CLINICAL ORAL IMPLANTS RESEARCH WILEY

Patient-reported outcomes of implant placement performed concomitantly with transcrestal sinus floor elevation or entirely in native bone

Journal:	*Clinical Oral Implants Research*
Manuscript ID	COIR-Aug-15-OR-5014.R1
Manuscript Type:	Original Research
Date Submitted by the Author:	05-Nov-2015
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Keywords:	Biomaterials, Bone substitutes, Clinical research, Clinical trials, Guided tissue regeneration, Bone regeneration, Patient centered outcomes, Sinus floor elevation, Surgical techniques

Revision of the manuscript entitled

"Patient-reported outcomes of implant placement performed concomitantly with transcrestal sinus floor elevation or entirely in native bone"

submitted to *Clinical Oral Implants Research*
(manuscript ID: COIR-Aug-15-OR-5014)

Authors' response to reviewers' comments

Referee: 1

The PROMs was limited to pain (VAS ratings) assessments which warrants discussion (although it is acknowledge that this in itself is useful).

IN OUR STUDY, DIFFERENT PATIENT-REPORTED OUTCOMES WERE CONSIDERED IN ADDITION TO THE ASSESSMENT OF PAIN LEVELS THROUGH A 100-MM VAS: LEVEL OF DISCOMFORT PERCEIVED BY THE PATIENT ($VRS_{DISCOMFORT}$); WILLINGNESS TO UNDERGO THE SAME TYPE OF SURGERY ($VRS_{WILLINGNESS}$); SELF-ADMINISTERED DOSAGE OF RESCUE ANTI-INFLAMMATORY DRUG. OBVIOUSLY, OUR STUDY HAS SOME LIMITATIONS, SINCE OTHER ASPECTS OF THE POST-SURGERY SEQUELAE (SUCH AS SWELLING, BLEEDING AND BRUISING) WERE NOT CONSIDERED. THIS WAS DUE TO THE RETROSPECTIVE NATURE OF THE STUDY, AND HAS BEEN MADE CLEAR IN A PARAGRAPH IN THE DISCUSSION SECTION: "*Due to the retrospective nature of the study, the assessment of patient-reported outcomes was focused on aspects related to pain and use of analgesics, discomfort, and patient acceptance. Among these parameters, the level of postoperative pain, as assessed through the use of a 100-mm Visual Analogue Scale (VAS), was regarded as the primary outcome variable of the study. The use of VAS as tools …*".

Data analyses. In assessing difference in VAS ratings over time - why was AUC (area-under-the curve) not determined. This would provide insight into pain experience over the one-week period.

WE AGREE WITH THE REVIEWER. THEREFORE, AUC WAS CALCULATED FOR EITHER TSFE AND N GROUPS IN ORDER TO EXPRESS THE PAIN EXPERIENCE THROUGH THE ENTIRE WEEK FOLLOWING SURGERY. THE METHODOLOGY AND RESULTS OF THIS ADDITIONAL ANALYSIS ARE NOW REPORTED IN THE REVISED VERSION OF THE MANUSCRIPT. ALSO, THE DISCUSSION HAS BEEN IMPLEMENTED WITH THIS INFORMATION: "*The pain experience during the entire first postoperative week (as evaluated through AUC_{pain}) was not significantly different between groups, thus indicating that tSFE and N are both well tolerated. This consideration is corroborated further by the fact that tSFE did not determine an increased consumption of analgesics compared to implant insertion entirely in native bone. While from day +3 the median value of VAS_{pain} in N group was 0, the persistence of low pain levels (< 5 on a 100-mm scale) was observed in tSFE group up to day +7. This finding could be explained, at least in part, by the longer operative time required for the tSFE group compared to the N group. In this respect, it was previously demonstrated that longer implant surgery sessions are associated with higher VAS pain scores during the first postoperative week when compared to shorter sessions (Tan et al. 2014). Also, it may be hypothesized that the detachment of the Schneiderian membrane may determine a transient increase in pain levels due to the stimulation of membrane innervation (Heasman 1984, van den Bergh et al. 2000). The absence of significant inter-group differences in AUC_{pain}, however, seems to suggest that persisting pain observed in tSFE patients at single time intervals was sporadic within each patient patient and of limited intensity compared to N treatment.*''.

I wondered if prevalence of use of anti-inflammatory is worthy to consider i.e. use of rescue anti-inflammatory meds at any time point.

WE AGREE WITH THE REVIEWER THAT THE PREVALENCE OF SUBJECTS USING ANTI-INFLAMMATORY AGENTS AT EACH TIME POINT IS A RELEVANT INFORMATION THAT SHOULD BE ADDED. THEREFORE, WE IMPLEMENTED TABLE 2 WITH THE PREVALENCE OF SUBJECTS ASSUMING AT LEAST 1 RESCUE ANALGESIC AT EACH TIME POINT. THE RESULTS ARE ALSO REPORTED IN THE TEXT.

The discussion lacks information on the implications of these findings to patients or clinical practice that is worthy of consideration.

AS REQUESTED BY THE REFEREE, WE HAVE ADDED A PARAGRAPH DEDICATED TO THE CLINICAL IMPLICATIONS OF THE FINDINGS FROM THIS STUDY AT THE END OF THE CONCLUSIONS SECTION: "*The results of the present study showed that implant placement performed either concomitantly with tSFE (according to the Trombelli et al. 2009) or entirely in native bone are associated with limited incidence of complications, low postoperative pain and medication and are both well tolerated. When considering that (i) tSFE allowed for the concomitant placement of implants of proper dimensions in cases where the residual bone height would have otherwise impaired the implant-supported rehabilitation, (ii) tSFE did not determine an increased consumption of analgesics compared to implant placement in native bone, and (iii) previous findings demonstrated that the proposed tSFE technique is a user-friendly, safe, predictable and minimally-invasive procedure (Trombelli et al. 2010a,b, 2012, 2014, 2015, Franceschetti et al. 2014, 2015), tSFE seems to represent a well-accepted option with a favorable risk-benefit ratio when used concomitantly with implant placement in the atrophic posterior maxilla.*".

In addition, given that pain (VAS) outcomes are often used as a basic PROM measures comparisons with other studies (albeit different treatment modalities) is worthy to contextualize pain experiences from implant treatment.

TO ADDRESS THIS ISSUE, WE HAVE IMPLEMENTED THE DISCUSSION SECTION WITH AN ADDITIONAL PARAGRAPH, INCLUDING SOME INFORMATION TO CONTEXTUALIZE THE VAS ASSESSMENT OF POSTOPERATIVE PAIN IN DENTAL AND IMPLANT RESEARCH: "*…Among these parameters, the level of postoperative pain, as assessed through the use of a 100-mm Visual Analogue Scale (VAS), was regarded as the primary outcome variable of the study. The use of VAS as tools for the assessment of patient perception has become increasingly frequent in dental research during the last decades due to their ease of administration and reproducibility. In this respect, VAS were used to measure the anxiety of patients before and after dental treatment as well as their level of pain following different non-surgical and surgical procedures (Seymour et al. 1983, Luyk et al. 1988, Matthews & McCulloch 1993, Canakçi & Canakçi 2007, Fardal & McCulloch 2012, Tan et al. 2014). More recently, the use of VAS has been extended to implant research. In particular, VAS were used to measure pain levels following implant surgery (Al-Khabbaz et al. 2007, Fardal & McCulloch 2012, Tan et al. 2014) and, less frequently, other aspects of post-surgery sequelae such as swelling, bleeding and bruising (Tan et al. 2014). In the present study, VAS levels reported for tSFE treatment were similarly low when compared with those reported in previous trials on the same procedure (Trombelli et al. 2012, 2014). In group N, pain levels were consistent with previous studies (Tan et al. 2014), but differed with those reported by other Authors for conventional implant surgery (Al-Khabbaz et al. 2007). It must be considered, however, that the comparison of data on pain levels among studies is complicated by differences in pain assessment methods, technical aspects (e.g. flap design and extension), and pharmacological protocol for pain control.* ".

Conclusion is supported by results.
NO COMMENTS ADDED.

