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RESEARCH

Comparison between flapless-guided and conventional surgery for implant placement: a 12-month randomized clinical trial

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Abstract

Objectives The study was aimed at comparing implants installed with guided and conventional surgery.

Material and methods Twenty-nine total edentulous patients were selected, and maxillary contralateral quadrants were randomly assigned to static computer-aided implant surgery (S-CAIS): flapless computer-guided surgery, and conventional surgery (CS): flap surgery with conventional planning. Tomography scans were performed at baseline and 10 days after the surgery for deviation measurement, and radiography was done at baseline and after 6 and 12 months, for peri-implant bone level (PIBL) analysis. Peri-implant fluid and subgingival biofilm were collected to evaluate bone markers and periodontal pathogens.

Results S-CAIS showed less linear deviation at the apical point and at the midpoint and, less angular deviation ($p < 0.05$), with greater depth discrepancy in the positioning of the platform ($p < 0.05$). Higher values of vertical PIBL were observed for the S-CAIS group at baseline ($p < 0.05$), while lower values of horizontal PIBL were observed for CS ($p < 0.05$). Bone markers presented higher levels in CS ($p < 0.05$).

Conclusion Flapless S-CAIS allowed smaller linear and angular deviations than the conventional technique. However, PIBL was higher in S-CAIS; the conventional technique led to a greater angiogenic and bone remodeling activity by elevating the angiogenic and bone markers levels.

Clinical relevance Evaluating the different implant insertion techniques can guide clinical and surgical regarding the accuracy, the release pattern of bone markers, and the peri-implant bone level.

Trial registration ReBEC-RBR-8556fzp.

Keywords Computer-assisted surgery · Dental implant · Patient-centered outcomes · Clinical trial

Introduction

Implant therapy has been widely used in the rehabilitation of partially and fully edentulous patients, with high rates of long-term clinical success [1–5]—approximately 99% in the mandible and 90% in the maxilla—obtained after a period of 10 to 15 years of follow-up [1, 4, 6]—and consequently, implantology has developed and sought to improve surgical techniques to increase the predictability and precision of treatment.

In this context, the insertion of implants through guided surgery with computerized virtual planning has been studied. Studies suggest that S-CAIS enables more precise execution of the treatment plan and implant insertion [7–14]. This approach brings the concept of a minimally invasive procedure without flap elevation and with immediate prosthesis installation. In addition, S-CAIS has been identified as a safe method related to less discomfort and shorter operative time [15–19].

Some randomized controlled clinical studies have compared S-CAIS and CS, showing greater accuracy for static computer-aided implant surgery [20], less procedure duration, pain intensity, and prosthesis installation in a more

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predictable way [10, 21–23]. On the other hand, through meta-analysis, Tahmaseb et al. [24] concluded that there is still no evidence that S-CAIS is superior to CS in terms of safety, morbidity, or efficiency.

Considering the survival of the implant with guided flapless surgery, the results of 4 systematic reviews suggest that conventional surgery (free-hand) is comparable with flapless static computer-aided implant surgery in terms of implant survival, marginal bone remodeling, and peri-implant variables [25–28]. Additionally, surgical and prosthetic complications have been reported in the literature, and the most frequently observed are fracture of the surgical guide, early loss of the implant due to loss of primary stability, changes in surgical planning, and fracture of the prosthesis [24, 29–31].

Given the aspects mentioned above, new evidence comparing the two surgical approaches (flapless static computer-aided implant surgery and conventional surgery) for implant placement is necessary to establish a predictable and safe clinical protocol that favors peri-implant repair. There is no knowledge regarding the influence of surgical approaches on the behavior of peri-implant tissues at the molecular level. In addition, no studies compared the insertion of implants by S-CAIS and CS in totally edentulous patients in a split-mouth model. Thus, the objective of the present study was to conduct a clinical, split-mouth, randomized, blinded, and controlled study that explores aspects related to the deviations between virtual planning and actual positioning, as well as the analysis of the behavior of bone tissue and angiogenic/osteoclast/blastogenic markers in peri-implant tissue.

Materials and methods

Population

The population of this prospective, randomized, double-blind, split-mouth, and controlled clinical study were recruited from patients who sought dental treatment at Paulista University, São Paulo, Brazil, between January 2015 and July 2017. The clinical procedures and assessments were carried out between August 2017 and January 2018. The statistical analysis of the data was performed in October 2018. Twenty-nine patients, aged between 18 and 76 years, were selected, and the study was approved by the Research Ethics Committee of Paulista University (2.059.143) and presented a CONSORT-based design (The Brazilian Registry of Clinical Trial platform—REBEC-RBR-8556fzp).

Inclusion and exclusion criteria

The inclusion criteria were total maxillary edentulous patients, with a minimum bone thickness of 5.5 mm and minimum bone height of 9 mm for placing six implants.

The exclusion criteria consisted of pregnancy; lactation; antibiotic therapy in the last 6 months; long-term use of medications that could alter osseointegration, such as anti-inflammatory drugs, bisphosphates, or immunosuppressive drugs; graft needs before or during surgery; and history of previous regenerative procedures in the area designated for implant installation. Patients with severe complications associated with type 2 diabetes, cardiovascular and peripheral vascular diseases, neuropathies, and nephropathies also were excluded.

Experimental groups

All the patients received six implants, three on each side of the maxilla (Fig. 1), and both surgical approaches followed a split-mouth design. For all patients, virtual planning was performed, printing a 3D-printed guide and the confection of a conventional guide using study models. The approach to be used on each side was randomly assigned using a computer-generated list (managed by M.Z.C.), and the groups were defined as follows:

- Static computer-aided implant surgery (S-CAIS) ($n=29$): guided flapless surgery and 3D-printed guide made using virtual planning
- Conventional surgery (CC) ($n=29$): conventional flap surgery and conventional guide made using a study model

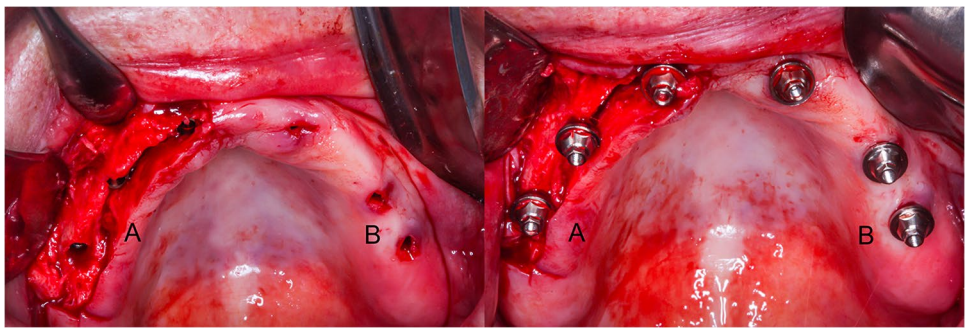

Fig. 1 Schematic illustration of the experimental. **A** Conventional surgery. **B** Static computer-aided implant surgery

