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CLINICAL RESEARCH

Evaluation of safety and efficacy of locally developed dental implants: A noninferiority randomized controlled trial

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ABSTRACT

Statement of problem. Various dental implants are available in India, but imported devices are expensive; an affordable locally produced dental implant system would be beneficial.

Purpose. The purpose of this noninferiority randomized controlled trial was to compare the safety and efficacy of a locally developed dental implant system to those of an established imported dental implant system with similar microsurface characteristics.

Material and methods. A total of 136 participants with 201 partially edentulous sites, aged 18 to 65 years, were enrolled in the trial, with 134 sites receiving test implants and 67 sites control implants (n ratio, 2:1). The implants received a delayed submerged healing protocol and were loaded 3 to 6 months after surgery. Maximum insertion torque (IT) was recorded during the implant surgery, and the implant stability quotient (ISQ) was evaluated on the day of surgery and at the second-stage procedure. The mean crestal bone loss (MCBL) was measured on periapical radiographs at prosthetic placement (baseline) and at 6 months and 12 months after loading. The primary measure of outcome was the implant survival rate, and the secondary measure of evaluation was the intergroup difference in MCBL at baseline, 6 months, and 12 months.

Results. A total of 127 test and 61 control implant sites were available for follow-up 1 year after prosthesis placement. At the end of 12 months, the test and control implant groups demonstrated a survival rate of 97% and 100%, respectively. The MCBL difference was significant between the 2 groups at baseline ($P<.05$). However, at 6 and 12 months, the difference between the test and control groups was not significantly different ($P>.05$).

Conclusions. The survival rate of the test group fell within the previously assumed 10% noninferiority margin. Therefore, the null hypothesis was accepted for the trial, and the locally developed implants were noninferior to the imported implants at a sample allocation ratio of 2:1. (J Prosthet Dent 2022;■:■-■)

Dental implant-supported prostheses have become the preferred mode of rehabilitation for partially and completely edentulous patients.[1] However, Indian dentists are dependent on imported dental implants, resulting in high treatment costs that prevent their use in a wide section of society. With the increase in the aging population[2] and a rise in dental tourism,[3] the local development of a cost-effective and ergonomic dental implant system would be beneficial.

A nationally evolved project was initiated to develop a locally produced dental implant (Test implant; Indian Institute of Technology, Delhi) to suit the needs of the population. The implant was manufactured from high-strength titanium alloy (Ti6Al4V) with airborne-particle abraded and acid-etched surface characterization to provide the optimal osseous integration.[4,5] The implant-abutment connection was an internal hexagon with a medialized implant abutment interface (integrated platform switching).[6,7] Macrosurface characteristics included variable thread and pitch dimensions, with V-shaped microthreads on the coronal one-third and reverse buttress threads on the implant body. The implant system was designed with a single prosthetic platform for all

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Clinical Implications

The development of local production can help increase the availability of affordable dental implant therapy to the Indian population.

implant diameters, alongside a multifunctional abutment. The developed implants were sequentially tested for biocompatibility and fatigue among other mechanical tests.[8,9] A trial in a rabbit model provided the safety and efficacy characteristics of the implants.[10,11]

As a dental implant is an implantable medical device that remains in contact with human tissues for a long duration, regulatory requirements mandate a clinical trial of the manufactured implant. Since randomized controlled clinical trials are considered the best method of assessing the effects of materials and interventions in oral implants,[12,13] the present study was designed as a prospective randomized controlled noninferiority trial with a parallel group hybrid design to compare the test-manufactured dental implants with the standard control implants replacing single missing teeth in terms of safety and efficacy.

The efficacy and safety of dental implants may be demonstrated through the assessment of parameters such as survival rate,[14] mean crestal bone loss,[15-18] and analysis of biological and prosthetic complications and failures.[14,19-21] The objectives of the study were therefore to compare the developed test implants with standard imported control implants with similar microsurface characteristics,[22] analyze the survival rate of implants, quantitatively assess the peri-implant mean crestal bone loss (MCBL), evaluate the mechanical complications related to implants and prosthetic restorations, and identify undesirable effects when weighed against the intended benefits after 1 year of function. The intent of this study was to demonstrate that the locally developed dental implant system was not inferior to a standard imported implant. Hence, the preferred mode of study was a noninferiority trial.[23] The null hypothesis was that the test dental implants were noninferior to the standard imported control implants and no statistically significant difference would be found while analyzing the primary and secondary endpoints of the study at 12 months.