Referee: 2
There are major concerns with regard to the following points:
- *Lack of a hypothesis;*
- *No precise definitions of primary and secondary outcomes (e.g. focus on patient-reported outcomes as primary outcome);*
- *Design of the case series, including selection of study participants, treatment protocol;*
- *Re-structure of the entire Discussion section without repetition of results but interpreting of the results icompared to the current literature;*
- *Some minor language improvements.*

ALL THE MAJOR ISSUES RAISED BY THE REFEREE HAVE BEEN ADDRESSED INDIVIDUALLY (SEE OUR RESPONSES REPORTED BELOW FOR DETAILS). IN PARTICULAR:
- A HYPOTHESIS HAS BEEN ADDED AT THE END OF THE INTRODUCTION SECTION;
- PRIMARY AND SECONDARY OUTCOMES OF THE STUDY HAVE BEEN DEFINED IN DETAILS;
- THE MATERIALS AND METHODS SECTION HAS BEEN IMPLEMENTED WITH ADDITIONAL INFORMATION REGARDING THE STUDY CENTERS, CLINICAL OPERATORS, AND MATERIALS (IMPLANT SYSTEM, GRAFTING MATERIALS, ETC.);
- THE DISCUSSION SECTION HAS BEEN ENTIRELY REVISED BY (I) ADDING A PARAGRAPH DEDICATED TO DISCUSS THE METHODOLOGICAL ASPECTS OF THE STUDY DESIGN; (II) OMITTING ALL REDUNDANT SECTIONS; AND (III) FOCUSING ON PATIENT CENTERED OUTCOMES.

In general, there is no need for a clinical trial to demonstrate that a more complex surgical procedure, as sinus floor elevation, takes more time compared to a straightforward implant placement. Therefore, please change the order of outcomes: primary "patient-reported outcomes", secondary "(surgical) complications".

WE TOTALLY AGREE WITH THE REVIEWER. FOR INSTANCE, OPERATIVE TIME HAS BEEN INCLUDED AMONG EXPERIMENTAL ASSESSMENTS SINCE IT WAS PREVIOUSLY DEMONSTRATED TO BE ASSOCIATED WITH VAS PAIN SCORES DURING THE FIRST POSTOPERATIVE WEEK FOLLOWING IMPLANT SURGERY (TAN ET AL. 2014). THEREFORE, OPERATIVE TIME IN TSFE AND N GROUPS MAY HELP TO BETTER INTERPRET OUR RESULTS IN TERMS OF PATIENT-CENTERED OUTCOMES (PAIN, IN PARTICULAR). FOR BETTER CLARITY, WE HAVE CHANGED THE ORDER OF THE OUTCOMES AS SUGGESTED. IN ADDITION WE HAVE CLARIFIED THAT THE PRIMARY AND SECONDARY OUTCOMES OF OUR STUDY WERE REPRESENTED BY VAS_{PAIN} AND THE OTHER PATIENT-CENTERED OUTCOMES, RESPECTIVELY ("*VAS_{pain} was regarded as the primary outcome variable. … The other patient-centered outcomes (i.e., $VRS_{discomfort}$, $VRS_{willingness}$, dosage of rescue anti-inflammatory drug) and the incidence of complications were regarded as the secondary outcome variables.*").

In conclusion, I would like to suggest that the short communication format for retrospective case series, as a type of preliminary clinical study, would be more suitable than the present long manuscript form.

WE ARE CONVINCED THAT THE PRESENT STUDY HAS PROVIDED WITH SOLID DATA ON A NOVEL ASPECT OF RECONSTRUCTIVE SURGERY IN THE ATROPHIC POSTERIOR MAXILLA. IN THE DISCUSSION SECTION WE HAVE SUSTAINED THE CHOICE AND VALIDITY OF A RETROSPECTIVE DESIGN. IN THE STATISTICAL ANALYSIS SECTION, THE POWER ANALYSIS INDICATED AN ACCEPTABLE STATISTICAL POWER OF THE STUDY. ON THE BASIS OF THESE CONSIDERATIONS,

WE STILL THINK THAT THIS MATERIAL DESERVES PUBLICATION IN ITS CURRENT (EXTENDED) FORMAT.

In detail:
Title:
The present title is confusing according to the order of investigated outcomes.
I would like to suggest changing the title in "Patient-reported outcomes of implant placement performed concomitantly with transcrestal sinus floor elevation or entirely in native bone".

WE AGREE WITH THE REFEREE. THE TITLE HAS BEEN CHANGED ACCORDINGLY.

Abstract:
The entire Abstract has to be re-written and adapted according to the aforementioned recommendations focusing on patient-reported outcomes.
A clear aim (including hypothesis) of the retrospective case series has to be stated.
The number of involved patients and also the number of implants are missing.
Please note the exact p-level whenever you want show a significant difference.

THE ABSTRACT HAS BEEN RE-ARRANGED IN ACCORDANCE WITH THE REFEREE'S INDICATIONS. MORE SPECIFICALLY:

- A CLEAR AIM (INCLUDING AN HYPOTHESIS) HAS BEEN INCLUDED;
- DATA ON THE NUMBER OF PATIENTS AND IMPLANTS HAVE BEEN ADDED;
- EXACT P LEVELS HAVE BEEN INDICATED WHEN STATISTICAL COMPARISONS WERE SIGNIFICANT. WHEN P LEVEL WAS LOWER THAN 0.001, HOWEVER, WE REPORTED "P< 0.001".

Introduction:
Please define the last section of the Introduction and add a clear aim (including hypothesis). Indicate the investigation as a multi-centered retrospective case series.

TO ADDRESS THE REVIEWER'S ISSUE, THE LAST PARAGRAPH OF THE INTRODUCTION SECTION HAS BEEN REPHRASED AS FOLLOWS: "*The present study was based on the hypothesis that tSFE does not increase the intra- and postoperative morbidity of implant surgery. To test this hypothesis, a multicenter retrospective case series was implemented to evaluate the patient-reported outcomes as well as the type and incidence of complications when implants are placed either concomitantly with tSFE or in native bone.*".

Material & Methods:
Please sub-divide the Material & Methods section in 3 major blocks:

- *Study design*

Details according to the 4 centers and calibration process/guarantee of the surgeons; Precise definitions of outcomes: explanation why do you use "Visual Rating Scales" and "Visual Analogue Scales", who defined the questions;
Descriptions of the study population and inclusion criteria: who did select retrospectively the patients? (why 2 groups with different number of patients n=14 vs n=17; see results)

- *Interventions*

More clinical protocol for test and control groups (e.g. implant system, augmentation material, …);
Add info with regard to the used implant system(s);
What is the used radiographic device; was it all the same in every center?

- *Statistical analysis*

What are the specific data you are using for the power calculation? Just assumption?

THE MATERIALS AND METHODS SECTION HAS BEEN RE-ARRANGED IN ACCORDANCE WITH THE SUGGESTIONS OF THIS REFEREE. IN PARTICULAR, THREE SECTIONS HAVE BEEN CREATED: ”STUDY DESIGN”, “INTERVENTIONS” AND “STATISTICAL ANALYSIS”. FOR BETTER CLARITY, WE HAVE PREFERRED TO MAINTAIN THE DESCRIPTION OF THE STUDY PARAMETERS IN A SEPARATE PARAGRAPH (“STUDY PARAMETERS”).
IN THE SECTION “STUDY DESIGN”, WE HAVE INCLUDED DETAILS ON THE 4 CLINICAL CENTERS, 3 CLINICAL OPERATORS AND THEIR EXPERIENCE IN THE INVESTIGATED TSFE PROCEDURE. DUE TO THE RETROSPECTIVE NATURE OF THE STUDY, IT WAS NOT POSSIBLE TO PERFORM A PRE-TRIAL TRAINING SESSION ON CLINICAL PROCEDURES. HOWEVER, ALL PARTICIPATING CLINICAL OPERATORS HAD BEEN PREVIOUSLY INVOLVED IN CLINICAL TRIALS ON THE INVESTIGATED TSFE PROCEDURE. ALSO, WE HAVE INCLUDED SOME INFORMATION WITH REGARD TO THE EXAMINER RESPONSIBLE FOR THE RETROSPECTIVE SELECTION OF PATIENTS.
IN THE SECTION “INTERVENTIONS”, WE HAVE IMPLEMENTED THE PARAGRAPH WITH ADDITIONAL DETAILS REGARDING THE ADOPTED IMPLANT SYSTEMS, BONE AUGMENTATION MATERIALS, AND INSTRUMENTS FOR RADIOGRAPHIC EXAMINATIONS.
IN THE SECTION “STUDY PARAMETERS”, WE HAVE CLARIFIED HOW THE QUESTIONNAIRE WAS PREPARED AND THE RATIONALE FOR THE USE OF VRS AND VAS SCALES.
IN THE SECTION “STATISTICAL ANALYSIS”, WE HAVE IMPLEMENTED THE STATISTICAL POWER CALCULATION WITH THE REQUESTED INFORMATION.