Presurgical planning protocol

Patients were first submitted to an initial evaluation to check occlusion, alignment, and adaptation in the upper prosthesis. At sequence, the prosthesis received marks using a radiopaque material (Guta Percha, Dentsply Maillefer, Tulsa, OK, USA) in the first molars and central incisor to be used as a radiographic guide, and then, a cone beam computed tomography (CBCT) was acquired. First, the CBCT was performed with the total prosthesis marked with gutta-percha positioned in the patient's mouth, and then, the prosthesis (tomographic guide) was scanned alone. Thus, the TC images of the patients and scanned guide were combined based on radiopaque markers for virtual planning. All tomographic images were performed by the same scanner (I-CAT, Imaging Sciences International, Hatfield, PA, USA—0.25 mm voxel, 120 kV, and 20.27 mAs). After image acquisition, files (DICOM—Digital Imaging and Communications in Medicine) were converted and imported into a virtual planning software (Dental Slice Virtual Navigation, Bioparts prototyping Biomedical, Brasília DF, Brazil). Virtual implant planning was performed for fixed implant-supported complete arch prosthesis considering the ideal position of the implants according to the available bone quantity, and the virtual planning was sent to a prototyping center (Bioparts Prototyping Biomedical, Brasília DF, Brazil) to produce the 3D-printed guide by SLA stereolithography. The superior conventional prosthesis was duplicated, and the conventional acrylic surgical guide was made. The central portion of the incisive was abraded, maintaining the buccal surface of the teeth as a reference for surgery in the conventional surgery group (Fig. 2).

Treatment protocol

All surgeries were performed by the same trained surgeon (L.M.N), and both treatment approaches were performed in the same session.

Static computer-aided implant surgery

Under local anesthesia (mepivacaine 2% 1:100,000, new DFL, Rio de Janeiro, RJ, Brazil), the 3D-printed guide was stabilized in the mouth through the drilling and installation of the three stabilization pins (in the molar and central incisor region) (Fig. 3). Subsequently, implant sites were prepared without flap elevation by full guided drilling, using a sequence of appropriate drill handles with a vertical stop system. The installation of Cone Morse Due Cone (Implacil De Bortoli, São Paulo SP, Brazil) using a surgical torquemeter was performed as recommended by the manufacturer of the Raptor Implacil/Bioparts system (Implacil De Bortoli, São Paulo SP, Brazil).

Conventional surgery

A linear crestal incision covering the entire region of the hemi-maxilla and two vertical releasing incisions were used

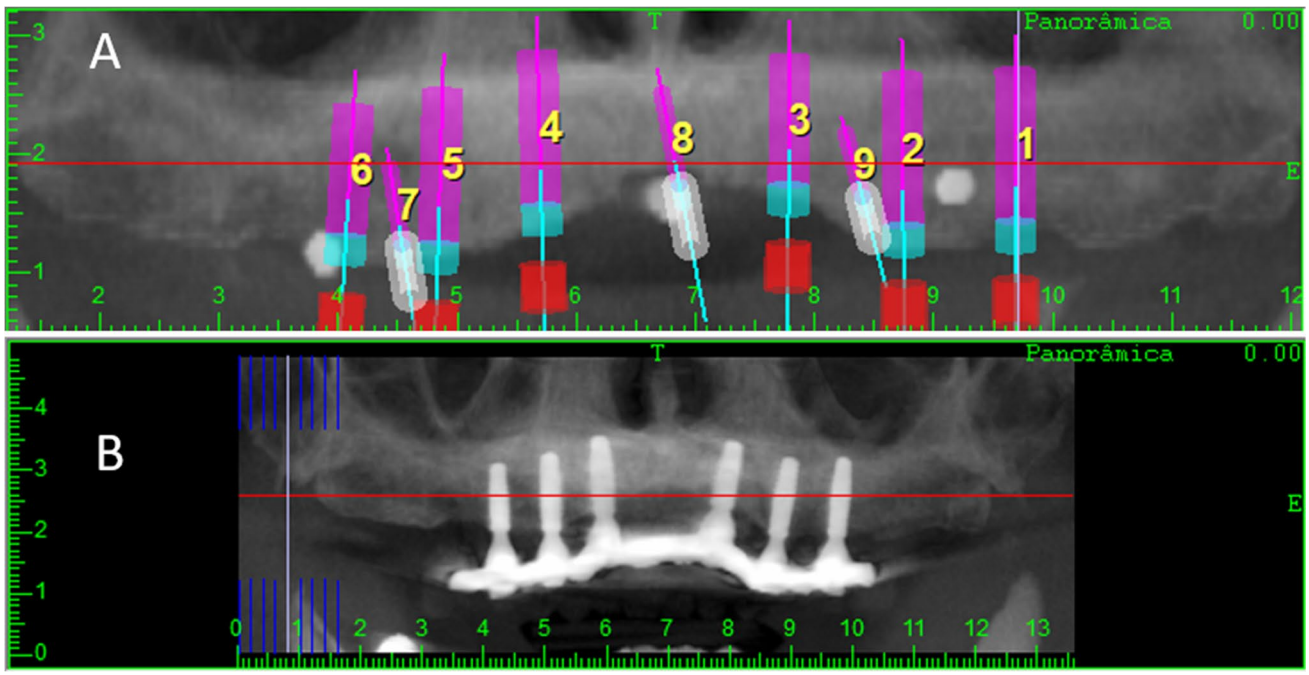

Fig. 2 Surgical planning (**A**) and tomography after implant placement (**B**)

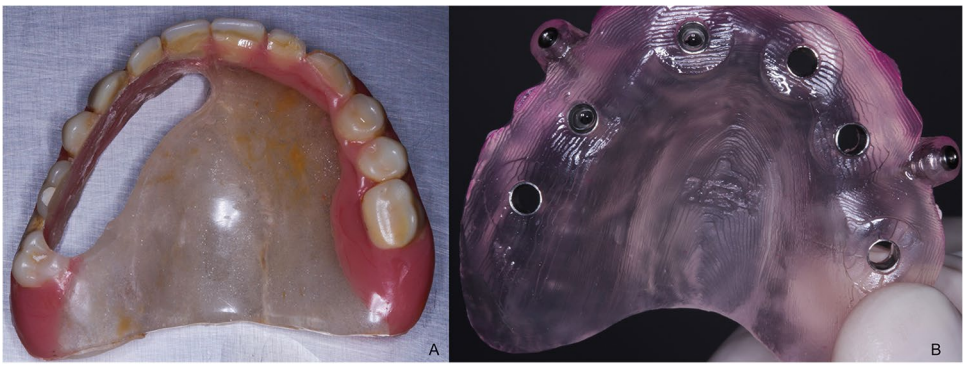

Fig. 3 Schematic illustration of the two different surgical guides. **A** Conventional surgery. **B** Static computer-aided implant surgery

for all surgeries. The 3D-printed guide was then positioned and stabilized without the guide pins to make the bone bed entry marking maintain the same position as the implants' virtual planning (Fig. 3). Subsequently, the 3D-printed guide was removed, and the surgical procedure and installation of the implants were performed based on the conventional surgical guide and in the visualization of the virtual planning, with appropriate drill handles recommended by the manufacturer (Implacil De Bortoli system, Implacil De Bortoli, São Paulo SP, Brazil).