MATERIAL AND METHODS

The study was carried out in the Departments of Prosthodontics and Periodontics, Maulana Azad Institute of Dental Sciences, New Delhi, India, between January 2016 and September 2019. The study protocol was reviewed and approved by the institutional ethical committee and was registered with the Clinical Trial Registry of India (REF/2014/09/007661-CTRI/2019/06/019758). The ethical principles outlined for clinical trials of medical devices involving human participants were followed while conducting the study.[24-26]

Sample size was estimated based on the phase I preliminary clinical trial (n=35) conducted before the present study by using the recorded mean difference and standard deviation during the observational periods (baseline and 12 months after implant placement) for the mean crestal bone loss (MCBL). The MCBL of 0.40 mm in 1 year was taken as the surrogate measure of the standard device survival.[27,28] The study demonstrated 90% survival rate for the standard marketed implant. The test implant was more cost-effective and had a higher rate of survival (100%). With the assumption of a noninferiority margin of 10%, an allocation ratio of 2:1 between the test and control implants, a type I error (α) =.05, and power=90%, a sample size of 120 participants for the test group and 60 for the control group was determined. Considering a loss of 10%, the final sample size was 134 and 67 in the 2 groups. The controls (CMI-IS II; NeoBiotech) were endosseous, root-form implants that are airborne-particle abraded, with an acid-etched surface, and an internal conical connection. They were selected on the basis of microsurface characteristics similar to those of the test implant.

Screening was conducted among partially edentulous, systemically healthy individuals with no signs of active periodontal or endodontic disease, who were aged between 18 and 65 years and consented to attend the follow-up visits. Written and audio-video consents were obtained. Partially edentulous sites opposing a natural or rehabilitated dentition, with a 16-week healing period after extraction[29] and sufficient bone volume,[30] were included in the trial. Exclusion criteria included debilitating systemic diseases, a history of radiation, bisphosphonate therapy, alcohol or drug abuse, signs of parafunctional habits, smokers of more than 10 cigarettes/d, pregnant women or those intending to conceive, and partially edentulous sites with a crown height space less than 7 mm.

The participants were randomized based on a computer-generated randomized sequence for an unequal (2:1) sample allocation ratio and were allocated to the test and control groups according to their serial numbers of recruitment. Double blinding was not possible, as the use of system-specific surgical kits, packaging, and radiographic identification of the implant macrocharacteristics unblinded the surgeon. Additionally, as per the ethical guidelines, the patients were provided with information about the name, batch number, and dimensions of the implants placed. However, whether the system was the test or control system was not revealed to the participants.

A periapical radiograph of the implant site at a 1:1 image ratio was obtained with a positioning device (XCP,

Rinn; Dentsply Sirona). Presurgical laboratory investigations were conducted, including a complete hemogram, serum blood sugar fasting and post prandial, prothrombin time, partial thromboplastin time, and blood pressure monitoring before the surgery.

The implant placement procedures were standardized among the operators. Buccal and lingual infiltration was used with lignocaine 2% with 1:80 000 epinephrine. A midcrestal incision was placed with sulcular releasing incisions around the adjacent teeth. A mucoperiosteal flap was raised. The osteotomy was prepared with sequential drilling by using the associated surgical kits (Test implant surgical kit; IIT-Delhi, and IS Full kit; NeoBiotech), and the implants were inserted in an equicrestal position. Insertion torque (IT) was measured by using a universal torque wrench (Torque ratchet; Josef Ganter Feinmechanik) or the physiodispenser setting (Implantmed classic-SI 9XX; W&H). Implant stability quotient (ISQ) values were measured by using a resonance frequency analysis device (Ostell Mentor; Ostell). The flap was approximated with #3-0 silk sutures with a 3/8" reverse cutting needle. A postoperative periapical radiograph was recorded with the positioning device for a 1:1 view to assess the implant position and record the peri-implant bone level.

