Evaluation of changes in postoperative sequelae in implant surgery after the administration of the association of bromelain and escin: a pilot study

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Abstract

The purpose of this pilot study was to evaluate the possible effect of two natural enzymes, bromelain and escin (test), in the treatment of post-operative sequelae after open flap implant placement in the posterior area compared with painkiller medications (control).
Fourteen patients were enrolled and randomly assigned to test and control groups. Bromelain and escin were administered in the test group, and a placebo was administered in the control group. Oedema, pain, and trismus were evaluated at the baseline, 2 and 7 days after surgery. Trismus was assessed using an analogue method; oedema was assessed using analogue and digital methods, while pain was reported using a numerical rating scale (NRS). Descriptive analysis and not paired-test were performed.
The analogue data for oedema for the test and control groups was 10.73 ± 0.77 cm and 10.67 ± 0.74 cm (p-value baseline–7 days = 0.1004) at 7 days post-surgery. The digital analysis showed at 7 days post-surgery 0.41 ± 0.24 mm for the test group and 0.56 ± 0.52 mm for the control group (p-value baseline–7 days = 0.3140). Pain (NRS 0–10) was higher for the test group at each time point. Trismus was accentuated in the test group at each time point after the surgery.
Statistically significant differences were found for the analogue oedema evaluation between baseline and day 2, for trismus in both baseline and day 2 and baseline and day 7 comparison, and for paracetamol tablets intake at day 2. Further observations of more patients are needed.

Keywords: Bromelain; Implant Surgery; Implantology; Pain; Inflammation; Oedema. tions.

Introduction

Today, patient-related outcomes measures (PROMs) are closely monitored during oral surgeries. Reducing pain, morbidity, oedema, or swelling is of utmost importance in order to ensure that there is no adverse impact on the patient's quality of life. Therefore, there are several natural active principles that are proposed to reduce post-operative (post-op) complications. Bromelain is a family of proteolytic enzymes extracted from the plant *Ananas comosus* (1,2). Unlike the other fruit proteases, bromelain is more represented when the fruit reaches maturity (3). The main characteristics of bromelain are fibrinolytic, anti-oedematous, antithrombotic, and anti-inflammatory activities. Bromelain is able to increase the time needed for the conversion of prothrombin to thrombin; therefore, it leads to an activation of plasminogen in plasmin, and this promotes degradation and induces the inhibition of fibrin formation (4). Many studies have been conducted on bromelain and have allowed it to be evaluated in various fields, including orthopaedics, obstetrics, otolaryngology, ophthalmology, and dentistry (2,5,6).
Escin is the active component of *Aesculus hippocastanum*, the horse chestnut; it has anti-oedematous, anti-inflammatory, and venotonic properties. Its specific anti-inflamma-

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tory properties are reduction of vascular permeability in inflamed tissues and inhibition of oedema formation, as well as potential anti-oxidative effects (7).
After oral surgery, patients face post-operative sequelae, in particular: pain, trismus, and swelling (4). It is for this reason that drug therapy plays an essential role in helping the patient deal with the discomfort of the post-operative period. In dentistry, non-steroidal anti-inflammatory drugs (NSAIDs) and steroid anti-inflammatory drugs (SAIDs) are very frequently used. Evidence-based medicine showed that NSAIDs are the best analgesics for dental pain (8). The use of glucocorticoids is mainly limited to local applications, especially in surgery, due to their excellent anti-oedematous and painkiller activity (9). The adverse effects of NSAIDs and corticosteroids are several, and the approach to sequelae using different substances, compared to traditional anti-inflammatory drugs, could be interesting to evaluate. This pilot study aims to evaluate the possible efficacy of bromelain and escin (Noflogo® (NFG), Mavenpharma srl., Rome, Italy) in managing trismus, pain, and facial oedema in patients undergoing implant surgery.