Interrupted absorbable polyglactin 910 sutures were placed (Vicryl; Ethicon, Somerville, NJ, USA). Amoxicillin (2 g administered 1 h before the procedure), dipyrone (500 mg every 6 h for 2 days post-operative), and 0.12% chlorhexidine mouthwash (every 12 h for 7 days) were prescribed.

All patients received fixed full-arch prostheses within 24 h of implant placement. Immediately after the implants were installed, they received pre-selected screwed abutments with a definitive torque of 25 Ncm. Subsequently, the prosthetic bar was made using plastic cylinders compatible with the pre-cast abutment, which were screwed over the implants, and the union was made in the mouth using acrylic resin. After resin polymerization in the mouth, the joined bar was removed to obtain an index of the implant position. While the laboratory performed the welding process, their respective protectors were placed in the definitive intermediates, which protected the access and maintained the gingival tissues in a post-suture position on the side treated with CS.

On the same day, the bar was positioned, and the necessary registrations were made. After the transfer molding with open stock mold, in which heavy and light condensation silicone elastomers were used, the teeth were assembled and a test of the assembly in the mouth was carried out to define the occlusion, seating the bar on the implants and the aesthetics of the patient's smile. After all these steps were verified, the prosthesis was acrylate with thermopolymerizable resin. All prostheses were installed, and the screws were tightened with a torque of 15 N. The holes were covered with sterile polytetrafluoroethylene tape to prevent the entry of any external residue and sealed with light-curing resin.

Measurement of linear and angular deviations

Ten days after the surgical procedure, patients underwent another CBCT in the same radiological clinic as the previous exam using the same image acquisition parameters and device. The images were again converted to the Dental Slice program (Dental Slice Virtual Navigation, Bioparts prototyping Biomedical, Brasília DF, Brazil) and matched with the virtual planning images performed before the surgery. The measurements were made by an experienced professional based on the measurement conducted by Soares et al. [32]. The measurement are summarized at Fig. 4. The examiner was also blinded and was not informed about the surgical technique performed on each operated side.

Anatomical points well defined were established, and the two images were combined. The preliminary alignment between the images was performed, and the superimposed image was matched. Then, the algorithm (vtkIterativeClosestPointTransform) was applied to match two surfaces using the iterative closest point (ICP). The algorithm's core is to match each vertex in one surface with the closest surface point on the other, then apply the transformation that modifies one surface to best match the other (in the least square sense). It must be iterated to get proper convergence of the surfaces. The algorithm is applied using the 3D mesh points until finding the best match. Then, the displacement matrix between the images is calculated. The same alignment matrix is applied on the 3D of actually placed implants. The 3D meshes of the planned and inserted implant are then performed using displacement (movement and rotation). Regarding the angle between the line segments formed by the planned and placed implants, a line segment is established by 2 points in 3D space, for example, P1 (center's platform of the implant) and P2 (center's apical of the implant). A point in 3D space is given by 3 coordinates (e.g., $P1 = \times 1, y1, z1$). The formula to find the angle between these

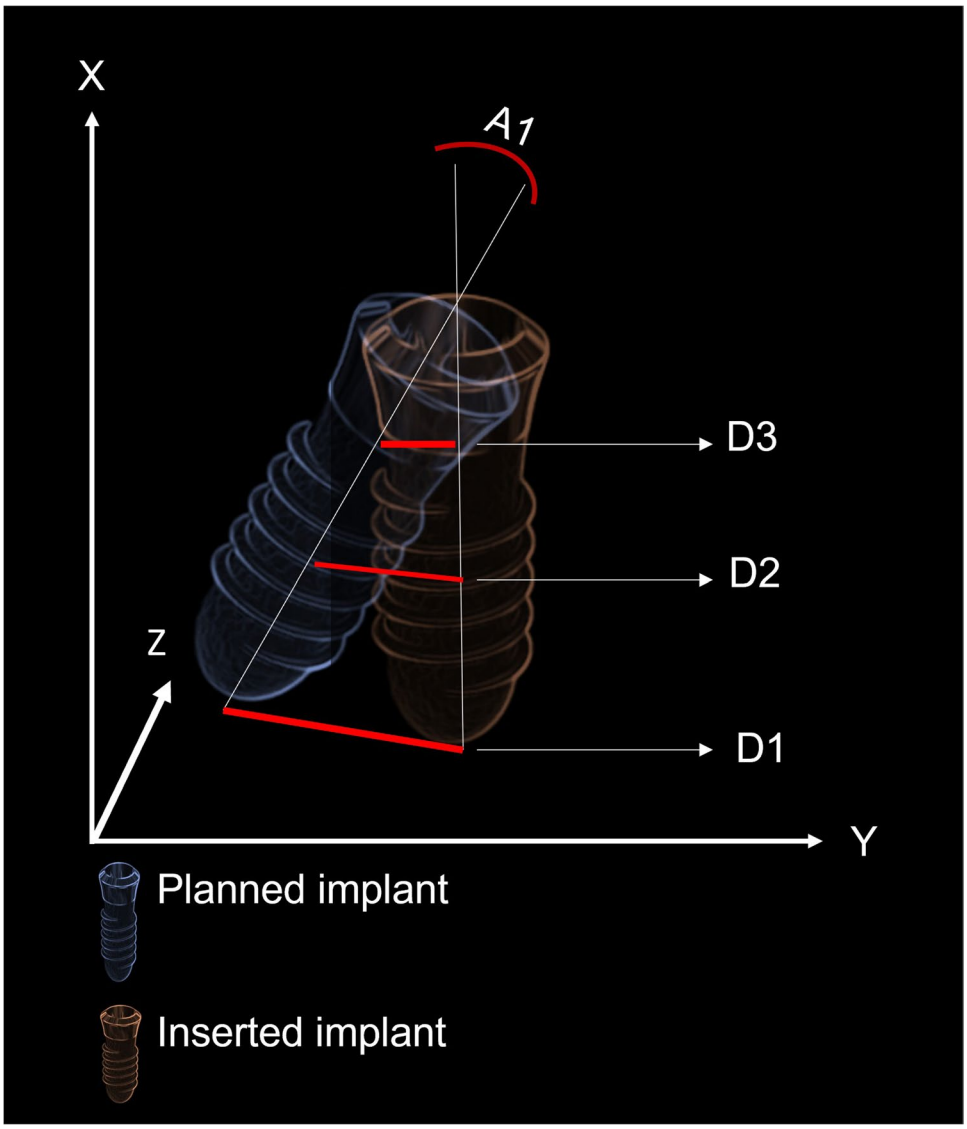

Fig. 4 Measurement of linear and angular deviations. D1 distance is calculated considering the linear distance between the implant apex; D2 linear distance between the points in the center of the implant and D3 on the implant platform. The angle A1 is calculated in degrees between the planned and executed vectors