The implants were allowed to osseointegrate for 3 to 6 months. [31] Each implant was classified as successfully integrated or an early failure according to preestablished criteria.[32] At the second-stage surgery, ISQ values were recorded, and a healing abutment was placed. After the assessment of soft-tissue healing, definitive impressions were made with a polyvinyl siloxane impression material (Putty and Light Body, Elite HD+; Zhermack), the prostheses were clinically evaluated, and the implant-supported crowns were delivered.

Postsurgical follow-up was conducted at 24 hours, 7 days, and 14 days to evaluate for inflammation, tenderness, suppuration, numbness, or tingling in the nerve distribution areas, flap dehiscence, and membrane/or graft exposure (if used). A follow-up was conducted for implants after the delivery of prostheses at 6 and 12 months. Peri-implant tissues were assessed for the presence or absence of bleeding on probing (BOP) and for peri-implant probing depth (PD). Interexaminer calibration was performed to reduce interobserver variability.[33] Periapical radiographs were obtained at prostheses delivery and at 6 and 12 months after loading. The radiograph images were exported from the imaging software program (Kodak dental imaging software v 6.12.26.0; Carestream Health Inc) as a Joint Photographic Experts Group (JPEG) file and transferred to an image analysis software program (Digimizer; MedCalc Software). The marginal bone levels were measured by using the implant-to-abutment junction as a reference. The total length of the implant body (known and measured) was used to calibrate the measurements. Prosthetic evaluation was performed to identify complications such as abutment screw loosening or fracture of the screw, prosthesis, abutment, or implant. Unrestorable damage to the prosthetic assembly, sleeping implants, implant mobility, and progressive peri-implant infections unresponsive to therapeutic attempts were considered failures.

All the findings were recorded and analyzed. Implant-level analysis was performed to account for the repeated observations (single-unit implant-supported prosthesis) available for a single participant.[21] The data were analyzed by using a statistical software program (SPSS v16.0; SPSS Inc). The normality of the distribution for continuous variables was assessed by the Shapiro-Wilk test. All outcome variables, including mean crestal bone loss (MCBL), met the assumption of normality. Data were described by using means and standard deviation (SD).

The intragroup variations in the MCBL over a period of 1 year were quantified by using the general linear model for repeated-measures analysis and were tested for significance by using the paired t test. Intergroup variations were analyzed via the Levene Test for equality of variances and further assessed with the independent sample t test for equality of means (α=.05).

RESULTS

A total of 136 participants were enrolled in the trial, and 201 partially edentulous sites were selected to receive the locally manufactured (test; n=134) or standard marketed (control; n=67) implants. The test group of participants (mean ±standard deviation age, 41.39 ±14.38 years; range, 20 to 68 years) and control group of participants (mean age ±standard deviation, 47.74 ±13.11 years; range, 20 to 65 years) were followed up for a period of 12 months after prosthesis delivery. There were 9 dropouts during the course of the study, leading to loss of follow-up for 13 implant sites (test n=7; control n=6) (Fig. 1). The demographic, clinical, and relevant implant characteristics of the participants are shown in Table 1. Sex distribution within the groups was similar (P>.05), with intragroup analysis demonstrating near to 1:2 female:male distribution. Age distribution demonstrated a significant difference between the age of participants in the groups (P<.05). Implant parameters such as implant length, diameter, IT, ISQ (recorded at the time of implant placement and second-stage surgery), and duration between the initial and second-stage surgeries were not statistically significant (P>.05).

The primary measure of evaluation was the 1-year survival rate of the implants. Statistical analysis was performed for 127 test and 61 control implants that were followed up for 12 months after prosthetic rehabilitation.