Materials and Methods

Trial design

The study was conducted following Consolidated Standards of Reporting Trials (CONSORT) and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement for parallel studies and registered on clinicaltrials.gov (NCT04657874) (Release date September 7, 2021).
All the procedures were performed in accordance with the guidelines of the Helsinki World Medical Association Declaration and the Good Clinical Practice guidelines updated in 2013. Moreover, the present trial achieved favourable opinions from the Internal Review Board of the University of L'Aquila (D.R.n. 5185, 2018).
Each patient was given a form to evaluate the patient's inclusion criteria and allergies. The absence of previous randomised clinical trials on the possible use of bromelain and escin in implant surgery did not allow an estimation of a sample size suitable for the study; however, the sample size was adapted from a previous study on the use of bromelain in third molar extraction (6). After signing an informed consent, patients underwent one or more implant placements, in the area from the first premolar to the second molar, after raising a full thickness flap.
The implants placed were PRAMA ROOT FORM (RF) (Sweden & Martina, Padua, PD, Italy) of different diameters and lengths, according to the clinical situation and bone condition.
After the surgical procedures, performed by a blinded surgeon, patients were randomised into two groups through a closed envelope system. NFG was administered in group A (test group), and the placebo was administered in group B (control group) by a blinded operator who was involved in the collection of analogue and digital measurements. Both groups received a pack containing 10 tablets to be taken twice a day for a total of 5 days. The tablets, both NFG and placebo (maltodextrin, magnesium stearate, corn starch, silicon dioxide, animal gelatine, and titanium dioxide), were taken 1 hour before the main meals. Paracetamol was indicated as rescue medication, of which the patient had to indicate the number of 1000 mg tablets taken. In the case of NSAID consumption, patients were excluded.

Inclusion and exclusion criteria

Patients under examination were enlisted in the dental clinic of the University of L'Aquila.
The inclusion criteria were:

- Age between 18 and 80 years
- Bleeding on probing (BoP) and plaque index (PI) below 20%
- Absence of systemic diseases (20)
- Absence of inflammation in the treated site
- Patients required implant surgery in the posterior area from the first premolar to the second molar, with a rising flap.

The exclusion criteria were:

- Presence of significant and serious systemic diseases (20)
- Allergy to study substances
- Pregnancy
- Patients not in line with the protocol (i.e., anti-inflammatory administration during the post-operative analysis)
- Treatments with antibiotics or anti-inflammatory drugs in the two weeks preceding the study
- Need of implant insertion in the anterior area (from canine to canine)

Smokers were included in the study, and the number of cigarettes consumed per day was noted on the medical records even if it is known smoking is a factor that can negatively affect healing and the outcome of implant treatment (19).

Analogue analysis and data recording

During the study, some PROMs were evaluated, including pain, oedema, and trismus. Data were collected before the surgery, 48 hours after the surgery, and 7 days after the surgery. All the analogue and digital analyses were assessed by a calibrated operator and were recorded in the patient's medical records.
The operator calibration for the analogue analysis was performed by the same investigator one week before the start of the project on 10 subjects. The measurements of changes in mid-facial profile revealed a mean measurement error of 0.11 ± 0.08 cm, while the changes of the maximum opening space (for the trismus assessment) were 0.15 ± 0.09 cm.

Analogue pain assessment

A numerical rating scale (NRS) was used for pain evaluation. Patients were asked to indicate on a line a value between 0 and 10 for each visit, where 0 indicates no pain and 10 indicates the worst pain.

Analogue oedema assessment

To evaluate the swelling, a tape measure was used to assess the distance from the ear lobe incision to the labial incision (EL-LI) and the distance from the angle of the jaw to the outer angle of the eye (AJ-AE). (Figure 1)

Trismus assessment

In order to evaluate trismus, maximum opening spacing was measured using a calliper, placing the two arms between the upper and lower central incisors (Figure 2).

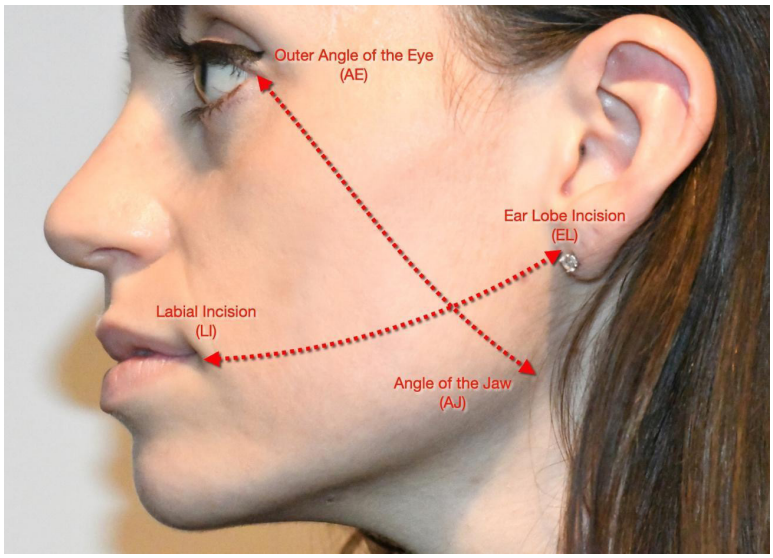

Figure 1. The reference points used for measurements.