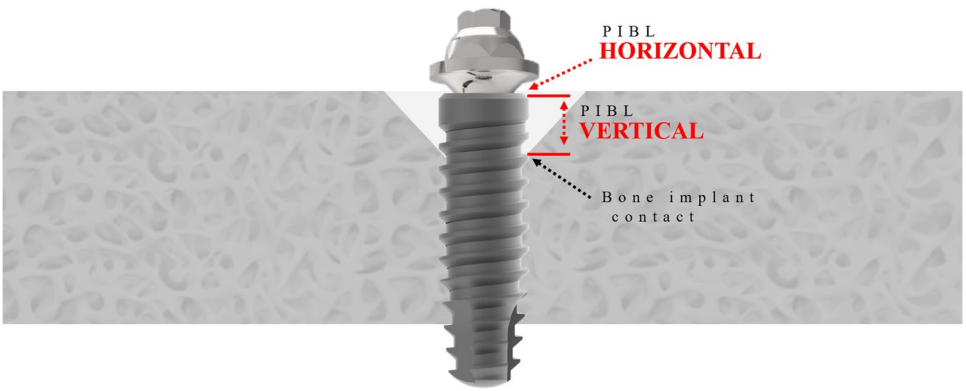

Fig. 5 Schematic illustration of the implant with vertical and horizontal bone levels

2-line segments is where $A1$, $B1$, and $C1$ and $B1$, $B2$, and $B2$ are the resulting direction vectors of the line segments from pre- and post-operative implants:

$$\mathrm{Cos}\theta = \frac{a_1 \cdot a_2 + b_1 \cdot b_2 + c_1 \cdot c_2}{\sqrt{a_1^2 + b_1^2 + c_1^2} \cdot \sqrt{a_2^2 + b_2^2 + c_2^2}}.$$

Peri-implant bone level (PIBL) evaluation

The periapical radiographs (E-Speed, Carestream Dental) were taken (Spectro X-ray 70 × Seletronic, Dabi Atlante, Ribeirão Preto, SP, BR) to evaluate PIBL. They were performed immediately after prosthesis installation (baseline) and 6 and 12 months after surgery, using a parallel technique using a radiograph positioner (Indusbello, Londrina, PR, BR). The software used to perform radiographic measurements was ImageJ (National Institutes of Health, Bethesda, MD, USA), and the measurements were calibrated using the implant diameter and performed by a single and blinded examiner (E.K.M). The examiner performed the PIBL measurement vertically and horizontally in the radiography of ten patients twice in 24 h. The intra-class correlation was calculated, and values greater than 0.95 were obtained in both parameters evaluated, demonstrating that there was excellent agreement (ICC ≥ 0.75) for all measures studied [33].

For the vertical bone level, the measure was established from the implant platform to the first point of bone/implant contact. The horizontal bone level was assessed by measuring the outermost edge of the implant platform to the crest interface nearest to the marginal bone (Fig. 5).

Evaluation of the angiogenesis- and bone-related marker and microbiologic profile

A blinded examiner (E.K.M) collected all microbial samples of subgingival biofilm and peri-implant crevicular fluid from the implants in each group using filter paper strips (PerioPaper; Oraflow, Hewlett, NY, USA) at 7, 14, 30, and 90 days after implant insertion, as described previously [34]. The levels of PLGF, BMP-9, OPG, endothelin-1, VEGF, and RANKL were determined using specific kits (HAGP1MAG–12 K, HBNMAG-51 K, and HRNKLMAG-51 K-01, respectively; Millipore Corporation, Billerica, MA, USA) and measured with a multiplex instrument (MAGpix; MiraiBio, Alameda, CA, USA), following the manufacturer's instructions. The results were adjusted for the volume of peri-implant crevicular fluid for each implant, and the values were expressed in picograms per milliliter (pg/mL). The microbiological evaluation was done by real-time polymerase chain reaction (PCR). Microbiologic assays, primers, and reaction templates were performed to measure the absolute quantification of Aa, Pg, and Tf. The detection level was set at 10^3 bacteria per plaque sample for all the target bacteria.

Statistical analysis

The primary outcome variable was angular deviations. Secondary outcomes comprised linear deviations, PIBL, cytokine concentrations, and microbiological levels. It was observed that, except for the angle, all other variables analyzed presented a high dispersion of values. Thus, the Box-Cox transformation was applied to verify the type of distribution and the appropriate transformation. The variables coronal, apical, and central region and depth were transformed with the value λ (lambda) 0.5, and the normality test was applied again, demonstrating adherence to the normality, when the paired t-test was applied. Therefore, the data were analyzed by a non-parametric (distribution-free) Wilcoxon test. For PIBL, a two-way ANOVA/Tukey test was used. The power test a posteriori was calculated for the primary quantitative variable (coronal, central, apical region, depth, and angle) using the SPSS 21 program (IBM, Chicago). In addition, the two-tailed paired t-test family was adopted using $\alpha = 0.05$. The effect sizes were calculated based on the averages and variances of each group and the sample size to calculate the test power. The effect size ranged from 0.37 to 1.25, with power ranging from 0.81 to 1, using SAS biostatistics (v.9.1, SAS Institute, Cary, NC.). A 5% experimental level of significance was determined for all statistical analyses.

Results

Twenty-nine patients were included in the study, and one individual did not return for the 12-month visit due to health problems (Fig. 6). The study population was 72.4% of females (mean age, 62.06 ± 8.61 years). A total of 174 implants were installed (86 were analyzed for the S-CAIS group and 85 for the CS group). Regarding the length of the implants, implants of 9 mm (7 in the S-CAIS group and 9 in the CS group), 10 mm (3 in the S-CAIS group and 4 in the CS group), 11 mm (42 in the S-CAIS group and 49 in the CS group), 12 mm (2 in the S-CAIS group and 2 in the CS group), and 13 mm (33 at S-CAIS group and 23 in the CS group) were used (Table 1).

Deviation measurement results

Angular deviation

Regarding angular deviation, the CS group presented higher mean values when compared to the S-CAIS group ($p < 0.05$),

