Comparative clinicoradiographical evaluation of effect of aminobisphosphonate (sodium alendronate) on peri-implant bone status: Controlled clinical trial

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Abstract

**Aim:** The present study aims to compare the peri-implant bone status around immediately loaded dental implants treated with aminobisphosphonate solution and untreated control implants in terms of clinical and radiographical parameters. **Materials and Methods:** A total of 24 patients were randomly divided equally into two groups. This study was conducted in accordance to the Helsinki’s declaration of 1975, revised in 2000, and with the approval of the institutional ethical committee. In the control group after preparation, osteotomy sites were irrigated with normal saline solution, whereas in the test group osteotomy sites were irrigated with modified bisphosphonate solution and then TRX-OP, Hi-Tec dental implants were inserted. Clinical parameters, such as modified plaque and gingival index, probing depth, mobility, and radiographic parameters were recorded at baseline (0), 3, 6, and 9 months. Data analysis was performed using the Statistical Package for the Social Sciences version 17 for windows, and the statistical techniques employed were repeated measures analysis of variance, independent sample t-test, and paired sample t-test. **Results:** Reduction in mean radiographic bone levels (height) was observed on the mesial and distal aspect of the control group in comparison to its baseline at all intervals. In the test group, there was reduction in mean radiographic bone levels on mesial and distal aspect of the implant site in comparison to its baseline till 6-month follow up, however, at 9 month, there was gain in bone level on both mesial and distal aspect of implant. This represents the effectiveness of sodium alendronate in enhancing the bone formation. On comparison, between both groups on mesial and distal aspect of implants, statistically significant differences were observed at 3 and 9 months on mesial and distal aspect, respectively, without any clinical evidence of mobility in the test group. **Conclusion:** Implant site treated with aminobisphosphonate solution represents greater efficacy in enhancing bone formation when used as an irrigant; thus, it is considered beneficial in implant dentistry.

**Key words:** Aminobisphosphonate, bisphosphonates, bone resorption, immediately loaded implants, sodium alendronate

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INTRODUCTION

The success of osseointegrated implants can be jeopardized by the low dentistry and high atrophic characteristics of the alveolar bone. Thus, in recent years, there has been growing interest in pharmacological agents, such as third generation aminobisphosphonates, that might affect bone metabolism by inhibition of osteoclast recruitment, proliferation, differentiation, and function. Aminobisphosphonate investigated in clinical trials for osteoporosis has shown that the administration of 20 mg/day for 6 months induces clinically relevant changes in the lumbar spine bone density and suppresses the indices of bone turnover. Meraw et al. confirmed that alendronate bound to the surface of endosteal implants considerably increased the percentage of bone implant contact. Zuffetti et al. confirmed that bisphosphonate-treated implant showed more contact with the newly formed bone than the control implant.

The present study aims to compare peri-implant bone status around immediately-loaded dental implants treated with modified bisphosphonate solution and untreated control implants in terms of clinical and radiographical parameters.

MATERIALS AND METHODS

Out of 100 patients examined in the Out Patient Department of Periodontics, 24 patients of both sexes were included in the study according to Helsinki's declaration of 1975 as revised in 2000 and with approval of institutional ethical committee. This double blind study was conducted between November 2012 to October 2013.

Inclusion criteria

Patients, at least 18 years of age, maintaining meticulous oral hygiene and having single/two teeth missing in either arch were included. Patients with healthy periodontal status and sufficient bone quantity (i.e., sufficient bone height and width), which was assessed clinically and radiographically (Intraoral periapical (IOPA), orthopantomogram, computed tomography (CT) scan) to allow the placement of implants of desired length and diameter. In addition, the included patients had bilaterally symmetrical occlusion.

Patients having maxillomandibular space discrepancies, parafunctional habits (e.g., bruxism, clenching, etc.), adverse habits (e.g., drugs or alcohol abuse, smoking, etc.), and medically compromised conditions were excluded.

Grouping of participants

Participants were divided into a control and test group by random sampling.

- Control group: After preparation, osteotomy sites were irrigated with normal saline solution, and then implants were inserted.
- Test group: After preparation, osteotomy sites were irrigated with modified bisphosphonate solution, and then implants were inserted.

Study material

Sodium alendronate: Novel third-generation aminobisphosphonate was used as modified bisphosphonate solution, i.e., sodium alendronate (osteophos 10, brand Cipla) 20 mg dissolved in 1 ml normal saline solution. One piece TRX-OP (Hi-Tech Lifecare dental implants, Israel) with large grit-sand blasted and acid-etched threaded surface (SLA) with smooth polished collar and abutment surface were used.