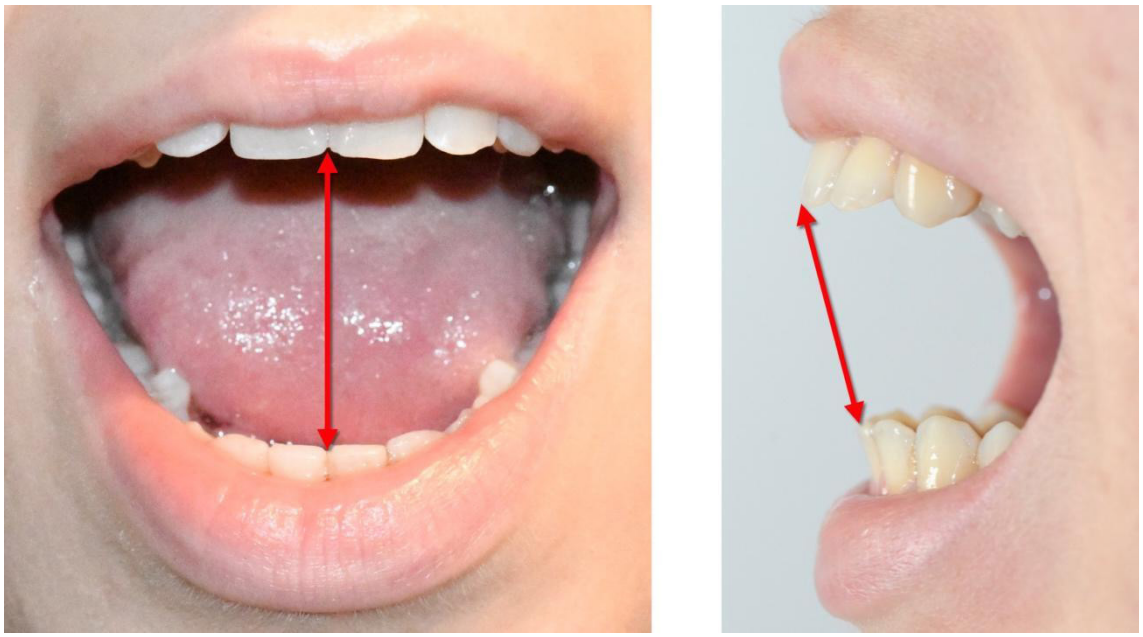

Figure 2. On the left, the maximum opening space considered. On the right, the points where the ends of the calliper arms were positioned for the measurement.

Digital analysis

A facial scan program (Bellus3D FaceApp, Bellus 3D Inc, Campbell, California, United Stated of America) was used to acquire a standard triangular language (.stl) file of the face before the surgery and at each follow-up. The tools used to perform the three-dimensional (3D) analysis were a tripod, a stabiliser (DJI Osmo Mobile 3, Nanshan District, Shenzhen, China, 518057), and an iPhone XS Max (Apple Inc., Cupertino, CA, USA) (Fig. 3). The appropriate distance for scanning was automatically detected from the software itself, using the front camera to visualise the patient's face in real time. As a reference point, an oval profile was reproduced on the iPhone screen. The correct alignment of the patient was detected automatically during the scan with a red/green colour. The scan program available was 'face + neck' and patients were instructed to follow these rules:

- 'Look at the camera'
- 'Turn left; turn to the middle'
- 'Turn right; turn to the middle'
- 'Tilt your head up; turn to the middle'
- 'Tilt your head down; turn to the middle'

All scans were imported into GOM Inspect (GOM Germany) (15-16). For each patient, the scans of each time point were superimposed: preoperative and after 2 days and preoperative and after 7 days. The region of interest (RoI) for each patient was set, considering these reference points (Fig. 4):

- Outer angle of the eye (AE)
- Anterior portion of the tragus (T)
- Projection of the lower part of the ear lobe on the posterior border of the mandible (ELM)
- Angle of the jaw (AJ)

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Figure 3. The devices and the equipment used to scan the faces of patients.

