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Effect of systemic administration of omeprazole on osseointegration around titanium dental implants: A histomorphometric study in dogs

Negar Kanounisabet[1], Ahmad Mogharehabed[2], Nakisa Torabinia[3], Seyedeh Marzieh Hashemi Nejad[4], Jaber Yaghini[2]

[1]Department of Periodontology, School of Dentistry, Tehran University of Medical Sciences, Tehran, [2]Department of Periodontology, Dental Implant Research Center, Dental Research Institute, Isfahan University of Medical Sciences, [3]Department of Oral Pathology, Dental Materials Research Center, Dental Research Institute, Isfahan University of Medical Sciences, [4]Department of Periodontology, Dental Research Center, Dental Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

Background: Dental implants are widely accepted substitutes for replacing missing teeth. Many factors, including the use of specific drugs such as proton-pump inhibitors (PPIs) (omeprazole), can affect the success of dental implantations. The aim of this study was to investigate the relationship between the use of omeprazole and osseointegration of dental implants.

Materials and Methods: This experimental animal study was performed on eight native male dogs weighted 11–13 kg and aged 16–20 months. The dogs were divided into two groups (receivers and nonreceivers of omeprazole). After extraction of mandibular teeth, treatment was started randomly with the administration of omeprazole and saline. After a 2-month recovery period, six titanium implants were placed in the jaws of all dogs and the administration of omeprazole was continued for 2 weeks. After 4 and 12 weeks, the dogs were anesthetized and dental implants with their bone marrow were removed. The samples were examined histomorphometrically to determine osseointegration. Data were analyzed with two-way ANOVA test for 95% confidence interval. The P value was set at 0.05.

Results: In the microscopic examination of the samples in week 4, the levels of bone–implant contact (BIC) in the study group were significantly lower than the control group (46.37 vs. 64.37%). In 12 weeks, BIC was significantly lower than that of the control group (67.33 vs. 82.00%). The type of bone formed in week 4 in both the groups was more woven, and in the 12th week, it was mostly lamellar.

Conclusion: Systemic administration of PPIs may interfere with osseointegration of dental implants.

Key Words: Bone–implant interface, dental implants, omeprazole, proton-pump inhibitors

INTRODUCTION

Dental implant is an accepted method for treatment of patients with partial or complete edentulism.[1] Osseointegration of implants is known as the final goal of implant surgery and one of the factors for long-term implant success.[2]

Several factors can enhance or inhibit the osseointegration process.[3,4] Factors that enhance osseointegration include implant design and chemical composition, topography of the implant surface, material, shape, and diameter of implant, the status

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of the host bone and its intrinsic healing potential, the mechanical stability and loading conditions,[3] the use of adjuvant treatments such as bone grafting,[5] and pharmacological agents such as simvastatin[6] and bisphosphonates.[7]

Factors that lead to inhibition of osseointegration include excessive implant mobility and inappropriate porosity of implant surface,[4] radiation therapy,[8] pharmacological agents such as cyclosporine A and methotrexate, warfarin and low-molecular-weight heparins, nonsteroidal anti-inflammatory drugs (NSAIDs), proton-pump inhibitors (PPIs),[3,9] and patients' related factors such as osteoporosis, rheumatoid arthritis, old age, nutritional deficiency, smoking, and renal insufficiency.[10]

Systemic drugs are commonly used by patients including those who are going to undergo implant treatment. However, the effect of drugs on implant treatment is a topic that is usually not addressed in studies. Some commonly prescribed drugs, namely statins, glucocorticoids, PPIs, and NSAIDs, affect the process of bone formation and healing, which may also affect bone healing around the implant.[11]

PPIs, including omeprazole, lansoprazole, and pantoprazole that are commonly used to treat gastric acid disorders such as gastroesophageal reflux disease and gastric ulcers, act by inhibition of acid secretion in the stomach.[12] The effects of these drugs on bone metabolism and osseointegration process have been shown in numerous studies on humans and animals. There is an increased likelihood of failure of implant therapy in patients taking such drugs.[13] On the other hand, PPIs have been associated with an increased risk of bone fractures.[14]

Various reasons can explain the association between PPI intake and the increased risk of dental implant failure. PPIs are irreversibly bound to the H^+-ATPase of the vacuolar osteoclasts and thereby directly alter bone metabolism through vacuolar H^+-ATPase in osteoclasts.[2,9] PPIs also reduce the intestinal absorption of calcium and decrease bone mineral density through hypochlorhydria.[15-17] The long-term use of PPIs is associated with a reduction in the absorption of Vitamin B12, followed by increased homocysteine concentration that interferes with collagen cross-linking and weakens bone (osteoporosis).[17]

In spite of the fact that the negative effects of PPIs on skeletons have been investigated and proven in different studies,[15-17] the effects of these drugs on bone-related clinical conditions, such as dental osseointegration of implants, have rarely been investigated.[12] Many candidates for dental implant, as well as clinicians, use and prescribe PPIs without knowing the potential effects of the drug on the outcome of the treatment.

