, Fusco M, Cenacchi T, Schievano C, Piroli A, Varrassi G. Palmitoylethanolamide, a special food for medical purposes, in the treatment of chronic pain: A pooled data meta-analysis. Pain Physician. 2016;19(2):11-24.

29. Artukoglu BB, Beyer C, Zuloff-Shani A, Brener E, Bloch MH. Efficacy of palmitoylethanolamide for pain: A meta-analysis. Pain Physician. 2017;20(5):353-62.