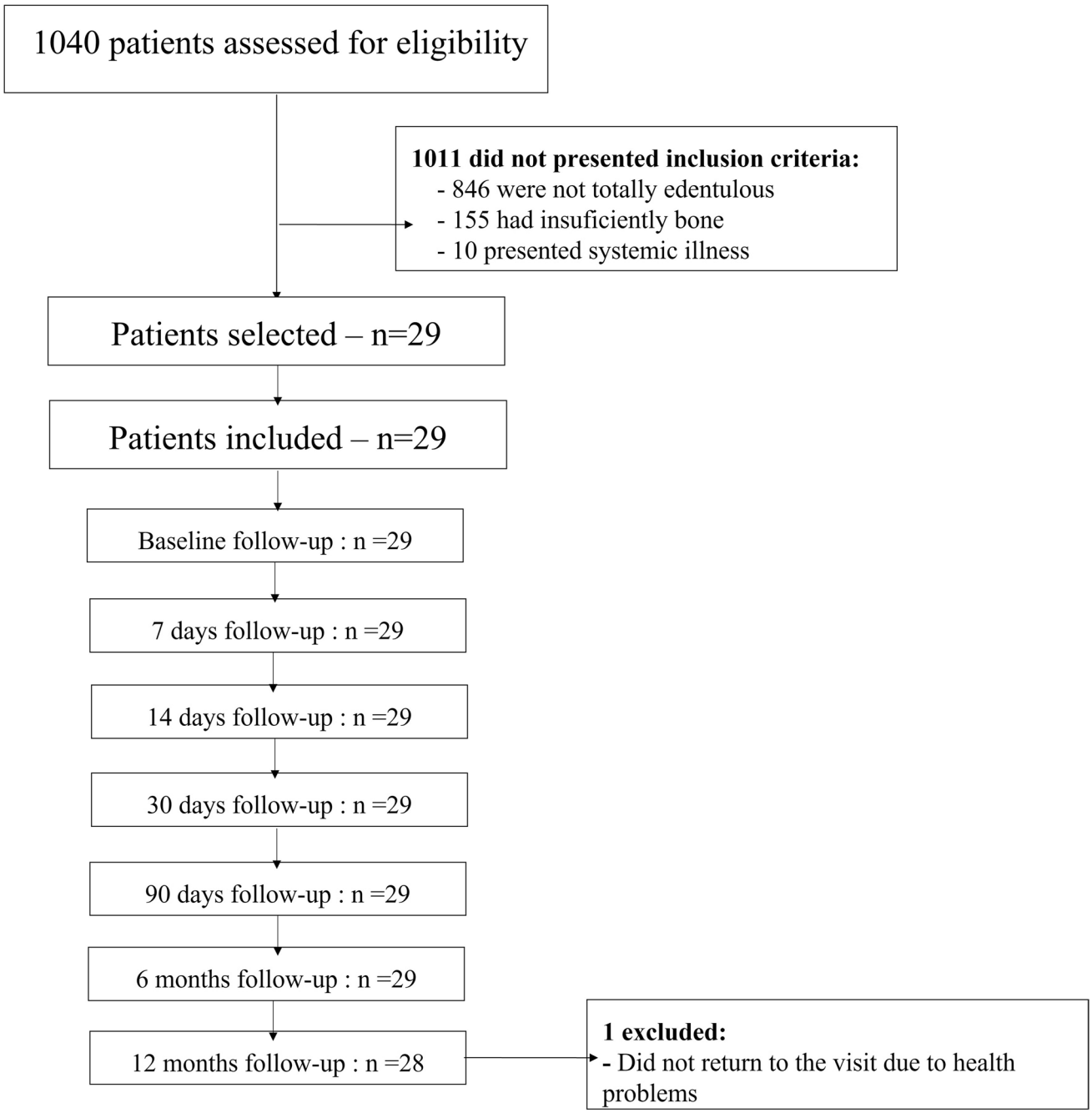

Fig. 6 Flowchart of the study showing the patients enrolled in the pre-study phase and the selection of individuals for the study phase

with a higher discrepancy in the differences between the angles formed between the planned and executed in the CS (Table 2).

Linear deviation

Considering apical and central regions, the CS group presented higher mean values when compared to the S-CAIS group ($p < 0.05$). No statistical differences were observed between implant planning and its subsequent execution regarding the difference in the coronal region between S-CAIS and CS groups ($p > 0.05$). Concerning the differences in the depth of the implant, considering the level of the implant platform in relation to the bone crest, the greater mean value of the difference between the planned and the executed was verified in the S-CAIS group when compared to the CS group ($p < 0.05$; Table 2).

Table 1 Demographic characteristics of the study population (mean-SD)

	S-CAIS	CS
Age (years)	62.06 (8.61)	62.06 (8.61)
Gender (man/woman)	8 (27.5%)	21 (72.4%)
Total of installed implants (*n*)	87	87
Total of analyzed implants (*n*)	86	85
Implant lost (*n*)	1	2
Implant length of 9 mm (*n*)	7	9
Implant length of 10 mm (*n*)	3	4
Implant length of 11 mm (*n*)	42	49
Implant length of 12 mm (*n*)	2	2
Implant length of 13 mm (*n*)	33	23

Peri-implant bone loss results

Vertical measurement

The S-CAIS group presented higher absolute vertical PIBL values at baseline compared to CS ($p < 0.05$). In the 6- and 12-month periods, there was no difference between the S-CAIS and CS ($p > 0.05$; Table 3).

Furthermore, when analyzing the bone level of S-CAIS group implants, it was found a vertical bone loss around the implants over time, statistically relevant to the end of the 12-month follow-up period ($p < 0.05$), with the mean vertical bone level displayed from baseline to 6 months similar to that found from 6 to 12 months ($p > 0.05$; Table 3).

Vertical bone loss was verified after 6 months in the CS group ($p < 0.05$), however, without its progression from 6 to 12 months, when a change in bone level was not significant ($p > 0.05$; Table 3).

Horizontal measurement

Regardless of the time analyzed, the CS group presented lower absolute values of horizontal PIBL than the S-CAIS group ($p < 0.05$; Table 4).

In both groups, horizontal bone loss was found after the period of 6 months ($p < 0.05$), however, without progression of loss from 6 to 12 months ($p > 0.05$; Table 4).

Table 3 Mean (SD) of the vertical bone level (mm) over time in both groups

	Baseline	6 months	12 months
S-CAIS	0.24 (0.37) Ab	0.48 (0.69) Aab	0.61 (0.83) Aa
CS	0.03 (0.10) Bb	0.24 (0.34) Aa	0.24 (0.35) Aa

Vertical capital letters compare groups within the same time; horizontally lowercase letters compare time within the group (ANOVA/Tukey test, $p < 0.05$)

Angiogenesis- and bone-related marker level results

The immune-enzymatic results are shown in Fig. 7. The inter-group analysis showed a significant difference in the levels of the angiogenic marker, with higher levels of VEGF in the CS group at a 7-day time point ($p < 0.05$). Higher levels of PLGF were observed in the CS group at 7- and 30-days' time point ($p < 0.05$). No inter-group difference was observed for endothelin-1 ($p > 0.05$). The intra-group analysis revealed a significant difference between 7 and the other time points for VEFG and PLGF levels in CS and ET-1 in S-CAIS ($p < 0.05$). Besides, for PLGF levels, a significant inter-group difference was found between 7 and 30 days in S-CAIS ($p < 0.05$). A significant difference was also seen for ET-1 between 7 and 30 days and 7 and 90 days in CS ($p < 0.05$).

Regarding osteoblastic markers, BMP-9 presented inter-group differences at 30 days' time point ($p < 0.05$), with higher levels in CS. OPG did not present any significant inter-group difference ($p > 0.05$). For intra-group analysis, a significant difference between 7- and 30-day periods and between 7 and 90 days was observed for BMP-9 in CS ($p < 0.05$) and between 7- and and the other time point for BMP-9 in S-CAIS ($p < 0.05$). Considering the intra-group analysis of OPG levels, both groups found a significant difference between the 7- and 90-day time point ($p < 0.05$).