No systematic study has ever been performed to investigate the effect of PPIs administered before and after implant placement on healing and osseointegration of dental implants from histomorphometric viewpoints. Therefore, the present study was an attempt to evaluate the effect of systemic administration of omeprazole on osseointegration around dental implants through histomorphometry in dog jaw.

MATERIALS AND METHODS

The present study was an experimental study performed on dogs. Eight mongrel dogs were used in this study. The dogs were similar in age, sex, and weight. In this study, eight adult dogs were used. The mean age of the dogs was 17.2 ± 1.29 months and their mean weight was 11.91 ± 0.83 kg.

The inclusion criteria were systemic health and the absence of any systemic diseases, and the exclusion criterion was the risk of having a dog's life at stake during the study. The project (code 396280) was approved in the implant research center of Isfahan University of Medical Sciences with ID number of IR: MUI.REC.1396.3.280. All procedures were in accordance with the ethical standards from the last update of the Helsinki Declaration.[18]

First, the necessary examinations were performed to confirm the dogs' healthy status and make sure that they did not suffer from diseases such as rabies. The dogs were vaccinated (including Biocan, polyvalent $DHPP_iL$, and antifungals) 2 weeks before the onset of the experiments according to the standard protocol.[19] The animals were kept in separate cages for 10 days in order to help them get used to their new life in confinement. They were washed on a weekly basis, and the shed near the animal operation room of the research center at the Dentistry Faculty of Isfahan University of Medical Sciences that was used as a place to keep the dogs was washed and disinfected regularly. The shed was equipped with ventilation and sewage facilities. The animals' health was checked out by a veterinarian every day, and in case the animals' lives were at risk, they were excluded from the study to receive appropriate treatment.

Surgical protocol, Stage 1

The surgical parts of this study were performed by one surgeon who was blinded to group allocation, using similar instruments and technique.

In the first surgery, the dogs were sedated and then anesthetized. Acepromazine 1% (0.2 cc/kg), ketamine 10% (10 mg/kg), and atropine (0.04 mg/kg) were used for anesthesia, and halothane was administered to keep the animals in anesthetized state. Then, a two-sided full-thickness flap was elevated under the mandibular premolar region (from the first to the fourth premolar). Next, the second, third, and fourth premolar teeth of each quadrant were sectioned buccolingually and furcally [Figure 1a]. The roots were extracted using periotome (the periotome is used to sever the periodontal ligament [PDL] from the root surface of the tooth). The tooth was then extracted without thrusting the extraction forceps deep into the PDL space, preventing damage to the alveolar bone)[20] [Figure 1b]. Finally, the flap was repositioned and sutured with 4-0 nonabsorbable sutures [Figure 1c]. The dogs were randomly divided into two groups: saline-receiving group (control) and omeprazole-receiving group (experimental). Administration of omeprazole was started for all the four dogs in the experimental group (20 mg bid per dog) and saline was prescribed for all the four dogs in the control group until the Stage 2 surgery. After a 2-month recovery period, ceftriaxone (2 g per dog) was systemically administered 1 h before surgery in order to provide the ground for the second stage of surgery and placement of implants.

Surgical protocol, Stage 2

In the second stage of surgery, after sedation and maintaining anesthesia, a horizontal crestal incision was made at the mandibular premolar region of each animal and three identical bone-level implants with 4.3 mm diameter and 10 mm length (SNU, Korea) were placed [Figure 2a-c]. Hence, a total of 48 implants were placed in the mouth of all the dogs. The

flaps were sutured with nonabsorbable sutures, and the implants were submerged [Figure 2d]. Ceftriaxone was administered systemically 1 g per day for 5 days. The animals were subjected to a soft diet for 14 days, and then, the sutures were pulled out. Administration of omeprazole was continued for 2 weeks in terms of effectiveness against the gastrointestinal (GI) side effects of NSAIDs.[21] The gingival healing was periodically evaluated by dichotomous score using the following parameters: edema, hematoma, suppuration, flap dehiscence, and patient complaints.[22]

The remaining teeth were cleaned with ultrasound at the time of implant placement, and after that, we cleaned the remaining teeth with gauze soaked in chlorhexidine daily until gingival healing was completed. The teeth were cleaned with toothbrush once a day during the study.

