

IMMEDIATE, EARLY (6 WEEKS) AND DELAYED (4 MONTHS) SINGLE POST- EXTRACTIVE IMPLANTS: 3-YEAR POST-LOADING DATA FROM A RANDOMISED CONTROLLED TRIAL



PIETRO FELICE, MD, DDS, PHD

Associate Professor, Odontostomatologic Surgery,
Department of Biomedical and Neuromotor Sciences,
University of Bologna, Italy

CARLO BARAUSSE, DDS, PHD

Research Fellow, Odontostomatologic Surgery,
Department of Biomedical and Neuromotor Sciences,
University of Bologna, Italy

JACOPO BUTI, DDS, PHD, MPERIO RCSED

Associate Professor, Unit of Periodontology, UCL
Eastman Dental Institute, London, UK

MANLIO GESSAROLI, MD, PHD

Resident, Unit of Maxillofacial Surgery, AUSL
Romagna, Bufalini Hospital, Cesena, Italy

MARCO ESPOSITO, DDS, PHD

Freelance researcher and Associate Professor,
Department of Biomaterials, The Sahlgrenska
Academy at Göteborg University, Göteborg, Sweden

Correspondence to:

Marco Esposito

Casella Postale 34, 20862 Arcore (MB), Italy
E-mail: espositomarco@hotmail.com

PURPOSE. To compare the clinical outcome of single implants placed immediately after tooth extraction with those placed 6 weeks after tooth extraction (early placement), and those placed 4 months after extraction and socket healing (delayed placement).

MATERIALS AND METHODS. Two hundred and ten patients requiring one single implant-supported crown to replace a tooth to be extracted were randomised into 3 groups of 70 patients each to receive immediate, early (at 6 weeks), or delayed (after 4 months of healing) post-extraction implants, according to a parallel-group design. When needed, patients from the immediate and early groups had bone substitute grafts in the extraction socket, covered with a resorbable membrane, at implant placement. Sockets randomised to delayed implants were grafted in the same manner if poorly preserved, or in the "aesthetic" areas (from second upper premolar to second upper premolar). Implants inserted with at least 25 Ncm torque were left to heal unloaded for 4 months, whereas those inserted with less than 25 Ncm were left to heal unloaded for 6 months. Temporary crowns were delivered, and were to be replaced by definitive ones after 4 months. Outcome measures were crown and implant failures; complications; peri-implant marginal bone level changes; aesthetics, as assessed using the pink aesthetic score (PES); and patient satisfaction, recorded by blinded assessors. Patients were followed-up for 3 years post-loading.

RESULTS. Three years after loading, drop-outs were: five (7.1%) patients from the immediate, nine (12.9%) from the early, and eight (11.4%) from the delayed group. Five implants (9.2%) failed in the immediate, four (6.6%) in the early, and one (1.6%) in the delayed group (P [Freeman-Halton] = 0.282). Apart from the crowns that failed due to implant losses, no other definitive crown had to be remade. Complications affected eleven patients from the immediate group, 12 from the early, and eight from the delayed group (P [chi-square test] = 0.596). Mean peri-implant marginal bone loss after 3 years was -0.33 ± 0.22 mm at immediate, -0.43 ± 0.26 mm at early, and -0.49 ± 0.30 mm at delayed implants; (P [Kruskal Wallis test] <0.001); there were significant pairwise differences between immediate and early (0.10 mm; CI 95% -0.02; 0.22; P [Dunn-Bonferroni post-hoc] = 0.0391) and immediate and delayed implants (0.16 mm; CI 95% 0.04; 0.27; P [Dunn-Bonferroni post-hoc] = 0.0004), but no difference between early and delayed implants (0.06 ± 0.05 mm; CI 95% -0.06; 0.18; P [Dunn-Bonferroni post-hoc] = 0.6015). Three years after loading, the mean overall PES were 12.25, 11.98 and 11.17 in the immediate, early and delayed groups, respectively (P [Kruskal Wallis test] <0.001); there were significant pairwise differences between immediate and delayed (1.08 ± 0.27 mm; CI 95% 0.45; 1.72; P [Dunn-Bonferroni post-hoc] = 0.0006), and early and delayed implants (0.81 ± 0.27 mm; CI 95% 0.17; 1.46; P [Dunn-Bonferroni post-hoc] = 0.0099), but no difference between immediate and early implants (0.27 ± 0.27 mm; CI 95% -0.37; 0.90; P [Dunn-Bonferroni post-hoc] = 1.0000). There were no significant diffe-

rences in patient satisfaction regarding function ($P = 0.353$) or aesthetics ($P=0.531$), and all patients would undergo the same procedure again.

CONCLUSIONS. No statistically significant differences in failure, complications or patient satisfaction were observed when placing single implants immediately, 6 weeks or four months after tooth extraction, even though failures were more frequent in immediate and early implants. Bone loss was significantly smaller at immediate implants, and aesthetic evaluation scores were higher for immediate and early implants.

CONFLICT OF INTEREST STATEMENT. This trial was partially funded by Nobel Biocare Services AG (code: 2010-894), the manufacturer of the implants evaluated in this investigation; however, the data belonged to the authors and the manufacturer by no means interfered with the conduct of the trial or the publication of the results. Bone substitutes and membranes were generously provided by Tecnos (OsteoBiol, Giaveno, Italy).

INTRODUCTION

Osseointegrated dental implants were traditionally placed in healed ridges¹. Delayed implant placement after healing of the socket is preferred as it may minimise the risk of implant failures and complications, leaving post-extraction sockets to heal for 3 to 6 months before placing dental implants. However, with the traditional approach, long treatment periods and a second surgical intervention are required for implant placement. In addition, removable temporary prostheses are often used during the implant healing period, which many patients find uncomfortable. It would therefore be beneficial if the healing period could be shortened without jeopardizing implant success.

It is possible to place implants immediately after tooth extraction, in the fresh extraction socket. The main advantage of immediate implant placement is to shorten treatment, although immediate post-extraction implants might be at higher risk of complications and failures². As a compromise between placing implants immediately (immediate post-extraction implants) and waiting for 4 to 6 months to obtain complete or almost complete bone healing in the socket (delayed implants), there is the third option of placing implants after soft tissue healing (early approach), usually after 2 to 6 weeks. The rationale behind this approach is to obtain sufficient soft tissue healing to facilitate its closure around/over the implants, and thereby to decrease the risk of implant failure due to infection associated with the extracted tooth. This risk needs to be further weighed against that of another physiological phenomenon, the alveolar bone remodelling and resorption that occurs after tooth extraction³⁻⁶. Indeed, within 1 year of extraction, the clinical width of the alveolar ridge is reduced by approximately 50%, two-thirds of which is lost within the first 3 months³⁻⁶. The mean vertical tissue loss at single extraction sites ranges from 1 to 4 mm³⁻⁶, depending on site location, but varies among different individuals in rate and degree, and in some cases may be very advanced³⁻⁶. This localised alveolar bone resorption may affect both the possibility of placing dental implants and their aesthetic outcome, particularly in frontal areas, and in those patients exposing visible portions of their gums when speaking and smiling, potentially causing social discomfort and embarrassment.