- Lateral portion of the chin, identified as the projection of the wing of the nose on the inferior border of the mandible (C)
- Labial incision (LI)
- Lower lateral surface of the external nose, named ala nasi (W) (18)

From the baseline to 7 days after surgery, oedema was evaluated according to the RoI, and the surface discrepancy between the scans was described using GOM Inspect (Fig. 5) (15-16).

Statistical analysis

A dataset was created using Microsoft Excel (Microsoft, 2019, Redmond, WA, USA). A not paired t-test was performed on the comparison between the test and the control groups for each parameter and was obtained after calculating the difference between the baseline and 2 and 7 days post-surgery. A p-value of 0.05 indicated a statistically significant difference.

Results

All patients enrolled in the study finished the trial, and no complications were recorded. Patients in the test group (5 men and 2 women) had a mean age of 54.43 ± 10.08 years (yr), while in the control group (4 men and 3 women), the mean age was 61.29 ± 12.01 years (Table 1). All the smoker patients smoked less than 10 cigarette/die.
All the data recorded were imported into an Excel file. For each group and type of sequelae, the mean and standard deviations were obtained (Table 2).+

Oedema

Analogue data assessing oedema at 2 days post-surgery were 10.90 ± 0.74 cm for the test group and 10.88 ± 0.77 cm for the control group (baseline–2 days p-value = 0.0328); at 7 days post-surgery, a mean of 10.73 ± 0.77 cm for the test group and 10.67 ± 0.74 cm for the control group (baseline–7 days p-value = 0.1004) was reported. The p-value obtained from the difference between the evaluation at 2 and 7 days was 0.3604.
From the digital results, the mean difference between the superimposed scans of the baseline and post-surgery was 0.44 ± 0.32 mm for the test group and 0.90 ± 0.65 mm for the control group. Between the baseline and 2 days after surgery, a mean of 0.78 ± 0.57 mm for the test group and 1.28 ± 1.31 mm for the control group was reported (p-value baseline–2 days = 0.0823); between the baseline and 7 days, a mean of 0.41 ± 0.24 mm for the test group and 0.56 ± 0.52 mm for the control group was reported (p-value baseline–2 days = 0.3140). Raw data for each patient are listed in (Table 3).

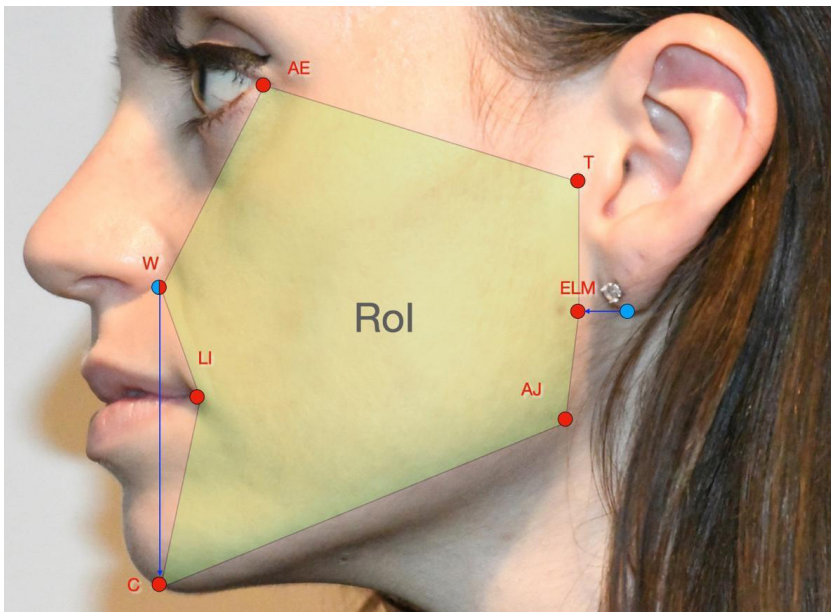

Figure 4. Graphic representation of the region of interest (RoI) for the digital analysis.