Sample preparation and statistical analysis

Half of the animals in each group (two dogs from the control group and two dogs from the experimental group) were sacrificed 4 weeks postoperatively and the other half 12 weeks postoperatively by anesthetic drug overdose.

According to studies by Berglundh *et al.*[23] and Abrahamsson *et al.*[24] that examined the bone formation and osseointegration of implants placed in the dog's mandible, most of the implant surfaces were covered with woven bone within 4 weeks and the highest osseointegration activity has been reported in the 2- to 6-week period (4-week average). During the 12th week, the woven bone is replaced by lamellar bone and bone marrow. Therefore, by choosing these two periods, we can examine the effects of omeprazole during the modeling and remodeling period.

All implants and their surrounding bones were removed with a trephine drill (size: 10 mm). The samples were immediately stored in a 10% formalin solution and then mounted in acrylic blocks. Hard tissue section tools (CNC cutting
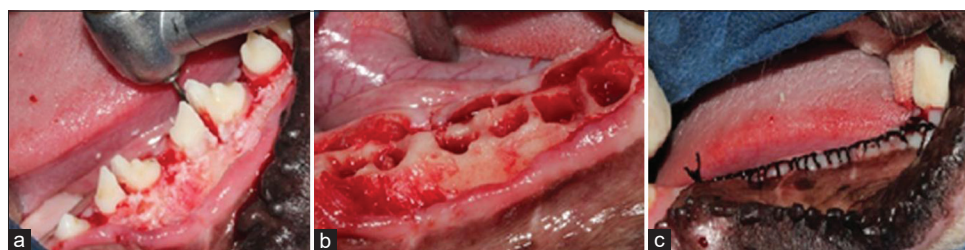

Figure 1: The second, third, and fourth premolar teeth of each quadrant were sectioned buccolingually (a), tooth sockets with intact walls (b), the flap sutured with 4-0 nonabsorbable sutures (c).

machine, Iran) were used for longitudinal section with a diameter of 50 μ. The samples were mounted on a Lam and painted by H and E staining. The samples were then examined at ×40 magnification by an optical microscope (Olympus CX21FS, Olympus Corporation, Tokyo, Japan) [Figure 3]. The bone–implant contact (BIC) of samples was histomorphometrically analyzed using the Nilu pathology image analyzer (version 1.0, Iran) and graded lens.

Two-way ANOVA with 95% confidence interval was used to compare the data. The Smirnov–Kolmogorov test was used to assess the normal distribution of data. The results of this test indicated that the distribution of all data was normal in both the groups and time intervals ($P < 0.05$). The methodology of this research was review by an independent statistician.

RESULTS

Table 1 shows the mean and standard deviation of BIC at 4 weeks postoperatively.

Table 2 shows the mean and standard deviation of BIC at 12 weeks for different intercepts.

The two-way ANOVA test was used to determine the effect of treatment types and the effect of postintervention time interval on BIC [Table 3].

According to the treatment modalities, the average BIC was significantly lower in the experimental (46.37% ± 5.57%) than in the control group at week 4 (64.37% ± 9.60%) ($P < 0.001$). Furthermore, based on postoperative time interval, the average BIC was significantly lower in the experimental group (67.33 ± 9.84) than the control group at week 12 (82% ± 8.01%) ($P < 0.001$) although the bilateral effect of treatment type and postoperative elapsed time was not significant ($P = 0.490$).

Figure 4 shows the BIC variation in groups.

According to histological evaluation, the newly formed bone was mostly of woven type in all samples and groups at 4 weeks and the newly formed bone was mostly of lamellar type in all samples and groups at 12 weeks.