Nevertheless, the naturally occurring bone resorption can be countered by subjecting sockets to a ridge preservation procedure just after extraction. Various ridge preservation techniques are currently used, ranging from soft tissue grafts to autogenous or bone substitute grafts⁵⁻¹⁹. The number of reliable RCTs is limited^{3,6,16}, but they appear to show that various ridge preser-

vation procedures are effective at reducing bone resorption^{3,5-7,12}. That being said, some preservation techniques have been associated with a substantial number of failures and complications^{5,20,21}, and some appeared to be ineffective altogether¹⁰.

It is, however, possible that immediate post-extraction implantation could reduce the bone resorption that occurs after tooth extraction, thereby improving the final aesthetic outcome, although this had yet to be proven² before the early findings of the present trial were published. Indeed, at that time there had only been a few randomised controlled trials (RCTs)²²⁻²⁶ comparing immediate and delayed placement of single implants in post-extraction sockets. No statistically significant differences were observed between the two procedures, with the exception of a greater frequency of complications at immediate with respect to delayed implant placement reported in one of the trials²⁴, and better aesthetics and less bone loss at delayed implants in another trial²⁶. However, in the latter study 6 to 8-mm-wide diameter implants were used in the post-extraction sites *versus* delayed implants of conventional 4 to 5 mm diameter in preserved sockets.

Even fewer RCTs have compared immediate *versus* early implants^{27,28} and early *versus* delayed implants²⁹, and reported evidence is therefore inconclusive. To the best of our knowledge, there had been no RCTs comparing all three procedures at the time of initiation of the current trial. It would, however, be very useful to know whether a better clinical outcome could be achieved by placing delayed implants after bone healing, or by waiting for few weeks to allow soft tissues to heal, or whether similar results could be yielded by placing implants immediately after tooth extraction, shortening the treatment time by several months. Hence, the aim of this RCT was to compare the clinical outcome of single implants placed immediately after tooth extraction with those placed 6 weeks (early placement) and 4 months after extraction (delayed placement), following socket healing. The null hypothesis was that there would be no difference in success rates, complications, peri-implant marginal bone level changes, aesthetics or patient satisfaction between the three procedures, against the alternative hypothesis of a difference. Articles reporting data at 4 months³⁰ and 1 year³¹ after loading were previously published, and the present article is their continuation to report the data at 3 years after loading. . At protocol stage, it was planned to follow the patients up to 5 years after loading. The present article is reported in line with the CONSORT statement for improving the quality of reports of parallel-group randomised trials (<http://www.consort-statement.org/>).

MATERIALS AND METHODS

Trial design

This was a single-centre RCT of parallel-group design with three arms, balanced randomisation and blind assessment. After tooth extraction, patients were randomised in equal numbers into three groups according to a parallel-group design: immediate post-extraction implant (**FIGS. 1A-C**), early implantation after 6 weeks (**FIGS. 2A-C**), and delayed implantation after 4 months (**FIGS. 3A-C**).

Eligibility criteria for participants

Any patient requiring at least one single immediate post-extraction implant, being at least 18 years old and able to sign an informed consent form, was eligible for inclusion. Sites were required to have sufficient bone to allow the placement of a single implant of at least 8.5 mm in length with a minimal diameter of 3.5 mm. Each patient provided only one implant site for the study. For patients with multiple edentulous areas to be restored, the operator was instructed to select the implant site in the most "aesthetic" area at the screening visit. Pre-operative radiographs (intraoral, panoramic, cone-beam computed tomography [CBCT] scans



Figs. 1A-C: Three-year post-loading results pertaining to one patient randomly allocated to immediate post-extraction implants: A) radiographic, B) vestibular and C) occlusal clinical views.



Figs. 2A-C: Three-year post-loading results pertaining to one patient randomly allocated to early implant placement: A) radiographic, B) vestibular and C) occlusal clinical views.



Figs. 3A-C: Three-year post-loading results pertaining to one patient randomly allocated to delayed implant placement: A) radiographic, B) vestibular and C) occlusal clinical views.

or other radiographical investigations, at the discretion of the operator), together with clinical examination, were used to determine bone volumes and anatomical landmarks.

Exclusion criteria were:

- General contraindications to implant surgery;
- Immunosuppressed or immunocompromised status;
- Irradiation to the head or neck area;
- Uncontrolled diabetes;
- Pregnancy or breast-feeding;
- Untreated periodontitis;
- Poor oral hygiene and motivation;
- Alcohol or drug addiction;
- Psychiatric disorders;
- Acute infection (abscess) in the site intended for implant placement;
- Need to lift the maxillary sinus epithelium;
- Inability to commit to 5-year post-loading follow-up;
- Previous or ongoing treatment with intravenous aminobisphosphonates;
- Participation in other studies interfering with the present protocol.

Patients were categorised into three groups based on the number of cigarettes they declared smoking per day: non-smokers, moderate smokers (up to 10 cigarettes per day) and heavy smokers (more than 10 cigarettes per day).

Setting and locations

Patients were recruited and treated by a single experienced operator (Pietro Felice) at the University of Bologna Dental Clinic and three private dental clinics, two located in Bologna and one in Conselice, Italy, following identical and standardised procedures. All patients received thorough explanation and signed an informed written consent form prior to being enrolled in the trial, to document that they understood the scope of the study (including procedures, follow-up evaluations, and any potential risks involved). The patients were given the opportunity to ask questions pertaining to this study, and were fully apprised of treatment alternatives. Ethical approval was obtained from the independent ethics committee of the Policlinic S. Orsola-Malpighi in Bologna on 22nd December 2011 (Prot. n. 2726/2011).

Interventions

Patients received a single dose of prophylactic antibiotic 1 hour prior to the intervention: 2 g of amoxicillin or 600 mg of clindamycin, if allergic to penicillin. Patients rinsed with 0.2% chlorhexidine mouthwash for 1 minute prior to the intervention. Patients were treated under local anaesthesia using articaine with 1:100,000 adrenaline. No intravenous sedation was used. Teeth were extracted as atraumatically as possible, using periostomes and small levers, attempting to preserve the buccal alveolar bone, when present. Flaps were raised only if necessary, after intrasulcular incision. Vertical releasing incisions were sometimes performed, but full-thickness flaps with minimal extension were attempted in order to minimise patient discomfort. Any remaining granulation tissue was carefully cleaned from sockets. The widest diameter of the socket was measured in mm, rounded to half mm, using a graduated periodontal probe.

Post-extraction sockets were categorised into:

- Well preserved, when the buccal plate was intact;
- Partially preserved, when up to 4 mm of buccal bone was missing;
- Poorly preserved, when more than 4 mm of buccal bone was missing.

The height of the buccal bone was assessed using the highest peak of the palatal wall as a reference point. After socket assessment, the sequentially numbered sealed envelope corresponding to the patient's recruitment number was opened to determine whether to place the implant immediately or to wait for 6 weeks or 4 months. In the situation that the investigator judged that no implant could be placed, the patient was excluded from the study and no envelope was opened.

NobelActive TiUnite implants (Nobel Biocare, Göteborg, Sweden) with conical internal connection were used. The operator was free to choose implant lengths (8.5, 10.0, 11.5, 13.0 and 15.0 mm) and diameters (3.5, 4.3 and 5.0 mm) according to the clinical indications and his preference.