Results:
Please explain… Why 2 groups with a different number of patients n=14 vs n=17? Is the number of patients identical with the number of implants?

IN BOTH THE MATERIALS AND METHODS AND RESULTS, WE HAVE CLARIFIED THAT THE PATIENT SAMPLE IS A CONVENIENCE SAMPLE (THUS RESULTING FROM THE RETROSPECTIVE SELECTION OF ALL PATIENTS SATISFYING THE INCLUSION CRITERIA).
WHEN LISTING THE SELECTION CRITERIA, WE HAVE PREVIOUSLY STATED THAT PATIENTS “UNDERGONE IMPLANT PLACEMENT FOR SINGLE-TOOTH REHABILITATION IN THE POSTERIOR MAXILLA” WERE SELECTED FOR THE STUDY. IN ADDITION, IN THE STATISTICAL ANALYSIS SECTION WE STATED THAT “THE PATIENT WAS REGARDED AS THE STATISTICAL UNIT. THEREFORE, ONLY ONE ELIGIBLE IMPLANT SITE WAS CONSIDERED FOR EACH PATIENT.“. THEREFORE, THE NUMBER OF PATIENTS WAS IDENTICAL TO THE NUMBER OF IMPLANTS.

Please note the exact p-level whenever you want show a significant difference.

IN THE ENTIRE RESULTS SECTION, SIGNIFICANT DIFFERENCES ARE NOW ACCOMPANIED BY THE EXACT P VALUE. WHEN THE P VALUE WAS LOWER THAN 0.001, WE INDICATED “P< 0.001”.

The distribution of implant sites is lacking for the control group. Please use a more simple way to show the distribution of the investigated n=31 implants.

TO ADDRESS THE REVIEWER’S ISSUE, WE HAVE IMPLEMENTED THE RESULTS WITH THE FOLLOWING SENTENCE: “*The frequency distribution of patients according to the location of the implant site (i.e., first premolar, second premolar, first molar, second molar) was 0, 2, 11, 1, respectively, in the tSFE group, and 8, 5, 4, 0, respectively, in N group.*“. WE BELIEVE THAT THE USE OF A SINGLE SENTENCE IS MORE STRAIGHT-FORWARD THAN A DEDICATED TABLE TO REPORT THIS INFORMATION.

Try to shorten the Result and do not repeat information that are already shown in the tables.

WE HAVE REVISED THE RESULTS SECTION, SHORTENING THE TEXT AND OMITTING THE REDUNDANT PARTS.

Discussion:
The Discussion section has to be re-structured in general.
Please do not just repeat results… Focus on patient-centred outcomes.
THE DISCUSSION HAS BEEN ENTIRELY REVISED FOR THE ELIMINATION OF REDUNDANT SECTIONS. WHEN STRUCTURING THE DISCUSSION, WE DID EVERY ATTEMPT TO FOCUS ON THE ORIGINAL ASPECTS (MAINLY RELATED TO PATIENT-CENTERED OUTCOMES) OF OUR STUDY, INCLUDING ALL PERTINENT AND UP-TO-DATE INFORMATION AVAILABLE IN THE LITERATURE.

Describe critically the limitations of the retrospective 4 centered case series.

AS REQUESTED, THE MAIN CHARACTERISTICS OF THE STUDY DESIGN ARE NOW DISCUSSED IN A DEDICATED PARAGRAPH OF THE DISCUSSION SECTION: "*In the present study, a retrospective multicenter design has been implemented to test our hypothesis. It may be argued whether or not the retrospective nature of the study may represent a methodological limitation. It must be considered, however, that the two investigated treatments (N and tSFE) have different local indications according to the height of the residual bone crest, thus limiting the possibility to apply a prospective, randomized controlled design. In this context, the scientific value of data from retrospective cohorts seem to be sufficiently adequate to test our hypothesis. In addition, the participation of three different clinical operators to the trial may raise an issue related to the potential influence of the level of experience in implant surgery, in general, and the investigated tSFE procedure, in particular, on the study outcomes. In a recent study (Franceschetti et al. 2015), the effectiveness of the procedure (in terms of extent of sinus lift) appeared to be affected by the level of experience in implant dentistry. However, we also demonstrated that the learning curve of the investigated tSFE procedure is steep, thus allowing for inexpert operators to reach a high performance within a limited number of cases. Also, the incidence of intra- and post-operative complications and the self-administered dosage of analgesics were similarly low irrespective of the level of operator experience (Franceschetti et al. 2015). Although considering that the three clinical operators were all expert in implant surgery and had been previously involved in clinical trials on the investigated tSFE procedure (Trombelli et al. 2010b, 2012, 2014, 2015, Franceschetti et. 2014, 2015), it can not be excluded that the presence of different operators within the trial may have had an influence on the study outcomes.*".

Conclusions:
Please indicate clearly a Conclusion section (not just a paragraph within the Discussion).

THE STUDY CONCLUSIONS ARE NOW REPORTED IN A DEDICATED SECTION.

Figures:
Figure 3 needs to be explained in detail.

IN THE RESULTS SECTION, THE PARAGRAPH DEDICATED TO THE DESCRIPTION OF FIGURE 3 HAS BEEN IMPLEMENTED AS FOLLOWS: "*VAS_{pain} in tSFE and N groups is reported in Table 3 and illustrated in Figure 3. On day +1, VAS_{pain} was low in both treatment groups. During the following postoperative days, a*

tendency of VAS_{pain} to decrease was observed in both groups. AUC_{pain} was 18.0 (IR: 8.5 – 85.0) and 11.5 (IR: 4.5 – 18.5) in tSFE and N groups, respectively, with no significant inter-group differences (p= 0.084).".

Statistical Advisor: 1

The primary endpoint is defined the VAS of pain. With this endpoint a power analysis is determined with an effect of 5 mm and a sd of 5mm. Are these values realistic?

UNFORTUNATELY, NO PREVIOUS STUDIES COMPARING TSFE AND N TREATMENTS IN TERMS OF POSTOPERATIVE PAIN WERE AVAILABLE TO OBTAIN DATA FOR POWER CALCULATION. AS NOW REPORTED IN THE REVISED VERSION OF THE MANUSCRIPT (ON THE BASIS OF AN ISSUE RAISED BY REFEREE #2), DATA ON EXPECTED INTER-GROUP DIFFERENCE AND SD WERE DERIVED FROM STUDIES EVALUATING THE LEVEL OF POSTOPERATIVE PAIN THROUGH A 100-MM VAS SCALE FOLLOWING IMPLANT SURGERY IN NATIVE BONE (AL-KHABBAZ ET AL. 2007) OR CONCOMITANTLY WITH TSFE (TROMBELLI ET AL. 2014). ACCORDING TO DATA REPORTED IN THESE PAPERS, THE DIFFERENCE IN 100-MM VAS PAIN (AS ASSESSED AT 7 DAYS FOLLOWING SURGERY) BETWEEN GROUPS AMOUNTS TO 7-8 MM. TO ENSURE AN ADEQUATE SAMPLE SIZE, WE USED A LOWER EXPECTED EFFECT (5 MM) AND A SD GREATER THAN THOSE REPORTED BY THE AUTHORS.

The power analysis is based on a t-test which assume normally distributed data. However, we consider often that the VAS scale has not a normal distribution because of the boundary effects. The resulting sample size is small. The sizes are not mentioned in the abstract and not highlighted in the text. The sample sizes are small. Many parameters are scores which should be described better with medians and quartiles. Also the test should be only nonparametric ones for such small samples.

IN ORDER TO ADDRESS THE ISSUE RAISED BY THE STATISTICAL ADVISOR, THE FOLLOWING AMENDMENTS WERE PERFORMED:

- THE SAMPLE SIZE HAS BEEN INDICATED IN THE ABSTRACT AND HIGHLIGHTED IN THE MAIN TEXT;
- ALL DATA WERE EXPRESSED (WHENEVER POSSIBLE) AS MEDIAN AND INTERQUARTILE RANGE;
- ALL INTRA- AND INTER-GROUP COMPARISONS WERE PERFORMED WITH NON-PARAMETRIC STATISTICAL TESTS;
- THE SECTION DEDICATED TO THE POWER ANALYSIS HAS BEEN IMPLEMENTED WITH ADDITIONAL DETAILS.

The power of the KS test for normality is low in such small samples. It should be not used, but only nonparametric test should be applied.