DISCUSSION

Our results showed that systemic administration of omeprazole could have a negative effect on the osseointegration of dental implants. According to the investigations carried out in the present study, BIC was 46.37 at 4 weeks in the omeprazole group, which was significantly lower than that of the control group (64.37%). In addition, the mean BIC in the experimental group was 67.33% at week 12, which was significantly lower than that in the control group (82%) [Tables 1 and 2]. Meanwhile, the effects of time interval on BIC were statistically significant in both the groups [Table 3]. In other words, the mean BIC percentage in both the groups was significantly higher at the 12-week period as compared with the 4-week period.
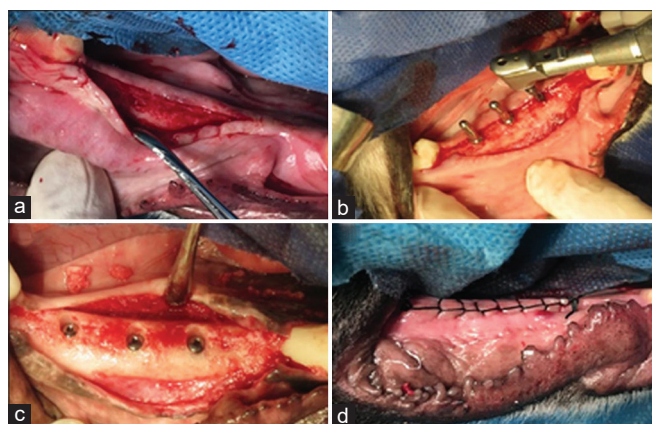

Figure 2: Horizontal crestal incision made at the mandibular premolar region (a), three bone-level implants with 4.3 mm diameter and 10 mm length were placed (b and c), the flap sutured with 4-0 nonabsorbable sutures (d).
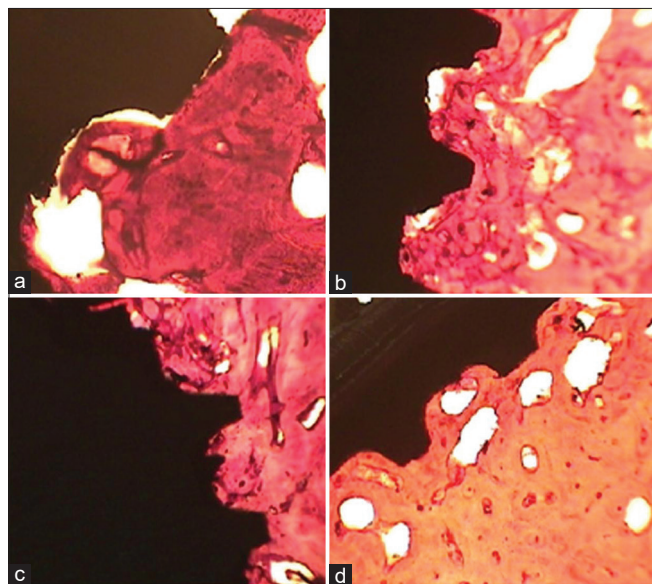

Figure 3: Samples were then examined at ×40 magnification by an optical microscope. Experimental group at 4 weeks (a), control group at 4 weeks (b), experimental group at 12 weeks (c), control group at 12 weeks (d).

Table 1: Mean and standard deviation of bone-implant contact at 4 weeks postoperatively

Group	Number of dogs	Number of implants	Minimum (%)*	Maximum (%)†	Mean‡ (%)±SD
Experimental	2	12	40	55	46.37±5.57
Control	2	12	45	80	64.37±9.60

*Minimum of BIC, †Maximum of BIC, ‡Average of BIC. BIC: Bone-implant contact. SD: Standard deviation

Table 2: Mean and standard deviation of bone-implant contact at 12 weeks for two groups (%)

Group	Number of dogs	Number of implants	Minimum (%)*	Maximum (%)†	Mean‡ (%)±SD
Experimental	2	12	50	85	67.33±9.84
Control	2	12	65	95	82±8.01

*Minimum of BIC, †Maximum of BIC, ‡Average of BIC. BIC: Bone-implant contact. SD: Standard deviation

Table 3: Two-way ANOVA test results/effect of treatment types and postintervention time interval on bone-implant contact

Factor/variable	P
Treatment type	<0.001
Time interval	<0.001
Treatment type* time interval	0.490

According to histological evaluation, the newly formed bone was mostly of woven type in all samples and groups at 4 weeks but changed to lamellar type in all samples and groups at 12 weeks. This finding is consistent with Berglundhe *et al.*'s histological findings in dogs. In that study of osseointegration, the newly formed bone was mostly of woven type at 4 weeks and mostly of lamellar type at 12 weeks.[25]

In a study by Al Subai *et al.* in 2016,[26] 2-week administration of omeprazole to rats was associated with failure of bone healing and osseointegration of implants. Their study was conducted on calvaria of 24 rats, while our study was conducted on dogs' alveolar bone, which is similar to humans and provides a more remarkable reconstruction of its effects on human jawbones.