The osteoclastic marker showed higher levels of RANKL CS at 30 days ($p < 0.05$). The intra-group analysis showed a difference for RANKL between 7 and 30 and 7 and 90 days for both groups ($p < 0.05$).

Table 2 Mean (SD) of different distances for both groups

Groups	Coronal region (D1, mm)	Apical region (D3, mm)	Central region (D2, mm)	Angle (°)	Depth (mm)
S-CAIS	2.01 (0.77) A	2.41 (1.45) B	2.05 (1.04) B	2.39 (0.79) B	1.67 (0.82) A
CS	2.27 (1.05) A	2.87 (1.36) A	2.38 (1.13) A	6.6 (3.15) A	1.36 (0.92) B
p value	0.105	0.005	0.018	0.000	0.008

Different capital letters indicate differences between groups (Student's *t*-test, $p < 0.05$). Coronal distances did not show statistical differences (Student's *t*-test, $p > 0.05$). Statistical differences were found for the apical, central, and depth regions (Student's *t*-test, $p < 0.05$)

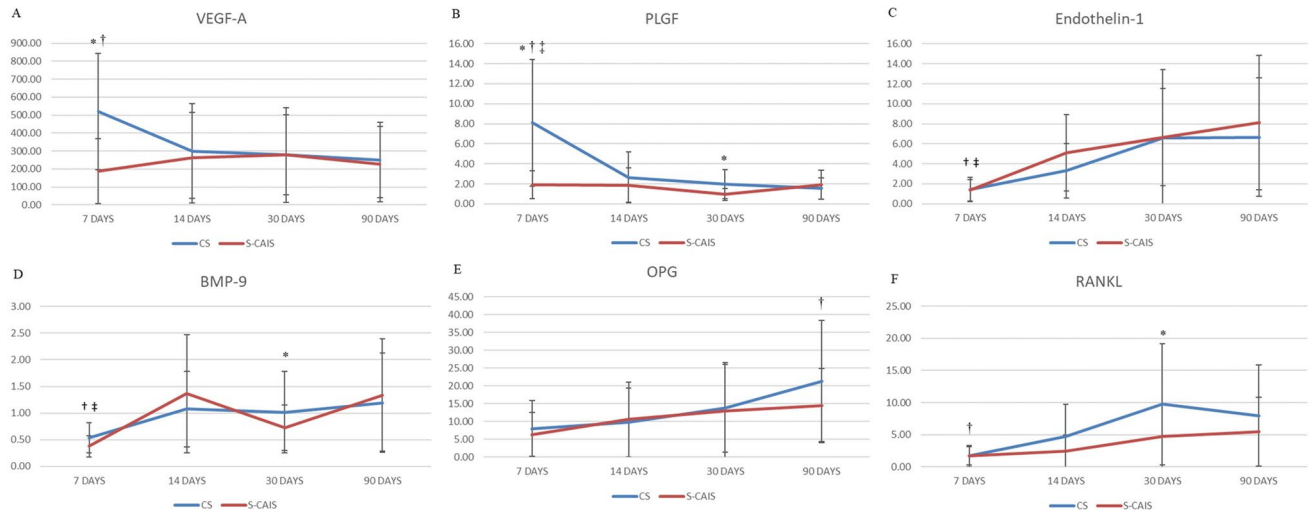

Fig. 7 Levels of Vascular endothelial growth factor (VEGF) (A), Placental growth factor (PLGF) (B); Endothelin-1 (C); Bone morphogenetic protein 9 (BMP-9) (D), Osteoprotegerin (OPG) (E), Receptor activator of nuclear factor kappa-B ligand (RANKL) (F), in the peri-implant fluid (pg/mL) in implants inserted with Conventional Flap Surgery and Static Computer-aided Implant Surgery. **A – VEGF** ⁎ Inter-group significant difference (Wilcoxon test; p<0.05). † Intra-group significant difference between 7 and 14 days, 7 and 30 days, and between 7 and 90 days for the CS (Friedman test; p<0.05). **B – PLGF** ⁎ Inter-group significant difference (Wilcoxon test; p<0.05). † Intra-group significant difference between 7 and 14 days, 7 and 30 days, and between 7 and 90 days for the CS (Friedman test; p<0.05). ‡ Intra-group differences between 7 and 30 days for S-CAIS (Friedman test; p<0.05). **C – ET-1** No inter-group significant difference (Wilcoxon test; p<0.05). † Intra-group significant difference between 7 and 30 days and between 7 and 90 days for the CS (Friedman test; p<0.05). ‡ Intra-group difference between 7 and 14 days, 7 and 30 days, and between 7 and 90 days for S-CAIS (Friedman test; p<0.05). **D - BMP-9** ⁎ Inter-group significant difference (Wilcoxon test; p<0.05). † Intra-group significant difference between 7 and 30 days and between 7 and 90 days for the CS (Friedman test; p<0.05). ‡ Intra-group difference between 7 and 14 days, 7 and 30 days, and between 7 and 90 days for the S-CAIS (Friedman test; p<0.05). **E – OPG** ⁎ No inter-group significant difference (Wilcoxon test; p<0.05). † Intra-group significant difference between 7 and 90 days for CS and S-CAIS (Friedman test; p<0.05). **F – RANKL** ⁎ Inter-group significant difference (Wilcoxon test; p<0.05). † Intra-group significant difference between 7 and 30 days and between 7 and 90 days for CS and S-CAIS (Friedman test; p<0.05)

Microbiological results

Data analysis revealed a statistically significant intergroup difference for Tf quantification, with a greater number of this pathogen in the CS group, within 30 days ($p < 0.05$). However, at 90 days, this difference was not maintained ($p > 0.05$). No significant differences were observed in the intergroup analysis for the other pathogens ($p > 0.05$). In addition, there were no differences in the intra-group analysis in both groups ($p > 0.05$). Table 5 summarizes the microbiological results.