Pre-surgical records

All patients were duly explained about the benefits and risks. Detailed medical and dental history with written informed consent was procured. Clinical parameters such as full mouth plaque index and gingival index were recorded on all four surfaces of teeth pre-surgically to know the oral hygiene maintenance of patients at different intervals (baseline, 3, 6, and 9 months). Pre-surgical radiographic evaluation was carried out using IOPA radiograph using the paralleling cone technique [Figure 1], orthopentalogram, and preoperative CT scan to accurately evaluate the mesiodistal and buccolingual dimensions of implant sites and illustrations from anatomical structures. All parameters were assessed by one clinician to avoid interoperative errors.

![Figure 1: Preoperative view (a) intraoral photograph #14 (b) intraoral periapical radiograph #14](image-url)
Surgical procedure

Under aseptic protocol and adequate anesthesia, mid-crestal incision was given at the implant site followed by full thickness mucoperiosteal flap elevation. Then, the osteotomy site was prepared according to manufacturer’s instructions. In the control group, the osteotomy site was irrigated with normal saline, whereas in the test group, it was treated with modified bisphosphonate solution. Then, the implants of the desired dimension were placed using a hand wrench with 40 Ncm torque. After implant insertion, suturing was done [Figure 2a-d]. Immediate postoperative radiograph was taken.

Prosthetic phase

Sutures were removed on day 8. Provisional crown was fabricated and cemented on the same day. After 6 to 8 weeks, porcelain fused to metal (PFM) definitive crowns were cemented and radiographs were taken [Figure 3].

Postoperative assessment

All selected patients were assessed for clinical parameters at the implant site such as modified plaque index (Mombelli et al; 1987), modified gingival index, peri-implant probing depth, and implant mobility index. Radiographical interpretation was done with standardized IOPA with the long cone paralleling technique and assessed using computer assisted image analysis. IOPA of all patients were scanned at 600 dpi using a Digital scanner: Medi2200 Dental X Ray Scanner by Microtek. Linear radiographic distance was analyzed and calculated by drawing a line from the first implant thread to the first bone implant contact on both aspects of the implant that helped to assess bone level at baseline, 3, 6, and 9 months for both groups using Image J analysis is a JAVA based image processing programme developed at National Institute of Health. Collected data were statistically analyzed using analysis of variance (ANOVA) and t-test using the Statistical Package for the Social Sciences (Released 2009, PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.).

RESULTS

Results were obtained from 24 implant sites. Statistical techniques employed for analysis of data obtained were repeated measures ANOVA, independent sample t-test, and paired sample t-test. No changes were made to methods after the trial commenced.

Mean modified plaque and gingival index of the implant site [Table 1] represents that the patients of both groups were maintaining good oral hygiene during the study period. Postoperative mean peri-implant probing depth at 3, 6, and 9 months for the control group was higher significant using t-test at the intervals [Table 2].

Mean bone level for control group on mesial and distal aspect [Table 3] demonstrated lower bone level at 3, 6, and 9 months from its baseline. The values when subjected to statistical analysis using the paired t-test demonstrated statistically significant reduction at 3 months on both the aspects. For the test group, the mesial aspect demonstrated lower bone level at 3 and 6 months from that at the baseline whereas higher bone level at 9 months. On comparison, between both the groups [Table 4] at mesial level, statistically significant (<0.05) reduction in the bone level was seen initially at 3 months interval from that at baseline, whereas on distal aspect statistically significant gain in alveolar bone level was seen at 9 month interval,
Table 1: Comparison of modified plaque and gingival index at the implant site between the control group and test group

| Assessment time | Group          | Modified plaque index | Modified gingival index |
|-----------------|----------------|-----------------------|-------------------------|
|                 |                | Mean±SD | t   | P   | Mean±SD | t   | P   |
| Baseline        | Control group  | 0.00±0.00 | 0   | >0.05 NS | 0.00±0.00 | 0   | >0.05 NS |
|                 | Test group     | 0.00±0.00 | 0   | >0.05 NS | 0.00±0.00 | 0   | >0.05 NS |
| Baseline-3 months | Control group | 0.65±0.14 | 0.29 | >0.05 NS | 0.70±0.20 | 1.09 | >0.05 NS |
|                 | Test group     | 0.68±0.14 | 0.29 | >0.05 NS | 0.60±0.12 | 0.27 | >0.05 NS |
| Baseline-6 months | Control group | 0.65±0.22 | 0.50 | >0.05 NS | 0.63±0.12 | 0.27 | >0.05 NS |
|                 | Test group     | 0.60±0.13 | 0.41 | >0.05 NS | 0.61±0.13 | 0.41 | >0.05 NS |
| Baseline-9 months | Control group | 0.70±0.21 | 1.67 | >0.05 NS | 0.65±0.22 | 0.41 | >0.05 NS |
|                 | Test group     | 0.57±0.01 | 0.60±0.20 | >0.05 NS |