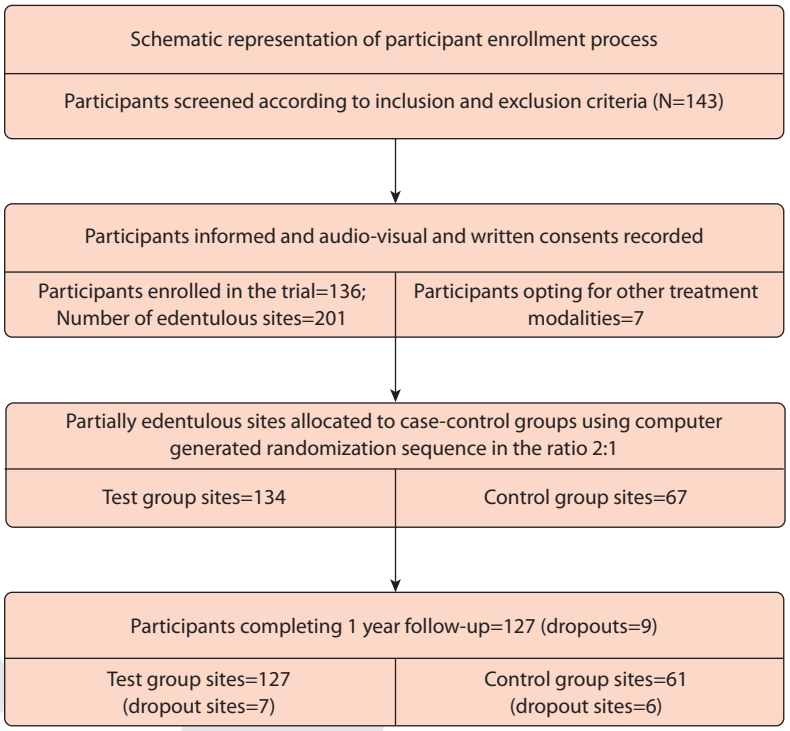

Figure 1. Schematic representation of participant inclusion and dropouts in test and control groups.

Table 1. Sociodemographic, clinical, and implant characteristics and primary and secondary evaluation measures of test and control group participants

Parameters	Test, Value ±SD (Range)	Control, Value ±SD (Range)
Demographics		
Age (y)	41.39 ±14.38	47.74 ±13.11[a]
Sex (M/F)	77/50 (60.6%/39.4%)	43/18 (70.5%/29.5%)
Implant site		
Maxillary/Mandibular	47/80 (37%/63%)	28/33 (45.9%/54.1%)
Anterior/Posterior	18/109 (14.2%/85.8%)	9/52 (14.8%/85.2%)
Implant dimensions		
Diameter (mm)	3.94 ±0.35	4.04 ±0.45
Length (mm)	10.54 ±0.72	10.34 ±1.10
Implant surgery		
Insertion torque (Ncm)	46.85 ±9.65	46.72 ±8.0
ISQ (at placement)	74.83 ±8.78	74.86 ±5.71
Second-stage surgery (mo)	5.35 ±1.23	5.77 ±1.38
ISQ-ss (at second stage)	75.51 ±9.37	77.01 ±4.65
Primary measure of evaluation		
Implant survived/Explanted (n)	123/04	61/0
Implant survival rate	~97%	100%
Secondary measure of evaluation		
MCBL at baseline (mm)	1.17 ±1.0 (95% CI: 0.99, 1.35) (n=125)	0.85 ±0.89[a] (95% CI: 0.62, 1.07) (n=61)
MCBL at 6 mo (mm)	1.17 ±0.93 (95% CI: 1.01, 1.33) (n=123)	1.09 ±0.74[b] (95% CI: 0.90, 1.28) (n=61)
MCBL at 12 mo (mm)	1.11 ±0.92 (95% CI: 0.94, 1.27) (n=123)	1.08 ±0.68[b] (95% CI: 0.90, 1.25) (n=61)

MCBL, mean crestal bone loss; SD, standard deviation. [a]$P<.05$ in intergroup analysis. [b]$P<.05$ in intragroup analysis when compared with MCBL baseline value.

The test and control implant groups demonstrated a survival rate of 97% and 100%, respectively, at the end of 12 months.