Immediate post-extraction implants

Sites allocated to immediate implant placement were prepared using drills of increasing diameters, as recommended by the implant manufacturer. In brief, a lance drill was used to mark the exact implant entrance point, usually on the palatal wall of the socket, followed by drills of increasing diameter (2.0, 2.4/2.8, 3.2/3.6 and when needed 3.8/4.2 mm). Implants were placed crestally, but in "aesthetic" areas, the operator placed the head of the implant subcrestally, about 1 to 2 mm below the most coronal bone peak, and slightly palatally. Implant insertion torque was evaluated using the drilling unit motor and reported as equal to or higher than 25 Ncm or lower than 25 Ncm.

Once the implant was placed, clinical photographs were taken, the largest gap between the bony wall and the neck of the implant was measured (rounded to half mm) with a periodontal probe, and all "poorly preserved" sockets and "partially preserved" sockets in "aesthetic" areas (from second to second upper premolar) were reconstructed with bone substitute granules. The bone substitute used was a sticky paste made of 600–1000 micron pre-hydrated collagenated corticocancellous granules of porcine origin, properly mixed with collagen gel in a sterile syringe (OsteoBiol mp3, Tecnoss, Giaveno, Italy). The grafted area was then covered with a resorbable membrane derived from equine pericardium (Fine 20 x 20 mm, OsteoBiol Evolution). The membrane was trimmed and adapted to cover the entire socket and at least 2 mm of the surrounding crestal bone, and fixed using Frios titanium tacks (Dentsply-Friadent, Mannheim, Germany). Soft tissues were sutured with a cross suture without mobilising the flaps, and barriers were therefore left partially exposed, since full soft tissue coverage was not achieved.

Early implant placement group (6 weeks)

Patients randomised to the early implant placement group had sockets closed with flaps just after tooth extraction, whenever possible. After 6 weeks of soft tissue healing, a mucoperiosteal flap was raised, the widest diameter of the socket was measured using a graduated periodontal probe (in mm, rounded to the nearest 0.5 mm), and implants were placed as previously described. Once the implant was placed, clinical photographs were taken, the largest gap between the bony wall and the neck of the implant was measured (rounded to the nearest 0.5 mm) with a periodontal probe, and the operator reconstructed all "poorly preserved" sockets and "partially preserved" sockets in the "aesthetic" areas (from second upper premolar to second upper premolar) with granules of bone substitute (mp3). The grafted area was then covered with a resorbable membrane (Evolution) fixed with tacks. The wound was completely covered by soft tissues.

Delayed implant placement group (4 months)

At tooth extraction, patients randomised to the delayed implant placement group had their sockets augmented with bone substitute (mp3) when the alveoli were "poorly preserved", and

only in "aesthetic" areas when sockets were "partially preserved". The grafted areas were then covered with resorbable collagen membranes (Evolution) fixed with tacks. No other sites were augmented. The wound could be left partially open if complete soft tissue closure was difficult to achieve. After 4 months, implants were placed as previously described, and the surgeon could decide whether an additional augmentation procedure was required.

For all patients in all groups, a baseline periapical radiograph of the implant was taken using the paralleling technique after implant insertion/site augmentation. If the marginal bone levels were not clearly discernible or the implant image was too distorted, a second periapical radiograph was taken. Flaps were sutured with 4-0 Vicryl (Ethicon, Johnson & Johnson, Sint-Stevens-Woluwe, Belgium). Implants in reconstructed areas were left to heal submerged, whereas implants in non-reconstructed areas could be left to heal transmucosally, at the discretion of the operator. Implants were to be left to heal unloaded for 4 months, but for implants inserted with less than 25 Ncm torque, the loading-free healing period was prolonged to 6 months.

Postoperative antibiotics were prescribed only after augmentation procedures: amoxicillin 500 mg 4 times a day for 6 days. Patients allergic to penicillin were prescribed clindamycin 300 mg twice a day for 6 days. Ibuprofen 400 mg (or paracetamol 1 g for patients allergic to non-steroidal anti-inflammatory drugs) was prescribed after all surgical interventions, but patients were instructed not to take analgesics in the absence of pain. Chlorhexidine mouthwash 0.2% for 1 minute twice a day for 2 weeks was prescribed after all surgical interventions. Patients were recalled and checked at weeks 1 and 2 and month 1 after tooth extraction and implant placement. Sutures were removed 1 week after their placement. No prosthesis compressing the implant or the augmented areas was used throughout the healing period.

Prosthetic procedures

All prosthetic procedures were identical in the three groups. Before abutment connection, a blinded outcome assessor measured the height of the vestibular keratinised mucosa in mm (to be rounded to 0.5 mm) at the study implant site using a graduated periodontal probe. If the implant was submerged, the assessor used the middle of the crest as a reference point for the measurement. When needed, implants were exposed after local anaesthesia, and if the height of keratinised mucosa was 2 mm or less, soft tissues were augmented using the roll technique³². If no keratinised mucosa was present at all, a connective tissue graft from the palate was placed³³. The stability of the implants was manually tested by tightening the abutment screw with a torque of 20 Ncm, and a healing abutment was placed. Two weeks after abutment connection, an impression with the pick-up impression copings was made using a polyether material (Impregum 3M/ESPE, Neuss, Germany) and individual resin impression trays. Provisional crowns in acrylic resin were screwed onto temporary abutments (Temporary Abutment Engaging Conical Connection, Nobel Biocare), and a periapical radiograph of the study implant was taken. If the peri-implant marginal bone levels were difficult to measure, a second radiograph was taken. At this point the operator subjectively assessed the profile of tissues vestibular to the implant-supported crown in aesthetic areas only. If he judged that profile to be deficient, he harvested a connective tissue graft from the palate and placed it into a pouch made with a horizontal incision two to three mm below the implant sulcus without releasing incisions, to increase tissue thickness and thereby improve aesthetics. Oral hygiene instructions were delivered.

Four months after initial loading, provisional crowns were removed, implants were manually tested for mobility by tightening the abutment screws with 20 Ncm torque by a blinded assessor, and definitive screw-retained metal-ceramic, metal-resin, metal-composite, zirco-

nia-stratified ceramic or monolithic zirconia single crowns were delivered on different types of abutments (Abutments Titanium, Procera Abutments Zirconia, Procera Abutments Titanium; Nobel Biocare). Occlusion was carefully checked. Periapical radiographs were taken of the study implants, and if the marginal bone levels were not readable, a second radiograph was taken. Vestibular and occlusal pictures of the study crown, including, when possible, one adjacent tooth per side, were taken for the aesthetic evaluation, and the blind assessor assessed patient satisfaction. Oral hygiene instructions were reinforced. Patients were recalled at least every 6 months for oral hygiene maintenance and prosthetic controls.

Outcome measures

Primary outcome measures were the following:

- Crown failure: cases in which it was not possible to place the crown due to implant failures or secondary to implant losses, or replacement of the definitive crown for any reason.
- Implant failure: defined as implant mobility and/or any infection dictating implant removal, or any mechanical failure rendering the implant unusable (such as implant fracture or deformation of the implant-abutment connection). The stability of each implant was measured manually by tightening the abutment screw at abutment connection and definitive crown delivery using 20-Ncm torque. At 1 and 3 years after loading, stability was tested by attempting to rock the implant using the metal handles of two metal instruments.
- Any complication or adverse event: recorded and reported by study group.