THIS IS EXACTLY WHAT HAS BEEN DONE. SINCE ALL PARAMETERS SHOWED A NON-PARAMETRIC DISTRIBUTION, NON-PARAMETRIC STATISTICAL TESTS WERE APPLIED TO ALL COMPARISONS. WE AGREE WITH THE REFEREE THAT THE POWER OF THE KS TEST IS LOW IN SUCH SMAL SAMPLES, AND THEREFORE WE OMITTED THE SENTENCE "*The Kolmogorov–Smirnov test was used to assess the normal distribution fitting of each variable.*".

Please explain the two-way nonparametric test which is not the Kruskal-Wallis test (this is for one-way ANOVA designs). Did one correct the level of significance for the post-hoc testing?

THE STATISTICAL ADVISOR IS CORRECT: THE APPLIED TEST WAS NOT APPROPRIATE. SINCE OUR ANALYSIS IS NOW IMPLEMENTED WITH THE CALCULATION OF THE AREA UNDER THE CURVE OF

VAS$_{PAIN}$ (AS REQUESTED BY REFEREE #1) AND NO SIGNIFICANT INTER-GROUP DIFFERENCES IN AUC$_{PAIN}$ WERE OBSERVED BETWEEN GROUPS, THIS PART OF THE ANALYSIS HAS BEEN OMITTED.

The intended primary endpoint is in the text no more treated as the primary one. Many parameters were tested which were described without any differences between primary and secondary one.

A SIMILAR ISSUE WAS RAISED BY REFEREE #2. THE REVISED VERSION OF OUR MANUSCRIPT IS NOW MORE CLEAR ABOUT THE PRIMARY AND SECONDARY OUTCOMES OF THE STUDY, AND MORE EMPHASIS IS GIVEN TO THE PRIMARY OUTCOME (VAS$_{PAIN}$) IN THE RESULTS AND DISCUSSION SECTION.

A retrospective study is usually biased because of not observed or uncontrolled factors.

IN GENERAL, WE AGREE WITH THE STATISTICAL ADVISOR. IN THIS SPECIFIC CASE, HOWEVER, WE BELIEVE THAT THE RETROSPECTIVE DESIGN WAS THE MOST ADEQUATE AND SIMPLE TO TEST OUR HYPOTHESIS. WE SUSTAINED OUR CHOICE IN A DEDICATED PARAGRAPH OF THE DISCUSSION SECTION, ALSO CONSIDERING THE POTENTIAL IMPACT OF UNCONTROLLED FACTORS (E.G., NUMBER OF OPERATORS AND LEVEL OF OPERATOR EXPERIENCE): "*In the present study, a retrospective multicenter design has been implemented to test our hypothesis. It may be argued whether or not the retrospective nature of the study may represent a methodological limitation. It must be considered, however, that the two investigated treatments (N and tSFE) have different local indications according to the height of the residual bone crest, thus limiting the possibility to apply a prospective, randomized controlled design. In this context, the scientific value of data from retrospective cohorts seem to be sufficiently adequate to test our hypothesis. In addition, the participation of three different clinical operators to the trial may raise an issue related to the potential influence of the level of experience in implant surgery, in general, and the investigated tSFE procedure, in particular, on the study outcomes. In a recent study (Franceschetti et al. 2015), the effectiveness of the procedure (in terms of extent of sinus lift) appeared to be affected by the level of experience in implant dentistry. However, we also demonstrated that the learning curve of the investigated tSFE procedure is steep, thus allowing for inexpert operators to reach a high performance within a limited number of cases. Also, the incidence of intra- and post-operative complications and the self-administered dosage of analgesics were similarly low irrespective of the level of operator experience (Franceschetti et al. 2015). Although considering that the three clinical operators were all expert in implant surgery and had been previously involved in clinical trials on the investigated tSFE procedure (Trombelli et al. 2010b, 2012, 2014, 2015, Franceschetti et. 2014, 2015), it can not be excluded that the presence of different operators within the trial may have had an influence on the study outcomes.*".

The last figure should be improved or deleted. Either one adds the information in a table with additional descriptive measures (not only mean) or delete the numbers in the figures and make it more readable by not using the scale up to 100, and adding also some info on the variability of the data.

AS REQUESTED, FIGURE 3 HAS BEEN IMPROVED. IN PARTICULAR, LABELS HAVE BEEN DELETED AND THE X-AXIS SCALE HAS BEEN REDUCED. INFORMATION ON MEDIAN VALUES OF VAS$_{PAIN}$ AS WELL AS DATA DISPERSION (INTERQUARTILE RANGE AND MINIMUM-MAXIMUM VALUES) ARE NOW REPORTED IN A DEDICATED TABLE (TABLE 3).

Many tests and post-hoc tests without any correction for the multiple testing were applied. The test for the primary endpoint is most important one.

IN THE REVISED VERSION OF OUR MANUSCRIPT, ALL COMPARISONS ARE NOW PERFORMED BETWEEN TWO SAMPLES USING NON PARAMETRIC STATISTICAL TESTS. WITH THE IMPLEMENTATION OF THE RESULTS WITH DATA ON THE AREA UNDER THE CURVE OF VAS_{PAIN}, THERE IS NO MORE NEED FOR MULTIPLE TESTING AND CONSEQUENT CORRECTION (SEE OUR PREVIOUS RESPONSE).

Patient-reported outcomes of implant placement performed concomitantly with transcrestal sinus floor elevation or entirely in native bone

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RUNNING TITLE: Implant placement with/without transcrestal sinus lift

KEY WORDS: dental implants;
dental implants, single tooth;
maxillary sinus;
sinus floor augmentation;
operative time;
morbidity.

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For *Clinical Oral Implants Research*, Ferrara 2015-08-19, revised 2015-11-05

ABSTRACT

Aim: Based on the hypothesis that maxillary sinus floor elevation with a transcrestal approach (tSFE) does not increase the morbidity of implant surgery, the study evaluated the patient-reported outcomes as well as the type and incidence of complications when implants are placed either concomitantly with tSFE (performed according to Trombelli et al. 2009) or entirely in native bone.

Methods: Data from the record charts of patients undergone implant placement for single-tooth rehabilitation in the posterior maxilla were retrospectively obtained from 4 clinical centers. Cases for tSFE group were included if they showed an extent of sinus lift ≥ 4 mm concomitantly to implant placement. Cases for N group were included when implant placement was performed entirely in native bone. Patient-reported outcomes had been assessed using 100-mm visual analogue scales (postoperative pain, VAS_{pain}) and visual rating scales (level of discomfort, $VRS_{discomfort}$; willingness to undergo the same surgery, $VRS_{willingness}$). The dose of analgesics had been self-recorded.

Results: A convenience sample of 14 patients and 17 patients (contributing with one implant site each) treated with tSFE and N, respectively, was obtained for the present study. Membrane perforation occurred in 1 tSFE case, without compromising the completion of the procedure. VAS_{pain} remained low (<12) in both groups. A tendency of VAS_{pain} to decrease with time was observed in both groups. The Area Under the Curve for VAS_{pain} (AUC_{pain}), indicating the level of pain experience through the first week following surgery, was 18.0 (IR: 8.5 – 85.0) and 11.5 (IR: 4.5 – 18.5) in tSFE and N groups, respectively, with no significant inter-group differences (p= 0.084). The dose of analgesics was similarly low between groups. No significant inter-group difference in $VRS_{discomfort}$ and $VRS_{willingness}$ was observed.

Conclusions: Implant placement performed either concomitantly with tSFE (according to Trombelli et al. 2009) or entirely in native bone are associated with limited incidence of complications, low postoperative pain and medication and are both well tolerated.

INTRODUCTION

The adjunctive use of dental implants significantly improves the oral health-related quality of life of edentulous patients undergoing oral rehabilitation (Peršić & Celebić 2014). For patients receiving dental implants, the impact of conventional implant surgery and the related postoperative sequelae on daily life was shown to be minimal, limited to the first postoperative days (Al-Khabbaz et al. 2007, Seferli et al. 2014), and even less relevant when compared to that reported for other common surgical procedures such as crown lengthening or open flap debridement (Tan et al. 2014).

In the posterior maxillary sextants, the insertion of implants of desired length and diameter may be limited by the dimensional alterations of the bone crest occurring following tooth loss (Eufinger et al. 1997, 1999, Pramstraller et al. 2011), partly due to the pneumatization of the maxillary sinus (Farina et al. 2011). Transcrestal maxillary sinus floor elevation (tSFE) represents an effective surgical option to vertically enhance the available bone in the edentulous posterior maxilla (Pjetursson & Lang 2014). tSFE, however, is not free of intra- and post-surgery complications, the most frequent being the perforation of the Schneiderian membrane and the occurrence of postoperative infection, respectively (Tan et al. 2008). In addition, when performed concomitantly with implant placement, sinus augmentation procedures were previously shown to increase the postoperative levels of pain and swelling associated with implant surgery (Gonzalez-Santana et al. 2005). When considering that patient satisfaction with graftless solutions for implant rehabilitation is generally high (Pommer et al. 2014), the development of new minimally invasive techniques for bone augmentation, in general, and for tSFE, in particular, becomes of paramount importance.