The secondary measure of evaluation was the assessment of MCBL at baseline, 6 months, and 12 months. The test group demonstrated a mean ±standard deviation of 1.17 ±1.004 mm (95% CI: 0.99, 1.35) of MCBL at baseline, stabilizing at around 1.17 ±0.93 mm (95% CI: 1.01, 1.33) at 6 months. At 12 months, the MCBL decreased to 1.11 ±0.92 mm (95% CI: 0.94, 1.27).

Table 2. Observed complications, failures, and management in test and control groups

Adverse Events Reported	Test	Control	Management
Biological			
Prolonged postoperative discomfort or tenderness	02	03	Medications and follow-up
Numbness or tingling in nerve distribution areas	–	–	–
Suture abscess	–	02	Suture removal+abscess drainage+irrigation. Follow-up to observe effect on crestal bone levels
Peri-implant suppuration and osseous defect	01	01	Open debridement+photodynamic therapy+bone grafting. Explantation if unresponsive
Nonintegration	02	–	Explantation+microscopic analysis of the implant surface
Flap dehiscence/Graft/Membrane exposure	–	–	–
Prosthetic	–	–	–
Screw loosening	02	02	Retightening of screw
Screw fracture	–	01	Screw retrieval+re-evaluation of prosthesis+screw replacement/refabrication of prosthesis
Abutment fracture	01	–	Refabrication of prosthesis
Porcelain chipping	–	02	Smoothing and polishing of margins
Prosthesis decementation	02	02	Recementation of prosthesis
–	–	–	Patient follow-up+PA abdomen radiograph+refabrication of prosthesis (in case of ingestion)
Implant fracture	–	–	–
Loss of integration	01	–	Explantation of implant+rehabilitation of patient

The change in the intragroup MCBL was not significant through the follow-up period of 1 year ($P>.05$).

The control group demonstrated a mean ±standard deviation of 0.85 ±0.89 mm (95% CI: 0.62, 1.07) of MCBL at baseline, increasing to 1.09 ±0.74 mm (95% CI: 0.90, 1.28) at 6 months. At 12 months, the MCBL stabilized at 1.08 ±0.68 mm (95% CI: 0.90, 1.25). The change in MCBL was significant between baseline and 6 months and between baseline and 12 months ($P<.05$). However, it stabilized between the 6- and 12-month period ($P>.05$).

The Levene test for equality of variances was applied to assess the intergroup difference in MCBL values at baseline, 6 months, and 12 months. Accordingly, the unpaired *t* test was applied to evaluate the equality of means. The difference in crestal bone loss was significant between the groups at baseline ($P<.05$), with the test group demonstrating higher initial bone loss. However, at 6 and 12 months, the difference between the test and control groups was not significant ($P>.05$).

The biological and prosthetic complications encountered during the course of the follow-up have been tabulated in Table 2. Of the 4 explanted implants, 2 demonstrated nonintegration at the second stage, and 2 developed mobility after loading.

DISCUSSION

The null hypothesis was accepted for the trial, as no significant difference was found in the implant survival and MCBL values between the test and control implants at 12 months. The trial assessed locally manufactured test and standard control implants rehabilitated with single crowns in the anterior and posterior regions, where 1 implant site was considered as 1 unit. The sample size allocation ratio between the test and control groups was kept at 2:1 to reduce costs, as the expensive imported control implants were purchased and not donated by the manufacturer.

The success of implant therapy depends on the interplay between procedural and patient-related factors.[34] Both the groups demonstrated similar sex distribution, mean age range of participants between 40 and 50 years, and similar implant-specific variables such as implant length and diameter ($P>.05$). The primary stability of dental implants is a function of local bone quality, implant geometry, implant surface morphology, and the placement technique used.[35] It can be evaluated by measuring insertion torque (IT)[36] and resonance frequency analysis (RFA).[37] In the present study, the IT and RFA values for the groups were found to be comparable. Hence, it may be suggested that the surgical protocols, implant parameters, and bone-implant contact dynamics indicating initial and secondary stability were similar for both the groups, thus limiting the effect of implant and procedural confounding variables over the results.[38]