Secondary outcome measures were the following:

- Peri-implant marginal bone level changes: assessed on periapical radiographs taken using the paralleling technique at implant placement, and at 4 months and 1 and 3 years after loading. In the case of unreadable radiographs, new radiographs were taken. Non-digital radiographs were scanned in TIFF format with a 600-dpi resolution. Peri-implant marginal bone levels were measured using OsiriX (Pixmeo Sarl, Bernex, Switzerland) software. The software was calibrated for each individual image using the known height of the implant collar. Measurements of the mesial and distal bone crest levels adjacent to each implant were made to the nearest 0.01 mm. Reference points for the linear measurements were: the coronal margin of the implant collar, and the most coronal point of bone-to-implant contact. Mesial and distal measurements of each implant were averaged, and a mean was calculated for each group.
- Aesthetic evaluation of the vestibular and occlusal clinical pictures including the two adjacent teeth, taken at 4 months and 1 and 3 years after loading was performed on a computer screen. The aesthetic evaluation was carried out using the pink aesthetic score (PES)³⁴. In brief, seven variables were evaluated: mesial papilla, distal papilla, soft tissue level, soft tissue contour, alveolar process deficiencies, soft tissue colour and texture. A 0, 1, 2 scoring system was used; 0 being the lowest and 2 being the highest value, with a maximum achievable score of 14 per implant.
- Patient satisfaction: at 4 months and 1 and 3 years after loading, the blind outcome assessor provided a mirror to the patients, who were asked to express their opinions about the implant-supported crown. Specifically, the patients were asked "are you satisfied with the function of your implant-supported tooth?". Possible answers were "yes absolutely", "yes partly", "not sure", "not really", and "absolutely not". Then they were asked "are you satisfied with the aesthetic outcome of the gums surrounding this implant?". Again, possible answers were "yes absolutely", "yes partly", "not sure", "not really", and "absolutely not". Finally, patients were asked whether they would undergo the same therapy again. Possible answers were: "yes" or "no". The questions were always posed with exactly the same wording.

Implant stability and patient satisfaction were assessed by blinded outcome assessors (by Stefano Chersoni up to 4 months after loading and then by Carlo Barausse), whereas marginal bone levels and PES score were assessed by a single experienced and blinded assessor (Carlo Barausse). Complications were assessed by the treating dentist, who was therefore not blinded.

Sample size, random sequence and allocation concealment

The sample size was calculated on the primary outcome measure as the proportion of patients experiencing implant failure. A two-group continuity-corrected chi-square test with a 0.050 two-sided significance level has 80% power to detect the difference between a Group 1 proportion of 0.100 and a Group 2 proportion of 0.200 (*odds ratio* of 0.184) when the sample size in each group is 162. However, our recruitment capacity could not match the required sample size, and it was therefore decided to include 70 patients per group.

A single computer-generated restricted randomisation list was created with three groups having an equal number of patients. Only one of the investigators, not involved in the selection and treatment of the patients (Marco Esposito), was aware of the random sequence, and had access to the randomisation list, which was stored in a password-protected laptop computer. The random codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes were opened sequentially following tooth extraction, and treatment allocation was therefore concealed to the investigator in charge of enrolling and treating the patients included in the trial.

Statistical methods

All data analysis was carried out according to a pre-established analysis plan. The patient was the statistical unit of the analyses. A dentist (Jacopo Buti) with expertise in biostatistics analysed the data, without knowing group allocation. The chi-square test (or the Freeman-Halton extension of the Fisher Exact test when 20% of cells with expected count <5) was used to compare dichotomous variables (failures and complications), and the Kruskal Wallis test for continuous (bone level changes and PES) and ordinal (patient satisfaction) outcomes, with the post-hoc Dunn-Bonferroni adjustment for pairwise multiple comparisons, was applied. Comparisons between each time point and baseline measurements were made in each study group using the Wilcoxon signed-rank test, to detect any changes in marginal peri-implant bone levels. All statistical comparisons were conducted at the 0.05 level of significance.

RESULTS

Two hundred and thirty-one patients were screened for eligibility, but 17 patients did not accept the treatment for financial reasons (the implant and the surgery was offered for free, but patients were required to pay for the crown and the prosthetic components), and four patients did not want to be randomised since they were not willing to wait for long treatment periods, preferring immediate rehabilitation. Two hundred and ten patients were consecutively enrolled in the trial and randomised: 70 to the immediate, 70 to the early, and 70 to the delayed placement group. All patients were treated according to the allocated interventions. Patients were recruited and treated from January 2012 to December 2014. The follow-up focused on the time between implant placement and 3 years after loading.

Twenty-two patients dropped out (**TABLE 1**). Available data from all remaining patients were evaluated in the statistical analyses. Deviations from the operative protocol were the following.

TABLE 1 DROP-OUTS UP TO 3-YEAR POST-LOADING BY STUDY GROUP, WITH REASONS

Group	Reason	Last seen
Immediate	Moved	Provisional delivery
	Health problems	Provisional delivery
	Moved abroad	2 months after provisional delivery
	Uncontactable	1 year after loading
	Moved	1 year after loading. Contacted by phone at 3 years—reported that the crown was fine
Early	Uncontactable	Provisional delivery
	Uncontactable	Provisional delivery
	Uncontactable	Provisional delivery
	Moved abroad	Provisional delivery
	Moved	1 month after provisional delivery. Contacted by phone at 3 years—reported that the crown was fine
	Uncontactable	1 year after loading
	Uncontactable	1 year after loading
	Health problems	1 year after loading
	Moved abroad	1 ½ years after loading. Contacted by phone at 3 years—reported that the crown was fine
Delayed	Moved	1 month after implant placement
	Moved abroad	1 month after implant placement
	Moved	Provisional delivery
	Moved abroad	Provisional delivery
	Uncontactable	Provisional delivery
	Uncontactable	Provisional delivery
	Uncontactable	1 ½ years after loading
	Health problems	1 ½ years after loading. Contacted by phone at 3 years—reported that the crown was fine

Immediate group

- Fifteen patients refused the definitive crowns at four months post-loading for financial reasons. However, one patient received it after 10 months, one patient after 11 months, one after 1 year and 6 months, one after 1 year and 7 months, two after 1 year and 8 months, one after 1 year and 9 months, one after 2 years, one after 2 years and 2 months, and two after 2 years and 3 months.
- In four patients, short healing abutments were used instead of flat cover screws, since the latter were not available.
- In three patients, no sutures were given for aesthetic reasons, and the wound was closed by the provisional crown.
- One patient delayed loading by 3 months for work reasons.
- One patient, lacking keratinised mucosa, refused connective tissue harvesting from the palate because he was afraid of post-operative pain.
- For the third year of follow-up, two patients had radiographs and pictures taken with a delay of 7 months, and 1 year and 2 months, respectively, and for four patients no pictures were taken, since the camera was not available; no radiographs were taken for two further patients.