In 2008, a procedure for tSFE was proposed (Trombelli et al. 2008). The major novelty resides in the fact that all manual and rotating instruments are used following a standardized sequence. Adjustable stop devices restrict the working action of burs and osteotomes to the vertical amount of residual bone, thereby preventing the accidental penetration of instruments into the sinus cavity. Several clinical trials consistently showed that the technique results in substantial apical displacement of the sinus floor (Trombelli et al. 2010a,b, 2012, 2014,

2015, Franceschetti et al. 2014, 2015), thus allowing for the concomitant placement of implants of proper dimensions in cases where the residual bone height would have otherwise impaired the implant-supported rehabilitation. Low incidence of intra- and post-surgical complications, low scores for patient pain/discomfort, limited postoperative assumption of analgesics and high propensity of patients to undergo the same surgery again if needed were reported for this technique (Trombelli et al. 2010b, 2012, 2014, Franceschetti et al. 2014, 2015).

The present study was based on the hypothesis that tSFE does not increase the intra- and postoperative morbidity of implant surgery. To test this hypothesis, a multicenter retrospective case series was implemented to evaluate the patient-reported outcomes as well as the type and incidence of complications when implants are placed either concomitantly with tSFE or in native bone.

MATERIALS & METHODS

Study design

The study was designed as a multicenter retrospective case series. The study protocol was approved by the Local Ethical Committee of Ferrara, Italy. The investigated treatments were implant placement entirely in native bone (N) or concomitantly with tSFE (tSFE).

Surgical procedures were performed at the Research Centre for the Study of Periodontal and Peri-implant Diseases, University of Ferrara, Italy, and 3 private dental offices by three clinicians (L.T., L.M., G.F.) expert in implant surgery and involved in previous clinical trials on the investigated tSFE procedure (Trombelli et al. 2010b, 2012, 2014, 2015, Franceschetti et. 2014, 2015).

De-identified data were derived by an examiner not involved in clinical procedures (R.F.) from the record charts of adult (≥ 18 years) patients without systemic or local contraindications to implant surgery undergone implant placement for single-tooth rehabilitation in the posterior maxilla. A convenience sample of tSFE and N

cases positive for the following criteria was selected: (i) availability of pertinent data on the investigated outcome variables; (ii) placement of single implant in the posterior maxilla. Cases for tSFE group were included if they showed an extent of sinus lift (see "Radiographic measurements" for details) of at least 4 mm concomitantly to implant placement. Cases for N group were included when implant placement was performed entirely in native bone (i.e., with the implant apex coronal to the sinus floor).

Interventions

Treatments were performed as part of the oral rehabilitation plan which had been previously agreed between patients and operators. Before the surgical procedure, all oral diseases, including periodontal disease, were thoroughly treated. Two grams of amoxicillin (Zimox 1 g; Pfizer Italia S.r.l., Borgo San Michele, Italy) were administered to each patient 1 hour prior to the initiation of the surgical procedure.

Mepivacaine 2% with 1:100,000 epinephrine was administered through supraperiosteal injection technique (Malamed 2004). A full-thickness flap with vertical releasing incisions was elevated, with the mesio-distal extension kept limited to the future implant site.

In N group, the preparation of the implant site required the consecutive use of drills of increasing diameter. The type and sequence of drills was dependent on the implant system adopted (Thommen Medical™, Grenchen, Switzerland; Nobel Biocare™, Zurich, Switzerland; Straumann™, Basel, Switzerland; Sweden™, Due Carrare, Italy). Drilling was performed by exerting slight pressure intermittently under abundant irrigation with saline solution.

In tSFE group, the preparation of the implant site was performed according to the standardized sequence of instruments of the investigated technique (Figure 1a-i) (Trombelli et al. 2008, 2010a,b 2012, 2014, 2015, Franceschetti et. 2014, 2015). A first drill was used to perforate the cortical bone at the site where the implant had to be placed (Figure 1a). A second drill was used to define the orientation of the implant, with an

adjustable stop device set at least 1 mm shorter than the rWL (Figure 1b). A calibrated osteotome was gently forced in an apical direction until the cortical bone resistance of the sinus floor is met, thus providing the "surgical working length" (sWL) (i.e.: the anatomical distance between the bone crest and the sinus floor in the exact location where the implant had to be placed) (Figure 1c). At the operator's discretion, a radiographic pin was used to confirm the rWL (Figure 1d). The working action of all manual and rotating instruments included in the succeeding surgical steps was set at the sWL by using the proper adjustable stop device. A drill was then used to create a crestal countersink (Figure 1e), where the trephine bur was subsequently inserted producing a bone core up to the sinus floor (Figure 1f). The bone core was condensed and malleted to fracture the sinus floor by means of the calibrated osteotome (Figure 1g,h). In all cases, an additional graft was pushed into the sinus by gradual increments using the calibrated osteotome. The type of graft material chosen among different hydroxyapatite-based (Bio-Oss® spongiosa granules 0.25-1.0 mm; Geistlich Pharma, AG, Wolhusen, Switzerland; Biostite®; GABA Vebas, S. Giuliano Milanese, Milan, Italy; Gen-Os®; Osteobiol Tecnoss Dental, Pianezza, Torino, Italy) or ß-tricalcium phosphate-based (Ceros®, granules 0.5-0.7 mm; Thommen Medical, Waldenburg, Switzerland) biomaterials. The amount of graft material was determined on the basis of previously reported criteria (Trombelli et al. 2014). The clinical application of the investigated technique is illustrated in Figure 2.

In both N and tSFE groups, the implant was inserted immediately after site preparation, and a transmucosal healing protocol was adopted.

All patients were prescribed a single dose of anti-inflammatory drug (i.e. ibuprofen 600 mg tablets) on the first postoperative day (evening) and were instructed to take it *pro re nata* (*prn*) for the following 6 postoperative days. A 0.12% chlorhexidine mouthrinse, to be used 10 ml t.i.d. for 3 weeks, was also prescribed. Sutures were removed 7 days after surgery.

Study parameters

Patient-reported outcomes

At the completion of the surgical procedure, each patient was provided with a self-administered questionnaire. The questionnaire had been prepared by an examiner not involved in the clinical procedures (R.F.) and had been used in previous clinical trials on the same investigated tSFE procedure (Trombelli et al. 2012, 2014). Each operator provided patients with verbal instructions on questionnaire filling.

The following patient-reported outcomes were recorded with the questionnaire:

- level of discomfort perceived by the patient ($VRS_{discomfort}$): recorded immediately after surgery on a 5-point visual rating scale (VRS) ranging from "0 – *no discomfort*" to "4 – *very severe discomfort*";
- willingness to undergo the same type of surgery ($VRS_{willingness}$): recorded immediately after surgery on a 4-point visual rating scale (VRS) ranging from "0 – *I will never undergo this type of surgery again*" to "3 – *no problem to repeat surgery if needed*";
- level of pain perceived by the patient (VAS_{pain}): recorded daily (evening) for 7 days following surgery on a 100-mm visual analogue scale (VAS) (ranging from "*0 - no pain*" to "*100 - intolerable pain*");
- dosage of rescue anti-inflammatory drug (i.e. number of ibuprofen 600 mg tablets) assumed by the patient from 2nd to the 7th postoperative day, as self-recorded by the patient on a specifically dedicated form.

Surgical and post-surgical complications

The incidence of membrane perforation was evaluated by the Valsalva maneuver after the preparation of the implant site (in N group) and after either the fracture of the sinus floor or the completion of the grafting procedure (in tSFE group). Other surgical or post-surgical complications, generally related to implant surgery in the posterior maxillary area (including post-operative infection, post-operative hemorrhage, nasal bleeding, blocked nose, hematomas) or specifically associated with tSFE procedures (including Benign Paroxysmal Positional Vertigo) were also recorded.

Duration of the procedure

The duration of the procedure was recorded as the time (in minutes) elapsed from 1) cortical perforation with the first drill to 2) either the completion of site preparation with the last drill of the sequence (for N group) or the completion of the grafting procedure (for tSFE group) immediately before implant insertion.