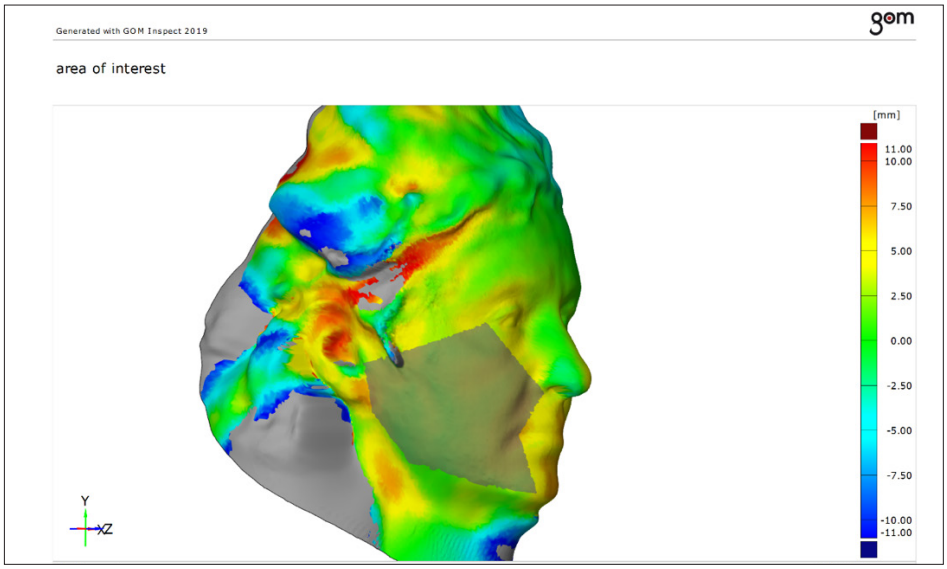

Figure 5. Region of interest (RoI) for the digital analysis highlighted on GOM Inspect.

Table 1. Patients' characteristics and percentage of males and females among test and control groups.

	NFG	Control	Total
Age (yr)	54.43 ± 10.08	61.29 ± 12.01	57.86 ± 11.23
Male	71%	57%	64%
Female	29%	43%	36%
Smokers	29%	43%	36%
Not smokers	71%	57%	64%

Table 2. Analogue data for oedema, pain, and trismus at each time point.

Oedema	Test	Control
Baseline	10.82 ± 0.77 cm	10.51 ± 0.92 cm
2 days post-op	10.90 ± 0.74 cm	10.88 ± 0.77 cm
7 days post-op	10.73 ± 0.77 cm	10.67 ± 0.74 cm
Pain *(NRS 0–10)*	Test	Control
Baseline	0.57 ± 1.51	0.29 ± 0.76
2 days post-op	3.57 ± 3.51	2.14 ± 1.86
7 days post-op	2.71 ± 2.93	2.00 ± 1.41
Trismus	Test	Control
Baseline	5.00 ± 1.08 cm	4.38 ± 0.70 cm
2 days post-op	4.19 ± 1.26 cm	4.48 ± 0.61 cm
7 days post-op	4.61 ± 0.99 cm	4.55 ± 0.51 cm

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Table 3. Raw data of the digital soft tissue discrepancy. L: left; R: right.

Patient code	Surgery area	Baseline–2 days (mean ± SD)	Baseline–7 days (mean ± SD)
T1	3.7	1.16 ± 2.08 mm	0.50 ± 0.86 mm
T2	2.6	1.45 ± 1.11 mm	0.81 ± 1.28 mm
T3	3.6; 4.5	0.13 ± 0.98 mm R 0.01 ± 0.80 mm L	0.64 ± 0.67 mm R 0.07 ± 1.09 mm L
T4	4.5–4.6	0.50 ± 1.61 mm	0.44 ± 1.05 mm
T5	4.4–4.5	0.59 ± 1.98 mm	0.31 ± 2.18 mm
T6	2.5	0.40 ± 1.20 mm	0.07 ± 0.94 mm
T7	2.6, 4.5	1.32 ± 1.73 mm R 1.45 ± 1.22 mm L	0.44 ± 1.21 mm R 0.41 ± 1.16 mm L
C1	1.6	4.33 ± 3.36 mm	1.00 ± 2.11 mm
C2	4.5, 4.6	1.10 ± 1.37 mm	0.08 ± 1.19 mm
C3	4.4, 4.5	1.78 ± 1.63 mm	0.31 ± 1.20 mm
C4	3.5, 4.5–4.6	0.58 ± 0.47 mm R 0.79 ± 0.39 mm L	0.40 ± 0.50 mm R 0.18 ± 0.60 mm L
C5	2.6	0.76 ± 1.25 mm	1.64 ± 1.41 mm
C6	1.5	0.45 ± 0.86 mm	0.26 ± 0.70 mm
C7	4.5–4.6	0.43 ± 1.35 mm	0.57 ± 1.51 mm