Table 4 Mean (standard deviation) of the horizontal bone level (mm) over time in both groups

	Baseline	6 months	12 months
S-CAIS	0.65 (1.07)Ab	0.90 (1.23)Aa	1 (1.35)Aa
CS	0.06 (0.21)Bb	0.34 (0.64)Ba	0.37 (0.70)Ba

Vertical capital letters compare groups within the same time; horizontally lowercase letters compare time within the group (ANOVA/Tukey test, $p < 0.05$)

Table 5 Quantity (log [] – standard deviation) of pathogens in the subgingival plaque over time for CS and S-CAIS

	Aa (log [ ])			
	7 days	**14 days**	**30 days**	**90 days**
S-CAIS	0.69 (0.92)	0.50 (0.71)	0.44 (0.75)	0.66 (0.79)
CS	0.77 (0.90)	0.61 (0.82)	0.65 (0.99)	0.37 (0.75)
	Tf (log [ ])			
	7 days	**14 days**	**30 days**	**90 days**
S-CAIS	0.60 (0.71)	0.78 (0.89)	0.75 (1.01)	1.21 (1.30)
CS	0.87 (1.05)	0.64 (0.99)	1.24 (1.39)*	0.88 (1.50)
	Pg (log [ ])			
	7 day	**14 days**	**30 days**	**90 days**
S-CAIS	0.61 (0.93)	0.75 (1.07)	0.85 (1.30)	1.07 (1.61)
CS	0.85 (1.25)	0.77 (1.24)	0.81 (1.59)	0.67 (1.52)

Discussion

Static computer-aided implant surgery has been considered more precise and minimally invasive than conventional surgery for some RCTs [7, 21, 22, 35, 36]. In addition, virtual implant planning associated with a 3D-printed guide allows the use of a flapless approach [16, 36–44]. However, within the author's knowledge, there is no study comparing flapless-guided and conventional surgery for implant placement in fully edentulous patients in a split-mouth design regarding the accuracy, angiogenic and bone-related markers, and microbiological outcomes. In general, the present study showed less linear deviation at the apical point and at the midpoint and, less angular deviation with S-CAIS in relation to CS, higher values of vertical PIBL for S-CAIS at baseline, and higher levels of horizontal PIBL for S-CAIS in all evaluated time points. Angiogenic and bone markers presented higher levels in CS.

In this study, S-CAIS showed a lower mean deviation between planned and executed implants for linear and angular deviations, while variation in depth was greater in S-CAIS than in CS. The founded deviation values are higher than those reported by Bover-Ramos et al. [40] in a systematic review that analyzed the accuracy of implant placement by the use of static computer-aided implant surgery and compared virtual treatment planning and outcome in relation to study type (in vitro, clinical, or cadaver). The fully guided protocol reached lower values for horizontal coronal, horizontal apical, and angular deviation (1.00, 1.23, and 3.13 mm, respectively) compared to partially static computer-aided implant surgery. Vercruyssen et al. [37] compared the measurement of these deviations between planned and executed implants. The authors found lower averages of deviation in S-CAIS (coronal 0.9 mm (0.1–4.5 mm), apical 1.2 mm (0.2–4.9 mm), angular 2.7° (0.0–6.6°), and depth 0.5 mm (0.0–3.2 mm)) than those found in the present study (coronal (2.01 ± 0.77 mm), central (2.05 ± 1.04 mm), apical (2.41 ± 1.45 mm), depth (1.67 ± 0.82 mm), and angle (2.39 ± 0.79°)). However, in a systematic review, the same authors reported that deviations of up to 2 mm are permissible [26]. Higher deviations could complicate prosthesis procedures and make impossible the installation of implants in limited bone volume situations or near important anatomical structures such as maxillary sinus or inferior alveolar nerve. Although the deviation values found in our study are higher than those discussed above, any problem regarding prostheses or implant installation was observed. Besides, a systematic review and meta-analysis suggest a notable discrepancy in the linear and angular deviations in the literature [40]. In addition, unlike Vercruyssen et al. [36], the authors considered some limit values of linear and angular deviations in S-CAIS (coronal deviations of 1.3 mm, apical of 1.7 mm, and angular of 4.7°) to prevent damage to anatomical structures. The deviation results observed in the present study are different from the limits considered by Vercruyssen et al. [36] and Bover-Ramos et al. [40]; however, they corroborate the study of Vieira et al. [45] (2.17 ± 0.19 mm, 2.32 ± 0.34 mm, 2.86 ± 0.49 mm, and 1.93 ± 0.17 mm for coronal, central, apical, and angle respectively in the maxilla), that used 3D guides printed in the same company used by the present study, as well as the same virtual planning software. Therefore, comparisons of results between studies are difficult due to some factors that can affect these discrepancies between linear and angular deviations, such as the different types of support for the guides (mucosupported, dentosupported, or supported directly on the bone), a variety of planning software and printers, and the different toothless spaces (unitary, partial, or complete) [45].

Considering the differences in deviation values between the planned and the executed implants in both approaches, greater precision for S-CAIS in relation to CS was observed. This result is in line with other authors' reports [21, 36, 46]. However, it is interesting to discuss the higher discrepancy observed when an angular deviation in the CS group (6.86 ± 3.15°) is compared to the S-CAIS group (2.39 ± 0.79°). This finding is relevant because the dental implant placement in an inappropriate position can make it difficult or impair the prosthesis placement and damage anatomical structures [42, 47, 48]. The inclination can influence linear deviations, especially at the implant top, where the angle extent is directly proportional to apical deviations. The apical area offers the highest probability of anatomical structure damage due to the distant access by the operator. Thus, this is an important variable to be controlled [38]. In this regard, the results of the present study support the idea that S-CAIS with a mucosupported 3D-printed guide could offer higher control in this parameter in cases of totally edentulous jaws. In line, Raico Gallardo et al. [48] demonstrated that mucosupported guides had a higher reduction in angle deviation ($p = 0.02$), deviation at the entry point ($p = 0.002$), and deviation at the apex ($p = 0.04$) when compared to the bone-supported guides.

In this study, bone marking with the pilot drill in CS was performed through the 3D-printed guide repositioning after the flap elevation. After this, the guide was removed, and the following steps were executed based only on the visualization of the virtual planning and using the acrylic guide. It may explain the absence of statistical differences between the two approaches for the planned and executed implants for the coronal region once the entry point was based on the prototyped surgical guide. It is important to highlight that the precision of transferring the position of planned implants in the software for flapless surgery using a 3D-printed guide can be influenced by each stage, from image acquisition to implant insertion. As a closed system, the inability to see anatomical markings and vital structures may increase the

risk of angulation and depth deviation [23, 26] between the planned and executed implants. Another factor that can influence the depth difference of installed implant, especially in S-CAIS of the edentulous jaw, is the lack of exact adaptation of the guide on the ridge or its movement at the time of bone instrumentation [36, 38, 42, 49]. These factors can help explain the statistically different values between the implants' planned and executed positioning concerning the depth parameter.

Another critical point is the implant survival rate that the present study reached an index of 96.6% for both groups. It is in line with systematic reviews that report survival rates between 97.2 and 97.8% [27, 50, 51]. Besides, some studies have shown that survival rates of guided implants can be compared to conventional implants [16, 27, 28, 50, 51].