Early group

- Twelve patients refused definitive crowns at four months post-loading for financial reasons. However, one patient received it after 8 months, one after 1 year and 4 months, one after 1 year and 5 months, two after 1 year and 6 months, one after 1 year and 7 months, one after 1 year and 8 months, one after 2 years and 1 month, and one after 2 years and 3 months.
- In four patients, short healing abutments were used instead of flat cover screws, since the latter were not available.
- One patient delayed loading by 5 months because she moved abroad, and the implant was mobile when she returned.
- One patient, lacking keratinised mucosa, refused connective tissue harvesting from the palate because she was afraid of post-operative pain.
- In one patient, no sutures were given for aesthetic reasons, and the wound was closed by the provisional crown.
- For the third year of follow-up, two patients had radiographs and pictures taken with delays of 8 months, and 1 year and 9 months, respectively, and for three patients no pictures were taken since the camera was not available; no radiographs were taken for one patient.

Delayed group

- Sixteen patients refused definitive crowns at four months post-loading for financial reasons. However, one patient had theirs fitted after 10 months, one after 1 year and 2 months, one after 1 year and 5 months, two after 1 year and 6 months, one after 1 year and 8 months, one after 1 year and 9 months, one after 2 years, one after 2 years and 1 month, two after 2 years and 3 months, and one after 2 years and 4 months.
- In eight patients, short healing abutments were used instead of flat cover screws, since the latter were not available.
- Two patients, lacking keratinised mucosa, refused connective tissue harvesting from the palate because they were afraid of post-operative pain.
- One implant was placed flapless because the patient was under treatment with aspirin for a cardiological issue, and, according to the treating physician, this treatment could not be suspended.
- In one patient, no sutures were given for aesthetic reasons, and the wound was closed by the provisional crown.
- For the third year of follow-up, six patients had radiographs and pictures taken with a delay ranging from 6 months to 1 year and 9 months, and for seven patients no pictures were taken since the camera was not available.

The main baseline patient characteristics are presented in **TABLE 2**. No relevant differences between the three groups were noted at baseline, with the exception for fewer immediate (30%) than delayed implants (78.6%) in mandibles and more immediate (70%) than delayed implants (21.4%) in maxillae.

Implant failures: ten implants failed; five from the immediate group, four from the early group and one from the delayed group (**TABLE 3**). However, there were no statistically significant differences in implant failures between the three procedures (P [Freeman-Halton] = 0.282). All failed implants were successfully replaced, but data pertaining to the replaced implants were not recorded since they were outside the scope of this study.

Crown failures: apart from the crowns lost due to implant failures, no additional crowns had to be remade.

Complications (TABLE 4): a total of 33 complications affected 11 patients treated with imme-

TABLE 2 PATIENT AND INTERVENTION CHARACTERISTICS

	Immediate (n = 70)	Early (n = 70)	Delayed (n = 70)
Females	36 (51.4%)	34 (48.6%)	33 (47.1%)
Males	34 (48.6%)	36 (51.4%)	37 (52.9%)
Mean age at implant insertion ± SD (range)	55.3±11.0 (34-79)	53.5±13.4 (29-76)	55.8±11.6 (34-75)
Smoking up to 10 cigarettes/day	18 (25.7%)	20 (28.6%)	21 (30%)
Smoking more than 10 cigarettes/day	4 (5.7%)	5 (7.1%)	7 (10%)
Well preserved sites	47 (67.1%)	39 (55.7%)	41 (58.6%)
Partially preserved sites	18 (25.7%)	27 (38.6%)	24 (34.3%)
Poorly preserved sites	5 (7.1%)	4 (5.7%)	5 (7.1%)
Mean buccal bone vertical loss in mm ± SD	1.1±1.8	1.1±1.5	1.1±1.6
Implants inserted in mandibles	21 (30%)	40 (57.1%)	55 (78.6%)
Implants inserted in maxillae	49 (70%)	30 (42.9%)	15 (21.4%)
Implants inserted in incisor sites	15 (21.4%)	12 (17.1%)	4 (5.7%)
Implants inserted in canine sites	8 (11.4%)	10 (14.3%)	11 (15.7%)
Implants inserted in premolar sites	26 (37.1%)	17 (24.3%)	24 (34.3%)
Implants inserted in molar sites	21 (30%)	31 (44.3%)	31 (44.3%)
Implants with 3.5 mm diameter	31 (44.3%)	32 (45.7%)	17 (24.3%)
Implants with 4.3 mm diameter	24 (34.3%)	30 (42.9%)	36 (51.4%)
Implants with 5.0 mm diameter	15 (21.4%)	8 (11.4%)	17 (24.3%)
Implants 8.5 mm long	21 (30%)	15 (21.4%)	16 (22.9%)
Implants 10 mm long	14 (20%)	23 (32.9%)	25 (35.7%)
Implants 11.5 mm long	21 (30%)	14 (20%)	22 (31.4%)
Implants 13 mm long	14 (20%)	18 (25.7%)	7 (10%)
Mean implant length ± SD	10.6±1.7	10.8±1.7	10.4±1.4
Mean implant diameter ± SD	4.1±0.6	4.0±0.5	4.3±0.5
Horizontal gap buccal bone-implant in mm ± SD	1.2±1.3	0±0	0±0
Bone augmentation	35 (50%)	0	0
Submerged implants	65 (92.9%)	63 (90%)	57 (81.4%)
Non-submerged implants	5 (7.1%)	7 (10%)	13 (18.6%)
Complete flap closure	28 (40%)	33 (47.1%)	20 (28.6%)
No provisional during unloaded phase	21 (30%)	28 (40%)	30 (42.9%)
Adhesive prosthesis during unloaded phase	20 (28.6%)	15 (21.4%)	17 (24.3%)
Removable prosthesis during unloaded phase	16 (22.9%)	16 (22.9%)	11 (15.7%)
Tooth crown attached to adjacent teeth during unloaded phase	13 (18.6%)	11 (15.7%)	12 (17.1%)
Incomplete wound closure 1 week after extraction	42 (60%)	38 (54.3%)	50 (71.4%)
Incomplete wound closure 2 weeks after extraction	42 (60%)	38 (54.3%)	50 (71.4%)
Incomplete wound closure 1 month after extraction	41 (58.6%)	36 (51.4%)	50 (71.4%)
Mean keratinised mucosa height in mm at abutment connection ± SD	3.6±0.9	3.8±1.1	3.3±0.8*
No graft at abutment connection	69 (98.6%)	65 (92.9%)	65 (95.6%)*
Roll technique at abutment connection	0	0	0*
Connective tissue graft at abutment connection	1 (1.4%)	5 (7.1%)	3 (4.4%)*
Connective tissue graft at provisional delivery	0	0	0*
Implants initially inserted with at least 25 Ncm torque	53 (75.7%)	54 (77.1%)	59 (84.3%)
Implants initially inserted with less than 25 Ncm torque	17 (24.3%)	16 (22.9%)	11 (15.7%)
Metal-resin/composite crowns	18 (36%)	23 (46%)	20 (41.7%)*
Metal-ceramic crowns	26 (52%)	24 (48%)	25 (52.1%)*
Zirconia crowns	6 (12%)	3 (6%)	3 (6.3%)*

*68 patients, since two patients never came back for abutment connection.