Two representative cases are described in Figure 6, where the superimposition between the baseline and the other time points revealed a surface discrepancy visualised with orange and red colours.

Pain (NRS 0–10)

Pain perception at 2 days post-surgery was 3.57 ± 3.51 (mean + SD) for the test group and 2.14 ± 1.86 for the control group, with an intragroup difference between the baseline and the 2 days evaluations of 3.00 ± 3.16 for the test group and 1.86 ± 1.86 for the control group (baseline–2 days p-value = 0.4262). At 7 days, a mean of 2.71 ± 2.93 for the test group and 2.00 ± 1.41 for the control group was reported, with an intragroup difference between the baseline and the 7 days evaluations of 2.14 ± 3.24 for the test group and 1.71 ± 1.11 for the control group (baseline–7days p-value = 0.7461).

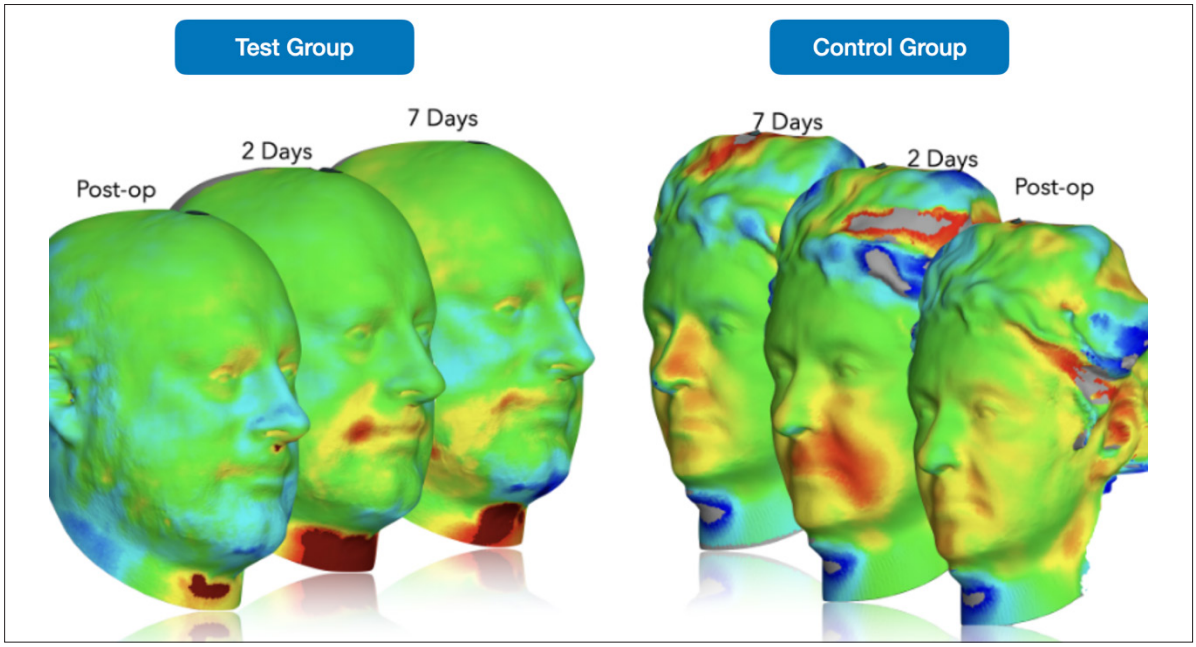

Figure 6. Two representative cases showing the 3D superimposition of the different time points (post-op, 2 days after surgery, and 7 days after surgery) in each group.