P>0.05 not significant

Table 2: Probing depth at the implant site in the control group and test group

| Assessment time | Group          | Mean±SD | Mean difference from previous | t   | P   |
|-----------------|----------------|---------|-------------------------------|-----|-----|
| 3 months        | Control group  | 3.45±0.33 | 3.06 | <0.05* |
|                 | Test group     | 2.89±0.30 | 1.96 | <0.05* |
| 6 months        | Control group  | 3.45±0.27 | 0.00±0.47 | 1.09 | <0.05 NS |
|                 | Test group     | 3.18±0.21 | −0.29±0.29 | 2.15 | <0.05 NS |
| 9 months        | Control group  | 3.35±0.29 | 0.10±0.45 | 2.15 | <0.05 NS |
|                 | Test group     | 3.00±0.27 | 0.18±0.34 | 2.15 | <0.05 NS |

*P<0.05 significant

Table 3: Radiographic bone level on the mesial and distal aspect of implant in the control group and test group at different intervals

| Group          | Assessment time | Mesial | Distal |
|----------------|-----------------|--------|--------|
|                | Mean±SD | Mean difference from baseline | Paired t | P   | Mean±SD | Mean difference from baseline | Paired t | P   |
| Control group  | Baseline | 0.39±1.14 | 0.13±0.98 | 0.17 | >0.05 NS | 0.55±0.71 | 0.95±0.61 | 0.91±0.71 | 3.47 | <0.05* |
|                | 3 months  | −2.44±1.74 | 2.82±0.88 | 3.05 | <0.05* | −1.41±1.35 | 1.54±0.86 | 2.66 | <0.05* |
|                | 6 months  | −0.23±0.83 | 0.62±0.64 | 0.98 | >0.05 NS | −0.70±1.25 | 0.83±0.72 | 1.17 | >0.05 NS |
|                | 9 months  | 0.04±0.50 | 0.35±0.87 | 0.61 | >0.05 NS | −0.42±0.63 | 0.55±0.71 | 1.06 | >0.05 NS |
| Test group     | Baseline | 0.30±0.71 | 0.04±0.33 | 0.97±0.99 | 1.62 | <0.05* | −0.91±0.71 | 3.47 | <0.05* |
|                | 3 months  | −0.46±0.68 | 0.76±1.04 | 1.69 | >0.05 NS | −1.17±1.17 | 1.20±1.30 | 2.63 | <0.05* |
|                | 6 months  | −0.73±1.87 | 1.03±1.80 | 1.55 | >0.05 NS | −1.11±1.33 | 1.15±1.20 | 2.22 | <0.05* |
|                | 9 months  | 1.27±0.87 | −0.97±0.99 | 1.62 | <0.05* | 0.95±0.61 | −0.91±0.71 | 3.47 | <0.05* |

*P<0.05 significant

Table 4: Comparison of radiographic bone level between the control group and test group at the mesial and distal aspect of implants

| Assessment time | Group          | Mesial | Distal |
|-----------------|----------------|--------|--------|
|                 | Mean±SD | t   | P   | Mean±SD | t   | P   |
| Baseline        | Control group  | 0.39±1.14 | 0.17 | >0.05 NS | 0.13±0.98 | 0.23 | >0.05 NS |
|                 | Test group     | 0.30±0.71 | 0.04±0.33 | 0.97±0.99 | 1.62 | <0.05* | −0.91±0.71 | 3.47 | <0.05* |
| Baseline-3 months | Control group | −2.44±1.74 | 2.77 | <0.05* | −1.41±1.35 | 0.33 | >0.05 NS |
|                 | Test group     | −0.46±0.68 | 2.82±0.88 | 3.05 | <0.05* | −1.17±1.17 | 1.54±0.86 | 2.66 | <0.05* |
| Baseline-6 months | Control group | −0.23±0.83 | 0.62±0.64 | 0.98 | >0.05 NS | −0.70±1.25 | 0.83±0.72 | 1.17 | >0.05 NS |
|                 | Test group     | −0.73±1.87 | 1.03±1.80 | 1.55 | >0.05 NS | −1.11±1.33 | 1.15±1.20 | 2.22 | <0.05* |
| Baseline-9 months | Control group | 0.04±0.50 | 1.68 | >0.05 NS | −0.42±0.63 | 3.79 | <0.05* | −0.91±0.71 | 3.47 | <0.05* |
|                 | Test group     | 1.27±0.87 | 0.95±0.61 | −0.97±0.99 | 1.62 | <0.05* |

*, Significant (P<0.05); NS=Not significant (P>0.05)
with the test group showing better results than the control group.