Radiographic measurements

At all centers, periapical radiographs were obtained immediately after surgery and at 6 months with a paralleling technique using a Rinn film holder with a rigid film-object X-ray source, then scanned and digitized. Using an image-processing software, digitized images were stored at a resolution of 600 dpi.

In the tSFE group, the following radiographic measurements were performed on radiographs taken immediately after surgery using a software for image analysis (NIS Elements® v4.2; Nikon Instruments, Campi Bisenzio, Firenze, Italy):

- radiographic implant length (rIL): distance (in mm) between the implant shoulder and the implant apex as assessed at the mid portion of the implant;
- residual bone height at the mesial (mRBH) and distal (dRBH) aspects of the implant: distance (in mm) between the mesial and distal aspect of the implant shoulder, respectively, and the sinus floor;
- height of the graft apically (aGH): distance (in mm) occupied by a radiopaque area between the implant apex and the sinus floor as assessed at the mid portion of the implant.

To account for radiographic distorsion, radiographic measurements (i.e., mRBH, dRBH and aGH) on each radiograph were adjusted for a coefficient derived from the ratio: true length of the implant / rIL.

For each patient, the following derived radiographic parameters were obtained:

- residual bone height (RBH): calculated as the mean value of mRBH and dRBH;
- implant penetration (IP): calculated as the difference between rIL and RBH;
- extent of the sinus lift (SL): calculated as the sum of IP and aGH.

All measurements were performed by a single trained examiner (G.F.) who had previously undergone a calibration session for aGH assessment on a sample of 15 patients not included in the study (Cohen's k-coefficient for intra-examiner agreement: 0.981) and had participated as clinical examiner in previous clinical trials using the same radiographic measurements (Trombelli et al. 2012, Franceschetti et al. 2014a, 2015).

Statistical analysis

Data were entered in a unique database file (STATISTICA software version 7.1; StatSoft, Italia s.r.l., Vigonza, Italy) and expressed as median and interquartile range (IR). The patient was regarded as the statistical unit. Therefore, only one eligible implant site was considered for each patient. VAS_{pain} was regarded as the primary outcome variable. In order to express the level of pain experience through the first week following surgery, for each patient the Area Under the Curve (AUC) was calculated for VAS_{pain} (AUC_{pain}). The other patient-centered outcomes (i.e., $VRS_{discomfort}$, $VRS_{willingness}$, dosage of rescue anti-inflammatory drug) and the incidence of complications were regarded as the secondary outcome variables.

Inter-group comparisons were performed with Fisher's exact test and Mann–Whitney U-test.

The level of statistical significance was fixed at 0.05. A web-based software (http://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/statisticalpowercalculators.aspx) was used for the calculation of the sample size of the study. Assuming a standard deviation in 100-mm VAS_{pain} of 5 and an expected inter-group difference in 100-mm VAS_{pain} of 5 on the basis of previous studies using VAS to evaluate postoperative pain at 1 week following implant surgery either in combination with tSFE (Trombelli et al. 2014) or not (Al-Khabbaz et al. 2007), a *per protocol* study population of 24 patients (i.e. 12 patients per treatment group) was needed to detect a significant inter-group difference (at $p = 0.05$) with a one-sided test with a statistical power of 80%. A *post-hoc* power calculation revealed that the study had a power of 87%.

RESULTS

Study population

A convenience sample of 14 patients (51 years, IR: 48.3 - 55.8; 2 current smokers) and 17 patients (52 years, IR: 39.0 – 57.0; years, 4 current smokers) treated from January, 2010 to January, 2014 with tSFE and N, respectively, was obtained for the present study. No significant differences in age and patient distribution according to either gender or smoking status were observed between groups. In the tSFE group and N group, 2 vials (IR: 2.0 – 2.8) and 3 vials (IR: 2.0 – 3.0) of anesthetics, respectively, were used during surgery ($p > 0.05$).

Treatment outcomes

The frequency distribution of patients according to the location of the implant site (i.e., first premolar, second premolar, first molar, second molar) was 0, 2, 11, 1, respectively, in the tSFE group, and 8, 5, 4, 0, respectively, in N group. Radiographic measurements in tSFE group are shown in Table 1. RBH was 6.0 mm (IR: 5.6 – 6.8), and the tSFE procedure allowed for the placement of implants with a length of 9.8 mm (IR: 9.5 – 11.0). Immediately after the tSFE procedure, IP was 4.0 mm (IR: 3.6 – 4.8) and SL was 6.8 mm (IR: 5.7 – 7.6). In N group, implants with a length of 9.5 mm (IR: 9.5 – 11.0) were placed. No significant difference in implant length was observed between groups. At 6 months after surgery, no implant failure was recorded, and the prosthetic rehabilitation was finalized at all implant sites.

Patient-reported outcomes

No significant difference in either $VRS_{discomfort}$ or $VRS_{willingness}$ was observed between groups (Table 2).

VAS_{pain} in tSFE and N groups is reported in Table 3 and illustrated in Figure 3. On day +1, VAS_{pain} was low in both treatment groups. During the following postoperative days, a tendency of VAS_{pain} to decrease was observed in both groups. AUC_{pain} was 18.0 (IR: 8.5 – 85.0) and 11.5 (IR: 4.5 – 18.5) in tSFE and N groups, respectively, with no significant inter-group differences ($p = 0.084$).

The total number of rescue anti-inflammatory drug used from the 2nd to the 7th postoperative day was 0 (IR: 0 – 1.8; min-max: 0 - 9) in tSFE group and 1 (IR: 0 – 1.0; min-max: 0 - 6) in N group (p= 0.860). No significant difference in either the prevalence of subjects using analgesics or the dose of rescue anti-inflammatory drug was observed between groups at each postoperative day (Table 2).

Surgical and post-surgical complications

Membrane perforation was detected at Valsalva maneuver only in 1 case in tSFE group after graft placement. No statistically significant difference in the incidence of membrane perforation was observed between treatment groups. Membrane perforation was treated with the insertion of a collagen matrix (Mucograft; Geistlich Pharma AG, Wolhusen, Switzerland) through the crestal access, and systemic antibiotics (amoxicillin + clavulanic acid, 1 g t.i.d. for 6 days) was administered post-operatively. The grafting procedure was completed, the implant was inserted and the case included for analysis.

No other intra- and postoperative complications were either observed by the operators or self-reported by the patients in both treatment groups.

Duration of the procedure

The duration of the procedure was significantly longer in tSFE group (25 min, IR: 20.8 – 34.8) compared to N group (10 min, IR: 9.0 – 11.0) (p< 0.001).

DISCUSSION

In the present study, a retrospective multicenter design has been implemented to test our hypothesis. It may be argued whether or not the retrospective nature of the study may represent a methodological limitation. It must be considered, however, that the two investigated treatments (N and tSFE) have different local indications according to the height of the residual bone crest, thus limiting the possibility to apply a

prospective, randomized controlled design. In this context, the scientific value of data from retrospective cohorts seem to be sufficiently adequate to test our hypothesis. In addition, the participation of three different clinical operators to the trial may raise an issue related to the potential influence of the level of experience in implant surgery, in general, and the investigated tSFE procedure, in particular, on the study outcomes. In a recent study (Franceschetti et al. 2015), the effectiveness of the procedure (in terms of extent of sinus lift) appeared to be affected by the level of experience in implant dentistry. However, we also demonstrated that the learning curve of the investigated tSFE procedure is steep, thus allowing for inexpert operators to reach a high performance within a limited number of cases. Also, the incidence of intra- and post-operative complications and the self-administered dosage of analgesics were similarly low irrespective of the level of operator experience (Franceschetti et al. 2015). Although considering that the three clinical operators were all expert in implant surgery and had been previously involved in clinical trials on the investigated tSFE procedure (Trombelli et al. 2010b, 2012, 2014, 2015, Franceschetti et. 2014, 2015), it can not be excluded that the presence of different operators within the trial may have had an influence on the study outcomes.

In our material, implant placement concomitantly with tSFE required longer operative time compared to implant placement in native bone. The operative time of tSFE is consistent with previous studies on the investigated technique (Trombelli et al. 2010, 2012, 2014, Franceschetti et al. 2014b). The longer time in tSFE group compared to N group is justified by the number of instruments included in the tSFE sequence (6 instruments) which was greater than the number of drills included in the conventional drilling sequence for implant site preparation. In all cases, a graft material was used in the tSFE procedure to expand the sinus membrane following the fracture of the sinus floor. In order to prevent membrane perforation, sinus grafting is based on repeated increments of small amount of the biomaterial, thus resulting in a time consuming procedure.