Any statistical difference in vertical bone level between S-CAIS and CS at 6- and 12-month periods was observed. This result is in line with a systematic review, where similar values of vertical bone loss were found after the first year of function for S-CAIS (0.04 ± 0.34 mm) and CS (0.01 ± 0.38 mm) [51]. Recent systematic reviews also showed similar values of marginal bone level between S-CAIS and CS (MD 0.11, 95% CI 0.27 to 0.04; $P = 0.16$) [52]; MD = 0.01, 95%CI (− 0.42, 0.44), $P = 0.97$ [53]). Although the two surgical approaches do not show statistical differences at the vertical marginal bone after 12 months, they showed a different behavior of bone loss throughout the study. By discussing each group separately, CS presented major changes in bone level in the first 6 months and S-CAIS at the end of the 12-month time point. This pattern of bone level change in these surgical approaches is different from that of Tsoukaki et al. [53], where greater vertical bone loss between 4 and 6 months in CS and no bone resorption were detected in flapless surgery. The same was observed in a systematic review and meta-analysis that reported less bone loss in flap surgery compared to open surgery in the same period [26]. In this context, one limitation observed in the S-CAIS approach regards areas with high mucosa thickness, which did not allow the conventional positioning (infra-bone) of switching platform implant position [54–56]. This limitation occurred due to the distance between the implant platform and the rings being static, making it impossible to change this measurement in the software. Thus, to insert the implant in an infra-bone position, it would be necessary to invade the mucosa, which could lead to mispositioning the 3D-printed guide. This fact could help explain the results observed in S-CAIS regarding implant depth, which presented different values compared to the implants installed in the CS.

On the other hand, all CS implants were installed in a subcrestal position, which may explain the higher horizontal bone level in S-CAIS. Since the implants were at a supracrestal position, the baseline was used a shorter abutment with a standardized diameter of 4.8 mm. In this respect, this discrepancy between implant platform diameter (3.5 mm) and the mini pillar (4.8 mm) used may have contributed to the greater horizontal bone resorption in the S-CAIS group.

Generally, the studied immunological markers presented higher levels in the CS group. It may be suggested that the flap elevation promoted higher remodeling activity, whereas the flapless approach did not promote this effect. However, differences between the groups were observed only at the early stages. At the 90-day time point, any inter-group difference was observed regarding the levels of angiogenic, osteoblast, and osteoclastogenic factors. In line with this, there were differences in vertical bone level between S-CAIS and CS only at baseline.

On the other hand, a different pattern of bone loss in the CS group can be observed along the time, with significant changes in bone level in the first months, while S-CAIS presented differences in later times (12 months). With respect to angiogenic markers, higher levels of VEGF and PLGF in CS at 7- and at 7- and 30-days' time point were observed. The VEGF results align with Lei et al. [57], which compared soft tissue healing after implant placement in the flap and surgery in dogs and observed a higher amount of VEGF expression in earlier stages (2 weeks) in the flap group than in a flapless group. Therefore, the higher concentration of both VEGF and PlFG in the early stages could suggest more pronounced angiogenic and osteoclastogenic activity in CS. It also suggests that the conventional approach leads to a higher inflammatory process during the early stages of healing. The osteoblastic marker (BMP-9) was also elevated in the CS group at 30 days. This finding suggests more osteoblastic activity when the flap was elevated once BMP-9 performs an important role in bone formation and the differentiation of undifferentiated mesenchymal cells [58]. Osteoclastic marker (RANKL) was elevated in the CS group at the early stages of healing (7 and 30 days). These results align with the concentration of angiogenic and osteoblastic factors suggesting that the CS approach leads to higher tissue remodeling activity. It can also be inferred that the flap surgery leads to vascular damage and acute inflammatory response due to the elevation of the periosteum from the underlying bone surface. This fact could lead to resorption of the alveolar crest bone and reduction of crestal bone height, which agrees with the changes in vertical bone level in the CS group from baseline to 6 months. On the other hand, the flapless approach preserves the periosteum and blood supply, reducing early bone resorption. In this respect, S-CAIS did not present vertical bone changes in the earlier healing phase.

CS group had a greater number of Tf at 30 days period. This result differs from Tsoukaki et al. [53], in which the number of Tf was higher in the flapless group in the first and twelfth post-operative weeks. These authors suggest that the increase in bacterial quantification in this group results

from an earlier maturation of the peri-implant sulcus. However, the individuals included by the authors were partially edentulous, and a justification for the higher bacterial count in the flapless group would be the maintenance of an intact pathogenic flora in the adjacent teeth since there was no disorganization of the biofilm by elevating the flap. In the present study, all individuals were totally edentulous; therefore, bacterial colonization could not have adjacent teeth as a source of contamination. However, periodontopathogenic bacteria can, even in edentulous individuals, lodge in the adjacent alveolar mucosa, oral epithelium, the floor of the mouth, vestibule, palate, tonsils, and back of the tongue after tooth extractions indicating that they can survive outside the periodontal pockets and transit through various niches of the oral cavity [59–61]. Therefore, the opening of the flap may have favored colonization by Tf, which remained lodged in the soft tissues, within 30 days in the CS group, and the absence of the flap reduced the count in the S-CAIS group.

Interestingly, the present study found no differences in microbial counts for Aa and Pg between groups. This result also differs from Tsoukaki et al. [53], in which the number of Pg was also greater in the flapless group in the second postoperative week. This difference between the Tsoukaki et al. [53] study and this study probably stems from the latter's inclusion of edentulous patients, reducing the possibility of early colonization of peri-implant sites.

Quirynen et al. [62] established that the initial peri-implant colonization occurs within 2 weeks after the implant installation. In addition, the microbiota of the adjacent teeth, in partially edentulous individuals, is considered the primary source of bacteria, and peri-implant colonization may begin as early as the first post-surgical week [63]. Although some studies [64–70] did not detect Pg and Aa in edentulous patients, the present study showed the presence of these pathogens in the individuals included, which corroborates the findings of other authors [60–63, 70, 71] who point out soft tissues as bacterial reservoirs, even after total extraction. In addition, other studies [62, 70, 72, 73] also detected the presence of peridontopathogens in edentulous patients, even if in lower counts. It is worth mentioning that the present study adopted molecular biology techniques, whose specificity and accuracy are greater than the culture techniques adopted in other studies. This way, it was possible to quantify the proposed microorganisms, even in low numbers.

Additionally, this study adopted a split-mouth design, which allows the comparison of the two treatments within the same individual, discarding the differences inherent in different individuals. This study carried out a 3-month follow-up for microbiological analysis, and no differences were observed over time within each group, even with the immediate protocol-type prosthesis in function. Perhaps a limitation of the study is the short follow-up time and, possibly, a longer time (from 6 to 12 months) of follow-up could reveal some differences within and between groups.

Conclusion

Within the study's limits, it can be concluded that flapless static computer-aided implant surgery for installing dental implants in total edentulous maxillary patients contributed to a greater degree of precision and predictability when compared to the conventional flap technique. However, PIBL was higher in S-CAIS, and the conventional technique led to greater angiogenic and bone remodeling activity by elevating the angiogenic and bone markers levels.

Author contribution LMN: worked at the experimental phase (clinical procedures and patient recruitment).

EKM: worked at experimental phase (clinical procedures and patient recruitment).

MGC: drafting the work.

FRV: analysis, and interpretation of data for the work and laboratorial analysis.

FRC: substantial contributions to the conception or design of the work.

SPP: final approval of the version to be published and clinical procedures.

MZC: final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors agree to be personally accountable for the author's own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate All eligible patients were thoroughly informed of the nature, potential risks, and benefits of their participation in the study and signed an informed consent document. This study was approved by the ethics committee of Paulista University (2.059.143).

Conflict of interest The authors declare no conflict of interest.

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