TABLE 3 IMPLANT FAILURES UP TO 3 YEARS POST-LOADING IN CHRONOLOGICAL ORDER, BY STUDY GROUP, AND RELATED TREATMENT

Immediate implants			
Pat #	Time*	Implant/Tooth #; symptoms	Treatment and outcome
#203	6 m.p-i	#46; implant mobile at surgical exposure	Successfully replaced
#17	3 m.p-l	#45; 2 months after loading, slight pain on chewing, no mobility or radiographic signs, implant removed from occlusion for one month, pain still present	Successfully replaced
#98	4 m.p-l	#26; 3 months after loading, slight pain on chewing, no mobility or radiographic signs, implant removed from occlusion for one month, pain still present	Successfully replaced
#109	3 m.p-l	#24; slight pain on chewing, implant mobile	Successfully replaced
#20	19 m.p-l	#26; slight pain on chewing, crown removed and implant was mobile when counter-torqueing	Successfully replaced
Early implants			
#86	6 m.p-i	#36; implant mobile at surgical exposure	Successfully replaced
#16	9 m.p-i	#46; implant mobile at surgical exposure	Successfully replaced
#78	3 m.p-l	#22; 2 months after loading, slight pain on chewing, no mobility or radiographic signs, implant removed from occlusion for one month, pain still present	Successfully replaced
#154	3 m.p-l	#36; 2 months after loading, slight pain on chewing, no mobility or radiographic signs, implant removed from occlusion for one month, pain still present	Successfully replaced
Delayed implants			
#54	6 m.p- i	#16; implant mobile at surgical exposure	Successfully replaced

Legend m.p-i = month post-implantation; m.p-l = month post-loading; *Failure time = when the implant was actually removed.

diate, 12 with early and eight with delayed implants. There were no statistically significant differences between the three procedures in the number of patients with complications (P [chi-square test] = 0.596).

Marginal bone level changes (TABLES 5 AND 6): at implant placement there was no statistically significant difference between the three groups: bone levels were 0.02 ± 0.03 mm (CI95% 0.01; 0.03) at immediate, 0.03 ± 0.04 mm (CI95% 0.02; 0.04) at early implants, and 0.03 ± 0.04 mm (CI95% 0.02; 0.04) at delayed implants (P [Kruskal Wallis test] = 0.635; **TABLE 5**).

However, three years after loading, there was a statistically significant difference between the three groups in terms of peri-implant bone levels, which were 0.35 ± 0.23 mm (CI 95% 0.29; 0.41) at immediate, 0.46 ± 0.27 mm (CI 95% 0.39; 0.53) at early, and 0.52 ± 0.32 mm (CI 95% 0.44; 0.60) at delayed implants (P[[Kruskal Wallis test] = <0.001]; there were significant pairwise differences between immediate and early (0.11 mm; CI 95% -0.01; 0.23; P [Dunn-Bonferroni post-hoc]) = 0.0241) and immediate and delayed implants (0.18 mm; CI 95% 0.06; 0.29; P [Dunn-Bonferroni post-hoc]) = 0.0002), but no difference between early and delayed implants (0.07 mm; CI 95% -0.05; 0.19; P [Dunn-Bonferroni post-hoc]) = 0.5988) (**TABLE 5**).

Similarly, there was a statistically significant difference between the three groups in terms of bone loss, which was -0.33 ± 0.22 mm (CI 95% -0.39; -0.27) at immediate, -0.43 ± 0.26 mm (CI 95% -0.50; -0.36) at early, and -0.49 ± 0.30 (CI 95% -0.57; -0.41) at delayed implants; P (Kruskal-Wallis test) = <0.001; there were significant pairwise differences between immediate and early (0.10 mm; CI 95% -0.02; 0.22; P [Dunn-Bonferroni post-hoc] = 0.0391) and immediate and delayed implants (0.16 mm; CI 95% 0.04; 0.27; P [Dunn-Bonferroni post-hoc] = 0.0004), but no difference between early and delayed implants (0.06 mm; CI 95% -0.06; 0.18; P [Dunn-Bonferroni post-hoc] = 0.6015) (**TABLE 6**).

TABLE 4 COMPLICATIONS UP TO 3 YEARS POST-LOADING IN CHRONOLOGICAL ORDER BY STUDY GROUP AND RELATED TREATMENT

Immediate implants			
Pat #	Time	Complication	Treatment
#66	day 0	Late haemorrhage after extraction of tooth #35	1 suture + compression with gauze soaked with hemostatic
#17	2 m.p-l	Pain at 45 implant #45 when chewing; no mobility or radiographic alterations	Out of occlusion for 1 month, no resolution, implant replacement
#97	3 m.p-l	Discomfort at implant #26 when chewing; no mobility or radiographic alterations	Out of occlusion for 1 month, no resolution, implant replacement
#8	4 m.p-l	Mobility of crown #15 due to screw loosening	Retightened at 35 Ncm
#109	4 m.p-l	Pain at implant #24 when chewing; no mobility or radiographic alterations	Implant replacement
#40	12 m.p-l	Mobility of crown #13 due to screw loosening	Retightened at 35 Ncm
#20	19 m.p-l	Discomfort at implant #26 when chewing; mobile implant	Implant replacement
#131	21 m.p-l	Mobility of provisional crown #14 due to screw loosening	Retightened at 35 Ncm
#34	24 m.p-l	Chipping of provisional crown #47	Repaired chairside
#131	25 m.p-l	Fracture of provisional crown #14	Repaired chairside
#170	26 m.p-l	Fracture of provisional crown #35	Repaired in lab
#112	29 m.p-l	Mobility of crown #24 due to screw loosening	Retightened at 35 Ncm
Early implants			
#16	9 m p-i*	Discomfort and mobility at implant #46	Implant replacement
#78	2 m.p-l	Pain at implant #22 when chewing; no mobility or radiographic alterations	Out of occlusion for 1 month, no resolution, implant replacement
#154	2 m.p-l	Pain at implant #36 when chewing; no mobility or radiographic alterations	Out of occlusion for 1 month, no resolution, implant replacement
#10	3 m.p-l	Chipping of provisional crown #46	Repaired chairside
#111	3 m.p-l	Mobility of crown #47 due to screw loosening	Retightened at 35 Ncm
#37	4 m.p-l	Mobility of crown #46 due to screw loosening	Retightened at 35 Ncm
#94	18 m.p-l	Chipping of provisional crown #45	Made definitive crown
#135	25 m.p-l	Peri-implant mucositis #46	Scaling + local chlorhexidine gel twice a day for 2 weeks; complete resolution after 2 weeks; suggested maintenance every 3 months
#42	27 m.p-l	Peri-implant mucositis #17	Scaling + local chlorhexidine gel twice a day for 2 weeks; complete resolution after 2 weeks; suggested maintenance every 3 months
#183	29 m.p-l	Chipping of provisional crown #15	Repaired chairside
#209	36 m.p-l	Mobility of crown #36 due to screw loosening	Retightened at 35 Ncm
#13	36 m.p-l	5 mm of vestibular recession #12	Patient refused surgical treatment
#10	36 m.p-l	Mobility of crown #46 due to screw loosening	Retightened at 35 Ncm
Delayed implants			
#116	5 days post-op	Throbbing pain at extraction site of ankylotic #46; dry socket with minor exudate	Curettage of the socket; 0.2% chlorhexidine rinse + local chlorhexidine gel three times a day for 2 weeks; pain killer (naproxen 550 mg) twice a day for 3 days, and afterwards as required; augmentin 1g twice a day for 1 week; complete resolution after 1 week
#91	2 m.p-l	Chipping of provisional crown #46	Repaired chairside
#152	2 m.p-l	Mobility of crown #36 due to screw loosening	Retightened at 35 Ncm
#190	10 m.p-l	Mobility of crown #14 due to screw loosening	Retightened at 35 Ncm
#118	24 m.p-l	Mobility of crown #24 due to screw loosening	Retightened at 35 Ncm
#124	27 m.p-l	Mobility of crown #14 due to screw loosening	Retightened at 35 Ncm
#14	31 m.p-l	Chipping of the provisional crown #14	Repaired chairside
#189	36 m.p-l	Peri-implant mucositis #24	Scaling + local chlorhexidine gel twice a day for 2 weeks; complete resolution after 2 weeks