The primary measure for implant efficacy assessment was the 12-month survival rate of the implants. Survival was defined as the reconstruction (implant and prosthesis) remaining functional at the follow-up examination irrespective of its condition.[14] The test and control groups demonstrated a survival of 97% and 100% at the end of 12 months ($P>.05$). This concurs with the preestablished noninferiority margin of 10%. Hence, the null hypothesis was accepted for the trial, and the test implants were established as noninferior to the standard implants at the sample allocation ratio of 2:1. Systematic

reviews of the survival and complication rates of implant-supported single crowns by Pjertursson et al[14] indicated an estimated 5-year survival of 94.5%. The third EAO consensus conference[39] estimated the 5- and 10-year survival rates of an implant-supported single-unit prosthesis to be 96.3% and 89.8%, respectively.

The secondary measure of evaluation was the intergroup difference in mean crestal bone loss (MCBL) at baseline, 6 months, and 12 months. Early MCBL is a consequence of adaptive bone remodeling subsequent to surgical and restorative procedural challenges.[16,18] In the first year after implant placement, 1.5 mm of MCBL is considered acceptable, and 0.2 mm thereafter.[15,17] In the current trial, the MCBL was significant between the 2 groups at baseline ($P<.05$), with the test group demonstrating higher crestal bone remodeling in the preloading period. The control group demonstrated a significant increase in MCBL values at 6 and 12 months ($P<.05$). Consequently, the difference between the test and control MCBL values was not significant at the 6- and 12-month evaluations ($P>.05$).

Early implant loss can occur because of overheating of the bone during osteotomy preparation, lack of primary stability, occlusal overload, or parafunction habits.[19] Popelut et al,[20] in a systematic review, reported annual estimated implant failure percentages ranging from 0% to 5.56% (95% CI: 0.00–14.76). The present study demonstrated a failure rate of 3.0%, within the annual reported limit. Chrcanovic et al[21] assessed the influence of local and systemic factors on implant failures, reporting a failure rate of 1.74% before the second-stage procedure. The present study recorded a failure rate of 1.5%, with 2 implants placed in the anterior maxillary segment demonstrating nonintegration at the second stage (Table 2, Supplemental Table 1 available online). Labial bone thinning was observed after implant insertion, and complete dehiscence with nonintegration was observed at the second stage. Of the 2 implants that failed after loading, one developed progressive peri-implant bone loss that was unresponsive to treatment. The other was in a region of high occlusal stress, with unilateral mastication, and 3 contralateral teeth demonstrating fractures. The losses observed could have been independent of the implant selection and directed more toward the importance of patient selection. Koka and Zarb[40] proposed the concept of osseosufficiency to describe the mutual interplay among the clinician, patient, and implant system in promoting and perpetuating osseointegration. Although it is common to associate implant loss with implant failure, this is clearly not the case in most cases, as was demonstrated by the present study.

Limitations of the present study included the short 1-year follow-up. The participants should be followed up for 5 or 10 years to ascertain long-term survival of the implant-prosthesis assembly in function. Unequal sample sizes were allocated for the 2 groups because of the financial constraints. However, the randomization and statistical measures were applied accordingly. The present study focused on implant placement in partially edentulous sites requiring a single-unit prosthesis. Further studies should be conducted to analyze the applicability of the implant system for different clinical indications.

CONCLUSIONS

Based on the findings of this noninferiority randomized controlled trial, the following conclusions were drawn:

1. The safety and efficacy of the locally manufactured dental implants compared with those of the standard marketed implants in partially edentulous situations were demonstrated.
2. The data generated demonstrated that the test implant system was noninferior to the controls and is safe and effective for human use.

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CRediT authorship contribution statement
Mahesh Verma: Conceptualization, Resources, Supervision, Project administration, Funding acquisition. **Farrukh Faraz:** Methodology, Validation, Investigation, Visualization, Writing – review & editing. **Smiti Bhardwaj:** Investigation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Abhinav Sood:** Conceptualization, Methodology, Visualization, Validation.

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