Due to the retrospective nature of the study, the assessment of patient-reported outcomes was focused on aspects related to pain and use of analgesics, discomfort, and patient acceptance. Among these parameters, the level of postoperative pain, as assessed through the use of a 100-mm Visual Analogue Scale (VAS), was

regarded as the primary outcome variable of the study. The use of VAS as tools for the assessment of patient perception has become increasingly frequent in dental research during the last decades due to their ease of administration and reproducibility. In this respect, VAS were used to measure the anxiety of patients before and after dental treatment as well as their level of pain following different non-surgical and surgical procedures (Seymour et al. 1983, Luyk et al. 1988, Matthews & McCulloch 1993, Canakçi & Canakçi 2007, Fardal & McCulloch 2012, Tan et al. 2014). More recently, the use of VAS has been extended to implant research. In particular, VAS were used to measure pain levels following implant surgery (Al-Khabbaz et al. 2007, Fardal & McCulloch 2012, Tan et al. 2014) and, less frequently, other aspects of post-surgery sequelae such as swelling, bleeding and bruising (Tan et al. 2014). In the present study, VAS levels reported for tSFE treatment were similarly low when compared with those reported in previous trials on the same procedure (Trombelli et al. 2012, 2014). In group N, pain levels were consistent with previous studies (Tan et al. 2014), but differed with those reported by other Authors for conventional implant surgery (Al-Khabbaz et al. 2007). It must be considered, however, that the comparison of data on pain levels among studies is complicated by differences in pain assessment methods, technical aspects (e.g. flap design and extension), and pharmacological protocol for pain control.

The pain experience during the entire first postoperative week (as evaluated through AUC_{pain}) was not significantly different between groups, thus indicating that tSFE and N are both well tolerated. This consideration is corroborated further by the fact that tSFE did not determine an increased consumption of analgesics compared to implant insertion entirely in native bone. While from day +3 the median value of VAS_{pain} in N group was 0, the persistence of low pain levels (< 5 on a 100-mm scale) was observed in tSFE group up to day +7. This finding could be explained, at least in part, by the longer operative time required for the tSFE group compared to the N group. In this respect, it was previously demonstrated that longer implant surgery sessions are associated with higher VAS pain scores during the first postoperative week when compared to shorter sessions (Tan et al. 2014). Also, it may be hypothesized that the detachment of the Schneiderian membrane may determine a transient increase in pain levels due to the stimulation of membrane

innervation (Heasman 1984, van den Bergh et al. 2000). The absence of significant inter-group differences in AUC_{pain}, however, seems to suggest that persisting pain observed in tSFE patients at single time intervals was sporadic within each patient patient and of limited intensity compared to N treatment.

Osteotome-based procedures for tSFE, which have been developed since the original introduction of the osteotome technique (Summers 1994), require an extensive use of malleting to prepare the implant site and fracture the maxillary sinus floor. This may cause substantial clinical discomfort during the procedure as well as relevant post-surgical complications such as the Benign Paroxysmal Positional Vertigo (Peñarrocha et al. 2001, Di Girolamo et al. 2005, Peñarrocha & Garcia 2006). In the investigated technique, the surgical sequence was designed to approach the sinus floor without the need for osteotomes, and malleting is restricted to the fracture of the cortical sinus floor (Trombelli et al. 2008, 2010a,b). This peculiarity of the technique may lead to limited to null incidence of BPPV, as observed in the present study and reported in previous trials (Trombelli et al. 2008, 2010a,b, 2012, 2014, 2015, Franceschetti et al. 2014, 2015). Also, the low patient discomfort and the high propensity to undergo the same surgery again, which were similarly observed in tSFE and N groups, seem to suggest that implant surgery concomitantly with tSFE is highly tolerated by the patient.

Complications were limited to 1 case of membrane perforation in tSFE group. Membrane perforation is the most frequent intra-operative complication during tSFE procedures (Tan et al. 2008). The low incidence of membrane perforation observed in the tSFE group, which is mainly due to the control of the working action of manual and mechanical instruments through the application of adjustable stop devices, is consistent with previous studies on the investigated technique (Trombelli et al. 2010a,b, 2012, 2014, 2015, Franceschetti et al. 2014a,b). In addition, membrane perforation did not compromise the completion of the grafting procedure and the success of the implant-supported rehabilitation.

CONCLUSIONS

The results of the present study showed that implant placement performed either concomitantly with tSFE (according to the Trombelli et al. 2009) or entirely in native bone are associated with limited incidence of complications, low postoperative pain and medication and are both well tolerated. When considering that (i) tSFE allowed for the concomitant placement of implants of proper dimensions in cases where the residual bone height would have otherwise impaired the implant-supported rehabilitation, (ii) tSFE did not determine an increased consumption of analgesics compared to implant placement in native bone, and (iii) previous findings demonstrated that the proposed tSFE technique is a user-friendly, safe, predictable and minimally-invasive procedure (Trombelli et al. 2010a,b, 2012, 2014, 2015, Franceschetti et al. 2014, 2015), tSFE seems to represent a well-accepted option with a favorable risk-benefit ratio when used concomitantly with implant placement in the atrophic posterior maxilla.

ACKNOWLEDGEMENTS

The study was entirely supported by the Research Centre for the Study of Periodontal and Peri-implant Diseases, University of Ferrara, Italy. The Authors wish to express their gratitude to Prof. Stefano Volpato and Dr. Elisa Maietti, Center of Clinical Epidemiology, University of Ferrara, Italy, for their precious help in data analysis.

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FIGURE LEGEND

Figure 1. tSFE procedure (Trombelli et al. 2009): sequence of rotating and manual instruments. a. The *Locator Drill*) is used to perforate the cortical bone at the site where the implant has to be placed. **b.** The *Probe Drill* is used to define the orientation of the implant, with an adjustable stop device set at least 1 mm shorter than the radiographic working length. **c.** The *Probe Osteotome* is gently forced in an apical direction until the cortical bone resistance of the sinus floor is met, thus providing the "surgical working length" (sWL). The working action of all instruments included in the succeeding surgical steps is set at the sWL by using the proper adjustable stop device. **d.** A radiographic pin may be used to check the orientation of the prepared site by means of a periapical radiograph. **e.** The "*Guide Drill*" is used to create a crestal countersink. **f.** The *Smart Lift Drill* produces a bone core up to the sinus floor. **g,h.** The bone core is condensed and malleted to fracture the sinus floor by means of the *Smart Lift Elevator*. A graft biomaterial may be placed into the sinus cavity by gradual increments with the *Smart Lift Elevator*. *(reprinted from: Trombelli, L., Franceschetti, G., Rizzi, A., Minenna, P., Minenna, L. & Farina, R. (2012) Minimally invasive transcrestal sinus floor elevation with graft biomaterials. A randomized clinical trial. Clinical Oral Implants Research 23, 424–432)*

Figure 2. Clinical application of the investigated tSFE technique. a. The pre-surgery tomographic exam showed a radiographic working length (rWL) of 6 mm. **b.** The Locator Drill was used to perforate the cortical bone at the future implant site. **c.** After the orientation of the implant had been defined by means of the Probe Drill used to with an adjustable stop device set at 5 mm, the Probe Osteotome was gently forced in an apical direction until the cortical bone resistance of the sinus floor was met, providing a surgical working length (sWL) of 5 mm. The working action of all instruments included in the succeeding surgical steps was set at the sWL by using the adjustable stop device of 5 mm. **d, e.** The "Guide Drill" was used to create a crestal countersink. **f.** The Smart Lift Drill produced a bone core up to the sinus floor. **g.** The bone core was condensed and malleted to fracture the sinus floor by means of the Smart Lift Elevator. **h, i.** A bovine-derived xenograft was placed into the sinus cavity by gradual increments with the Smart Lift Elevator. **j.** The implant was placed and a transmucosal healing protocol was adopted. **k, l.** Clinical and radiographic aspect at 6 months following surgery.

Figure 3. Median values of VAS_{pain} in N group and tSFE group.