Legend m.p-l = month post-loading; m.p-i = month post-implantation; *patient moved abroad and come back 9 months after implantation with the implant still to be restored.

TABLE 5 MEAN RADIOGRAPHIC PERI-IMPLANT MARGINAL BONE LEVELS BETWEEN GROUPS AND TIME PERIODS UP TO 3 YEARS POST-LOADING

	Implant placement	4 months after loading	1 year after loading	3-year after loading	
	N Mean±SD (95% CI)	N Mean±SD (95% CI)	N Mean±SD (95% CI)	N Mean±SD (95% CI)	Within-group P-value
Immediate	70 0.02±0.03 (0.01; 0.03)	63 0.19±0.12 (0.16; 0.22) ^a	63 0.26±0.18 (0.22; 0.31) ^a	58 0.35±0.23 (0.29; 0.41) ^a	<0.001*
Early	70 0.03±0.04 (0.02; 0.04)	61 0.23±0.10 (0.20; 0.25) ^{ab}	61 0.31±0.14 (0.28; 0.35) ^{ab}	56 0.46±0.27 (0.39; 0.53) ^b	<0.001*
Delayed	70 0.03±0.04 (0.02; 0.04)	63 0.27±0.13 (0.24; 0.30) ^b	63 0.34±0.17 (0.30; 0.39) ^b	60 0.52±0.32 (0.44; 0.60) ^b	<0.001*
Between-Group P-value	0.635	0.001*	0.007*	<0.001*	

*Statistically significant difference; all within-group pairwise differences were statistically significant; for between-group pairwise comparisons, subsets not connected by the same letter are significantly different.

TABLE 6 MEAN RADIOGRAPHIC PERI-IMPLANT MARGINAL BONE LEVEL CHANGES BETWEEN GROUPS AND TIME PERIODS UP TO 3 YEARS POST-LOADING

	Placement – 4 months	Placement – 1 year	Placement – 3 years	
	N Mean±SD (95% CI)	N Mean±SD (95% CI)	N Mean±SD (95% CI)	Within-group P-value
Immediate	63 -0.17±0.11 (-0.20; -0.15) ^a	63 -0.25±0.17 (-0.29; -0.20) ^a	58 -0.33±0.22 (-0.39; -0.27) ^a	<0.001*
Early	61 -0.20±0.09 (-0.23; -0.18) ^{ab}	61 -0.29±0.14 (-0.32; -0.25) ^{ab}	56 -0.43±0.26 (-0.50; -0.36) ^b	<0.001*
Delayed	63 -0.24±0.12 (-0.27; -0.21) ^b	63 -0.31±0.16 (-0.35; -0.27) ^b	60 -0.49±0.30 (-0.57; -0.41) ^b	<0.001*
Between-Group P-value	0.006*	0.015*	<0.001*	

*Statistically significant difference; all within-group pairwise differences were statistically significantly different; for between-group pairwise comparisons, subsets not connected by the same letter are statistically significantly different.

All three groups had gradually lost statistically significant amounts of marginal peri-implant bone at 3 years post-loading: P (Wilcoxon signed-rank test) < 0.001 for all groups.

PES score: four months after loading (**TABLE 7**), the average total PES score, as assessed by a blind assessor, was 12.48 for immediate, 12.38 for early and 11.71 for delayed implants, the difference being statistically significant [P (Kruskal Wallis test) < 0.001]. More specifically, soft tissue levels and alveolar process deficiencies scored better at immediate and early implants than at delayed implants, with no difference in the five remaining aesthetic variables. The average total PES scores one year after loading (**TABLE 8**), as assessed by a blind assessor, was 12.52 for immediate, 12.49 for early and 11.78 for delayed implants, the difference being statistically significant [P (Kruskal Wallis test) < 0.001]. More specifically, soft tissue levels scored better at immediate implants than at delayed implants, and alveolar process deficiencies scored better at immediate and early implants than at delayed implants, with no difference for the five remaining aesthetic variables.

Three years after loading (**TABLE 9**), the average total PES score, assessed by a blind assessor, was 12.25 for the immediate, 11.98 for early and 11.17 for delayed implants, the difference being statistically significant [P (Kruskal Wallis test) < 0.001]; there were significant pairwise differences between immediate and delayed (1.08 mm; CI 95% 0.45; 1.72; P [Dunn-Bonferroni post-hoc] = 0.0006) and early and delayed implants (0.81 mm; CI 95% 0.17; 1.46; P [Dunn-Bonferroni

TABLE 7 MEAN PES SCORES AT 4-MONTHS POST-LOADING BY GROUPS AND BY DIFFERENT AESTHETIC DOMAINS; STANDARD DEVIATIONS ARE IN BRACKETS

	Mesial papilla	Distal papilla	Soft tissue level	Soft tissue contour	Alveolar process deficiencies	Soft tissue colour	Soft tissue texture	Total PES score
Immediate = 63	1.95 [0.22]	1.87 [0.34]	1.90 [0.30] ^a	1.95 [0.22]	1.71 [0.46] ^a	1.86 [0.40]	1.22 [0.46]	12.48 [0.95] ^a
Early = 61	1.95 [0.22]	1.84 [0.37]	1.92 [0.28] ^a	1.98 [0.13]	1.70 [0.46] ^a	1.87 [0.34]	1.11 [0.32]	12.38 [0.93] ^a
Delayed = 63	1.94 [0.25]	1.73 [0.45]	1.73 [0.45] ^b	1.94 [0.25]	1.49 [0.50] ^b	1.75 [0.44]	1.14 [0.35]	11.71 [1.11] ^b
Between-Group P-value	0.910	0.104	0.005*	0.422	0.014*	0.110	0.244	<0.001*

*Statistically significant difference; for between-group pairwise comparisons, subsets not connected by the same letter are statistically significantly different.