Trismus

The maximum opening space measured at 2 days was 4.19 ± 1.26 cm for the test group and 4.48 ± 0.61 cm for the control group; at 7 days, trismus was 4.61 ± 0.99 cm for the test group and 4.55 ± 0.51 cm for the control group. The intragroup differences between the baseline and 2 days evaluations were -0.81 ± 0.56 cm for the test group and 0.10 ± 0.40 cm for the control group (baseline–2 days p-value = 0.0044), while the intragroup differences between the baseline and 7 days evaluations were -0.40 ± 0.20 cm for the test group and 0.17 ± 0.65 cm for the control group (baseline–7 days p-value = 0.0485).

Paracetamol

The intake of paracetamol tablets at 2 days was 2.57 ± 1.40 tablets for the test group and 0.57 ± 0.53 tablets for the control group (baseline–2 days p-value = 0.0041). At 7 days, a mean of 3.43 ± 4.20 tablets was recorded for the test group, and 1.29 ± 1.25 tablets were recorded for the control group (baseline–7 days p-value = 0.2200). The intragroup difference in tablet intake between the baseline and 2 days and the baseline and 7 days was as reported before because the initial intake was 0 for both groups.

Intragroup comparison and p-value

It can be observed that from all the intragroup comparison, p-value < 0.05 were found in the baseline-2 days comparison of analogue oedema (0.0328*), trismus (0.0044*) and paracetamol tablet intakes (0.0041*) and in the baseline-7 days comparison only of trismus (0.0485*) (Table 4).

Discussion

The present pilot study, assessing the use of bromelain and escin in the post-operative sequelae after open flap implant placement, predominately revealed that:

- NoFlogo® had a statistically significant effect on the reduction of oedema when analogically evaluated.
- Trismus was significantly reduced in patients when a placebo was administrated.

Bromelain and escin are the substances contained in NFG: bromelain is an extract obtained from the pineapple plant, and the pharmaceutical value of bromelain has been demonstrated in many surgical specialisations. Various biological processes, like anti-inflammatory, analgesic, anti-oedematous, and anti-thrombotic, are involved in bromelain's therapeutic actions. These actions are mediated either through the kallikrein-kinin and arachidonic acid pathways or through effects on cell-mediated immunity. Generally, bromelain is administered for oral or topical use for surgical wounds and inflammation caused by surgical trauma. Literature suggests an encouraging role of bromelain in surgical care (5). Escin, the active component of *Aesculus hippocastanum*, or the horse chestnut, is generally dispensed as orally absorbable pills or as a transdermal gel. Escin has anti-inflammatory and anti-oedematous effects, due to the property of reducing vascular permeability in inflamed tissues, thereby inhibiting oedema formation (7). Many studies have highlighted the effect of substances like bromelain and escin, mainly for the extraction of third molars, such as the study of de la Barrera-Núñez et al. , where bromelain and escin showed a trend towards less inflammation and improved oral aperture compared to the placebo (4-14).

A gradual facial swelling occurs in response to tissue trauma, usually with a peak swelling after 48 hours. In investigations, there are different and various methods used to evaluate oedema after oral surgery, for example, measuring with a silk suture or a tape, visual analogue scale, plethysmography, or even ultrasound. In this study, we used a measuring tape for the analogue method and a facial scanner app on an iPhone for the digital method. A statistically significant result for the test group compared to the placebo group was found in the baseline–2nd day comparison of the analogue measurements (p-value = 0.0328), while no statistical significance was found for the digital method (10).

Trismus refers to the restriction of the range of motion of the jaws. Initially described in the setting of tetanus, it now can refer to restricted range of mouth opening due to any aetiology. It is normally temporary and resolves in less than two weeks, and it causes interferences with

Table 4. Mean + standard deviation (SD) of each PROMs and paracetamol intake for each evaluation and p value from the t-test. *Statistically significant results (p-value < 0.05).