Table 1. Residual bone height (RBH), implant length, and post-surgery extent of sinus lift (SL) as observed in each case treated in tSFE group.

	tSFE group (n= 14)		
Case number	RBH (mm)	implant length (mm)	post-surgery SL (mm)
#1	5.8	9.5	7.7
#2	2.7	9.5	8.2
#3	5.7	11.5	7.4
#4	6.1	11.0	6.4
#5	6.8	10.0	5.7
#6	5.8	9.5	7.5
#7	6.7	10.0	4.6
#8	7.2	9.5	4.6
#9	3.8	9.5	8.2
#10	7.0	11.5	5.7
#11	5.6	9.5	5.1
#12	6.8	11.0	7.6
#13	5.5	9.5	7.2
#14	7.5	11.0	6.1

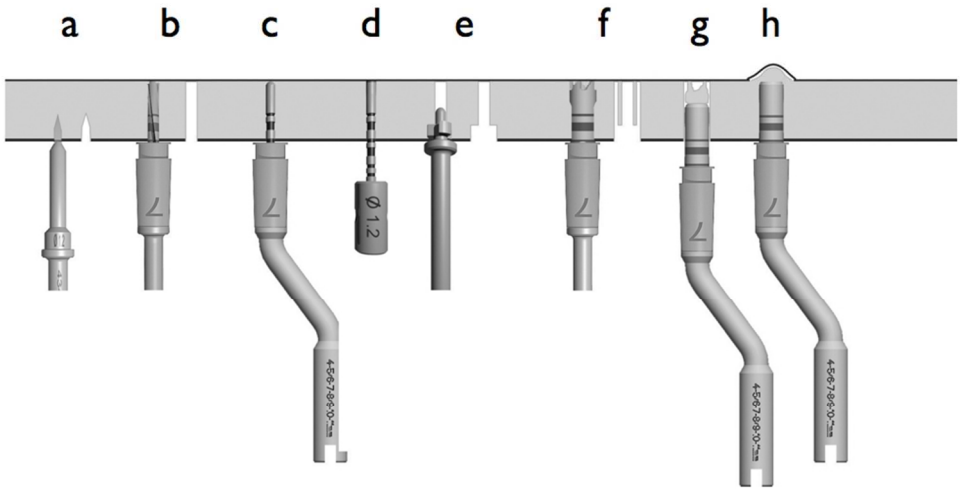
Table 2. $VRS_{discomfort}$, $VRS_{willingness}$, and use of rescue anti-inflammatory drug in N group and tSFE group.

	tSFE group (n= 14)	N group (n= 17)	p
Post-surgery discomfort ($VRS_{discomfort}$)	median, IR (min-max)	median, IR (min-max)	(Mann-Whitney)
0 - no discomfort 1 - slight discomfort 2 - mild discomfort 3 - severe discomfort 4 - very severe discomfort	0, IR: 0 - 2 (0-3)	0, IR: 0 - 0 (0-1)	0.200
Willingness to undergo the same surgery ($VRS_{willingness}$)	n° patients	n° patients	(Fisher's exact test)
3 - "*No problem to repeat surgery if needed*"	13	17	0.452
2 - "*I will repeat the surgery, but I would prefer to procrastinate it*"	1	0	
1 - "*I will repeat the surgery, but I expect to suffer severe pain*"	0	0	
0 - "*I will never undergo this type of surgery again*"	0	0	
Use of rescue anti-inflammatory drug (ibuprofen 100 mg tablets)	n° of patients assuming at least 1 tablet	n° of patients assuming at least 1 tablet	(Fisher's exact test)
	n° tablets median, IR (min-max)	n° tablets median, IR (min-max)	(Mann-Whitney)
2nd postoperative day	5	9	0.473
	0, IR: 0 - 1 (0-2)	1, IR: 0 - 1 (0-2)	0.710
3rd postoperative day	3	1	0.304
	0, IR: 0 - 0 (0-2)	0, IR: 0 - 0 (0-2)	0.493
4th postoperative day	3	1	0.304
	0, IR: 0 - 0 (0-3)	0, IR: 0 - 0 (0-2)	0.468
5th postoperative day	2	0	0.196
	0, IR: 0 - 0 (0-2)	0, IR: 0 - 0 (0-0)	0.518

6th postoperative day	1	0	0.452
	0, IR: 0 - 0 (0-1)	0, IR: 0 - 0 (0-0)	0.739
7th postoperative day	1	0	0.452
	0, IR: 0 - 0 (0-1)	0, IR: 0 - 0 (0-0)	0.739

Table 3. VAS_{pain} in tSFE and N group.

		postoperative day						
		+1	+2	+3	+4	+5	+6	+7
tSFE group (n= 14)	median	7.0	4.0	4.5	1.0	2.0	2.0	1.5
	IR	4.3 – 13.8	1.3 – 22.3	1.3 – 14.8	0 – 17.8	0 – 6.0	0 – 2.8	0 – 2.8
	min - max	0 – 51.0	0 – 62.0	0 – 59.0	0 – 64.0	0 – 63.0	0 – 58.0	0 – 60.0
N group (n= 17)	median	11.0	5.0	0	0	0	0	0
	IR	7.0 – 15.0	0 – 10.0	0 - 0	0 - 0	0 - 0	0 - 0	0 - 0
	min - max	0 – 80.0	0 – 60.0	0 – 40.0	0 – 20.0	0 – 0	0 – 0	0 – 0



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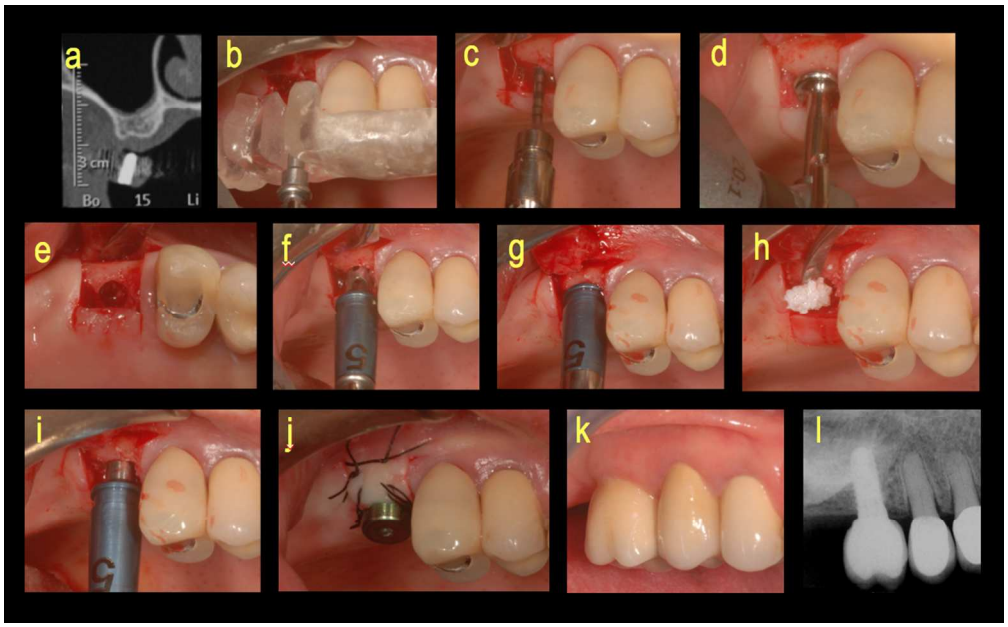

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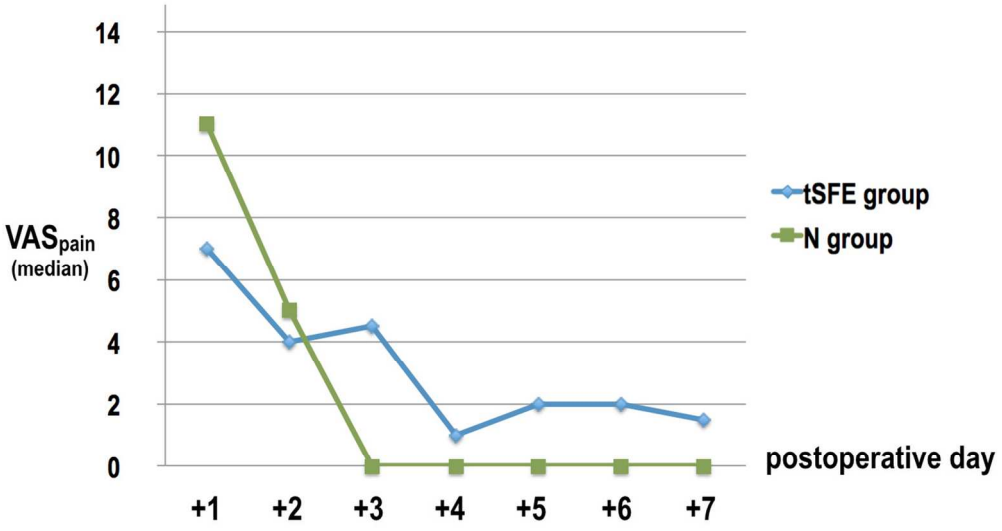

Figure 3
495x280mm (72 x 72 DPI)