TABLE 8 MEAN PES SCORES AT 1-YEAR POST-LOADING BY GROUPS AND BY DIFFERENT AESTHETIC DOMAINS; STANDARD DEVIATIONS ARE IN BRACKETS

	Mesial papilla	Distal papilla	Soft tissue level	Soft tissue contour	Alveolar process deficiencies	Soft tissue colour	Soft tissue texture	Total PES score
Immediate = 63	1.90 [0.30]	1.84 [0.37]	1.89 [0.32] ^a	1.97 [0.18]	1.70 [0.46] ^a	1.87 [0.38]	1.35 [0.51]	12.52 [1.08] ^a
Early = 61	1.93 [0.25]	1.82 [0.39]	1.87 [0.34] ^{ab}	1.98 [0.13]	1.69 [0.47] ^a	1.90 [0.30]	1.30 [0.46]	12.49 [0.96] ^a
Delayed = 63	1.90 [0.30]	1.70 [0.46]	1.71 [0.46] ^b	1.95 [0.22]	1.43 [0.50] ^b	1.81 [0.40]	1.27 [0.45]	11.78 [1.10] ^b
Between-Group P-value	0.795	0.110	0.020*	0.616	0.002*	0.273	0.586	<0.001*

*Statistically significant difference; for between-group pairwise comparisons, subsets not connected by the same letter are statistically significantly different.

TABLE 9 MEAN PES SCORES AT 3-YEAR POST-LOADING BY GROUPS AND BY DIFFERENT AESTHETIC DOMAINS; STANDARD DEVIATIONS ARE IN BRACKETS

	Mesial papilla	Distal papilla	Soft tissue level	Soft tissue contour	Alveolar process deficiencies	Soft tissue colour	Soft tissue texture	Total PES score
Immediate = 56	1.82 [0.39]	1.66 [0.51]	1.86 [0.35] ^a	1.91 [0.29]	1.64 [0.48] ^a	1.88 [0.38]	1.48 [0.54]	12.25 [1.25] ^a
Early = 54	1.72 [0.45]	1.67 [0.48]	1.81 [0.44] ^a	1.93 [0.26]	1.65 [0.48] ^a	1.87 [0.34]	1.33 [0.48]	11.98 [1.37] ^a
Delayed = 54	1.70 [0.46]	1.57 [0.54]	1.54 [0.50] ^b	1.81 [0.39]	1.35 [0.48] ^b	1.83 [0.42]	1.35 [0.52]	11.17 [1.59] ^b
Between-Group P-value	0.309	0.586	<0.001*	0.148	0.002*	0.818	0.217	<0.001*

*Statistically significant difference; for between-group pairwise comparisons, subsets not connected by the same letter are statistically significantly different.

post-hoc]) = 0.0099), but no difference between immediate and early implants ($0.27 \pm \text{mm}$; CI 95% -0.37; 0.90; P [Dunn-Bonferroni post-hoc] = 1.0000). In other words, soft tissue levels at immediate and early implants scored better than at delayed implants, and alveolar process deficiencies scores were better for immediate and early implants than for delayed implants, there being no differences in the five remaining aesthetic variables.

Patient satisfaction: patient satisfaction was assessed at 4 months, and 1 and 3 years after loading, but only in those patients who did not experience implant failure. At 4 months and at 1 year, the vast majority of patients declared that they were fully satisfied with both the function and aesthetics of their implant-supported prostheses, and that they would undergo the same procedure again; there were, however, four exceptions (one from the immediate, one from the early and two from the delayed group), who were only partially satisfied with the aesthetics (P [Kruskal Wallis test] = 0.785).

Similarly, at three years, almost all patients declared that they were fully satisfied with both function and aesthetics, and would undergo the same procedure again. The only exceptions were one patient from the early group who was only partially satisfied with the function (P [Kruskal Wallis test] = 0.353), and 10 patients who were not fully satisfied with the aesthetics (three from the immediate, one from the early and five from the delayed group who were only partially satisfied; and one from the early group who was uncertain) (P [Kruskal Wallis test] = 0.531).

DISCUSSION

This investigation was designed to evaluate whether immediate and early implant placement 6 weeks after tooth extraction of single implants could provide similar clinical outcomes to delayed implant placement in a healed ridge, since shorter treatment periods are highly appreciated and requested by many patients. Roughly 9.2% of the immediately placed implants and 6.6% of those placed after 6 weeks failed over a 3-year post-loading period, as compared to only one (1.6%) of the delayed implants. Although we found no statistically significant difference between groups in terms of implant failures or complications, these results suggest that delayed implant placement should remain the gold standard, especially when fitting single implants. Such observations are in agreement with other, similar studies²²⁻²⁶.

Regarding bone level changes, at 3-year post-loading delayed implants had lost 0.17 mm more bone than immediate implants. While such a difference was statistically significant (P = <0.001), it is unlikely to have any clinical significance. Our results are similar to those from another RCT, also conducted by our group, where significantly more bone loss (0.06 mm) was observed at delayed implants²⁴. A similar difference (0.05 mm), though not significant, was observed in another RCT²⁵, but the opposite trend was observed when 6 to 8-mm wide implants were used as immediate post-extraction implants²⁶.

With respect to aesthetics, at 3 years post-loading immediate and early implants scored significantly better than delayed implants. In particular, only differences in soft tissue levels and alveolar process deficiencies were observed. This is in agreement with the results of another trial²², but contrasts with those reported in three other RCTs conducted by our group²⁴⁻²⁶. In particular, one trial²⁶ showed the opposite result at 1 year, i.e., better aesthetics for delayed implants. This can be explained by the fact that the immediate implants considered in that case were of wider diameter (6 to 8 mm), which may have caused more peri-implant bone resorption.

There are two plausible explanations for the present findings which could act synergistically; first, delayed sites were not subjected to any bone preservation procedures unless in "aesthetic" areas, or if severely damaged, as per typical clinical practice. It is known that site

preservation procedures are able to better preserve the site dimensions than not implementing any¹⁵. In addition, the immediate or early placement of an implant in a post-extraction site might also contribute to partial preservation of the width and height of the surrounding tissues. In order to better understand these mechanisms, however, further trials with larger sample sizes are needed.

Nevertheless, there could be some potential aesthetic advantages to deciding to place an implant immediately or a few weeks after tooth extraction. In addition, such an option greatly reduces the treatment time. Therefore, the decision on which procedure to choose remains in the hands of clinicians and patients, who have to decide between a potentially higher risk of failures and complications associated with immediate and early implants, against shorter treatment times and slightly better aesthetic outcomes.

Despite being the largest RCT ever published on implant placement timing, the main limitation of this trial remains the limited sample size. However, in future systematic reviews this limitation could hopefully be overcome by increasing the sample size by combining patients from different RCTs.

With respect to the generalisability (external validity) of these findings, it should be recognized that these procedures were tested in real clinical conditions, and that patient inclusion criteria were broad, mean that the results could be generalised to a wider population. However, it should be borne in mind that the operator who performed the immediate post-extraction procedures was highly experienced.

CONCLUSIONS

No statistically significant differences in failures, complications or patient satisfaction were observed when placing single implants immediately, 6 weeks or four months after tooth extraction. However, the absolute frequency of failures was greater at implants placed immediately and early. Nonetheless, bone loss was significantly smaller at immediate implants, and aesthetics was better at immediate and early implants.

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