Furthermore, statistical analysis using paired t-test demonstrated significant gain at 9 months for the test group. On the distal aspect, significant reduction in bone level was demonstrated at 3 and 6 months from its baseline whereas significant gain was demonstrated at 9 months from its baseline.

DISCUSSION

To best of our knowledge, this is the first study aiming to clinicoradiographically compare peri-implant bone status around immediately-loaded dental implants treated with modified bisphosphonate solution and untreated control implants.

Distance from the first implant thread to the first bone-implant contact was measured on both aspects of all the implants. There was reduction in radiographic bone levels on both aspects of the control group in comparison to its baseline at all the intervals, whereas in the test group, reduction was observed till 6-month follow-up but gain at 9 months. On comparison between both groups, significant difference (<0.05) in the radiographic bone levels on mesial and distal aspect of implants were observed only at 3 and 9 months, respectively, which represents the effectiveness of sodium alendronate in enhancing the bone formation. These results were in accordance with the results by Veena and Prasad,[10] Oh et al.,[11] and Zuffeti et al. It was evident from the mean values that modified plaque and gingival index at the implant sites of both groups showed no significant difference at different intervals indicating that patients of both groups were capable of maintaining good oral hygiene, as seen in earlier studies by Abboud et al.[12] and Luongo et al.[13]

Mean peri-implant probing depth at all intervals was significantly higher in the control group as compared to the test group. Similar trend toward decreased pocket depth after treatment with alendronate was observed in a study by Rocha et al.[14] Sharma et al.[15] showed that a local delivery of 1% alendronate in treatment of chronic periodontitis stimulated significant increase in pocket depth reduction, clinical attachment level gain, and bone fill compared to the placebo gel.

In the original protocol, studies have advocated a two-stage surgical protocol for load-free and submerged healing to ensure predictable osseointegration. However, discomfort, inconvenience, and anxiety associated with the waiting period remains a challenge to both the patient and clinician. Therefore, immediate loading of implant was attempted which gained popularity among clinicians.[16–20]

Bisphosphonates are widely utilized in the management of systemic metabolic bone disease because of their ability to inhibit bone resorption. Several modes of action have been investigated including bisphosphonate-mediated inhibition of development of osteoclasts, induction of osteoclastic apoptosis, reduction of activity, prevention of the development of osteoclasts from hematopoietic precursors, and stimulation of production of osteoclast inhibitory factor.[21]

Given their known affinity to bone and their ability to increase osteoblastic differentiation and inhibit osteoclast recruitment and activity, there exists possible use of bisphosphonates in the diagnosis and management of periodontal diseases, thereby providing interesting management strategy to stimulate osteogenesis in conjunction with regenerative materials around osseous defects and promotion of bone formation around endosseous implants.

Limirio et al.[22] investigated the local effect of 10% doxycycline and 1% alendronate combined with poly (lactic-co-glycolic acid) (PLGA) on bone repair by quantifying bone density and resulted association of 10% doxycycline and 1% alendronate with PLGA-accelerated bone repair with significant increase in bone neoformation. Moon et al.[23] studied the effect of heparin and alendronate coating on titanium surfaces on inhibition of osteoclast and enhancement of osteoblast function, and suggested that alendronate-immobilized titanium enhances activation of osteoblast differentiation and inhibits osteoclast differentiation. Stress around implant should be consider in its success; it has been observed that stress was around cervical portion in implant supported model, whereas it will be at surrounding bone of root in tooth supported model.[24]

The present study has a limitation of short follow-up without histomorphometric analysis to establish any claim regarding the effectiveness of sodium alendronate in immediately-loaded implants. In addition, the study included a small sample size due to which the generalizability of the study is questionable. Thus, further studies with larger sample size should be conducted and the effect of aminobisphosphonates on peri-implant bone status should be established.
Within the limitations of the study, the present clinical trial offers encouraging and promising evidence to evaluate the possible applications of bisphosphonates in implant dentistry. It opens new vistas for future research, however, further longitudinal and histological studies on larger sample size are still required, which may find indications based on surgical, host, implant, and occlusal conditions for the clinical implications of alendronate in the long-term success of dental implants. Additional data will provide clinicians and researchers improved foundations for decision making relative to selecting the most appropriate implant treatment protocol.

CONCLUSION

The present study showed that implant sites treated with aminobisphosphonate solution had significantly improved peri-implant bone status around immediately-loaded dental implants, thereby providing evidence that aminobisphosphonate solution can be an effective irrigant in enhancing the bone formation.

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Conflicts of interest

There are no conflicts of interest.

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