	NFG (mean ± standard deviation (SD))		**Control (mean ± SD)**		***p*-value**	
Difference	Baseline–2nd day	Baseline–7th day	Baseline–2nd day	Baseline–7th day	Baseline–2nd day	Baseline–7th day
Analogue oedema	0.08 ± 0.50 cm	-0.09 ± 0.53 cm	0.44 ± 0.46 cm	0.17 ± 0.39 cm	0.0328*	0.1004
Digital oedema	0.78 ± 0.57 mm	0.41 ± 0.24 mm	1.28 ± 1.31 mm	0.56 ± 0.52 mm	0.0823	0.3140
Trismus	-0.81 ± 0.56 cm	-0.40 ± 0.20 cm	0.10 ± 0.40 cm	0.17 ± 0.65 cm	0.0044*	0.0485*
Pain (NRS 0–10)	3.00 ± 3.16	2.14 ± 3.24	1.86 ± 1.86	1.71 ± 1.11	0.4262	0.7461
Paracetamol (number of tablets)	2.57 ± 1.40	3.34 ± 4.20	0.57 ± 0.53	1.29 ± 1.25	0.0041*	0.2200

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daily activities (11). Trismus is considered as an unwanted, but typically reported, limited mouth opening, especially after oral surgery procedures. In several studies, the inter-incisal distance measurements at different time points are commonly used for the evaluation of trismus, as in our study (12). In this study, a reduction of the trismus was observed in patients where the placebo was administrated in both time-point comparisons (baseline–2nd day p-value = 0.0044; baseline–7th day p-value = 0.0485).

Paracetamol is an effective drug to use for post-operative pain after oral surgery, and the low number of adverse events make it a safe drug (13). In this study, paracetamol was used as a rescue medication drug because it does not have anti-inflammatory action, only painkiller and antipyretic actions, and also because is a well-tolerated drug and produces few side effects for the gastrointestinal tract (14). A statistically significant result for the control group compared to the test group was found in the baseline–2nd day comparison (p-value = 0.0041).

Facial scanning seemed to be an interesting alternative to the analogue methods for measuring the oedema of the face, as the reference points examined may vary between the different assessments due to operator-dependent errors. The software used to analyse the scans in standard triangular language (.stl) format, GOM Inspect®, allowed us to precisely overlap the scans by means of a dedicated alignment system (a reference point system (RPS) alignment—hierarchical alignment based on geometric elements, alignment in a local coordinate system, and alignment by reference points, as well as various best-fit methods, such as global or local best-fit) (15-16).

Regarding the equipment used in the three-dimensional assessment of the face, the stabiliser seemed to have reduced the acquisition errors mainly due to incorrect movements of the patient, such as vibrations, oscillations, simultaneous movements of the smartphone and the head, and inclination of the smartphone. It could be interesting to mount the stabiliser on a slider in that way the device moves while the patients' head stays still, in a similar way to the study of Raffone et al. (17).

As for the trismus, the calliper used to measure the inter-incisive distance of maximum opening was found to be a good method for the compliance of the patients. Nevertheless, the use of this instrument can lead to slightly different or deviated results depending on its inclination in the oral cavity. Limitations of the study can be found in the number of analysed patients and in the lack of standardised universal protocols to compare the results with other studies in literature.

Conclusions

Based on the results of this pilot study, the following conclusions could be reported:

- The main statistically significant differences in the reduction of the sequelae of implant surgery on posterior areas were found for analogue oedema between baseline and day 2, for trismus in both baseline and day 2 and baseline and day 7 differences, and for paracetamol tablet intake at day 2.
- The use of bromelain and escin, NoFlogo®, seemed to be effective only at day 2 for the analogue evaluation, while the other p-values (<0.05) showed better results for the placebo in the maximum opening space (trismus) at days 2 and 7 and for the paracetamol intake only at day 2.
- Digital oedema and pain did not show statistically significant results (p-value > 0.05).

To evaluate the association of bromelain and escin for the treatment of post-operative sequalae, future randomised clinical trials are needed.

Author Contributions:
E.M. and M.D. conceived the study design and drafted the protocol. T.P. participated in the patient recruitment and in the digital and analogue data recording. L.M. evaluated the digital data. P.R. was the main operator. F.C. performed the statistical analysis. All authors read and approved the final manuscript.

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Conflicts of Interest
The authors declare no conflict of interest.

Informed Consent Statement
Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

Internal Review Board Statement
All the procedures were performed in accordance with the guidelines of the Helsinki World Medical Association Declaration and the Good Clinical Practice guidelines updated in 2013. The present trial achieved favourable opinions from the Internal Review Board of the University of L'Aquila (D.R.n. 5185, 2018).

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