The results of the present study and the one conducted by Al Subai *et al.*[26] were consistent with the results of two retrospective cohort studies.[9,12]

In the study of Chrcavonic,[9] 3559 implants were evaluated in 999 patients, of which 178 implants were failed. The patients were divided into PPI receiver and non-PPI receiver groups. Implantation failure was 12% in the PPI group and 4.5% in the non-PPI group. These findings showed that PPI administration had a significant effect on the implantation survival rate. They concluded that administration of PPIs could be associated with a high risk of implant failure.

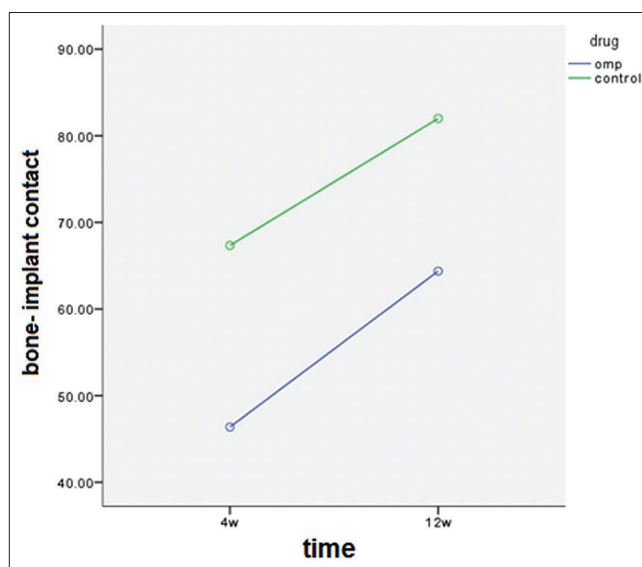In a retrospective study conducted by Wu *et al.* in 1993,[12] implants were evaluated in 799 patients. The

Figure 4: Bone–implant contact variations in groups.

patients were divided into PPI receiver and non-PPI receiver groups. Implantation failure was 6.8% in the PPI group and 3.2% in the non-PPI group. The patients in the PPI group had a higher risk of implant failure. The findings of this study indicate that treatment with PPIs can be associated with an increased risk of osseointegrated dental implant failure.

Various reasons can explain the relationship between PPI administration and the increased risk of dental implant failure. Osseointegration of implants involves three stages: homeostasis, bone formation, and remodeling.[27] PPIs affect bone formation through reduction of bone markers, such as BMP-2, BMP-4, and cysteine-rich protein, which reduces the transverse growth of endosteum, increases the width of osteoid, and decreases the amount of bone mineral content, leading to inhibition of bone formation and failure of mineralization.[28]

On the other hand, the effect of PPIs on bone remodeling can be explained through the study of

osteoclasts. Osteoclasts, the cells responsible for bone resorption, contain proton pumps that can be inhibited by PPIs.[29] Therefore, PPIs can prevent bone remodeling by inhibiting osteoclastic activity.[15]

Furthermore, these drugs can interfere with mineralization of osteoblastic matrix through inhibition of phosphoethanolamine/phosphocholine phosphatase[30] and have a direct negative effect on bone cells and reduce bone turnover.[31]

Osteoclasts and osteoblasts work closely together in the bone remodeling process. Bone remodeling is a very important process in osseointegration. Therefore, the effect of PPIs on bone remodeling can interfere with osseointegration of dental implants.[27]

Other factors that can account for the negative effects of PPIs on osseointegration are the formation of hypochlorhydria with the administration of PPIs and decreased intestinal absorption of calcium, which leads to a decrease in bone mineral density.[32-34] Administration of PPIs is also associated with hypogastrinemia, which could lead to parathyroid hyperplasia, increased parathormone secretion, and reduction of bone density.[34]

PPIs are considered the first choice and most commonly prescribed drug for treating peptic ulcers, dyspepsia, *Helicobacter pylori* infections, eosinophilic esophagitis, gastrinomas, and stress gastritis[35] and are routinely prescribed along NSAIDs to avoid adverse GI effects of these drugs for receivers of dental implants.[36] Considering the proven effects of PPIs on bone metabolism, it is clinically logical to pay a special attention to the treatment of dental implant candidates who are subjected to treatments using the aforementioned drugs and the prescription of PPIs following bone surgeries and implant placement should be re-evaluated.

This study and other similar studies[9,12] conducted on humans and animals clearly show the role of PPIs in bone formation and bone remodeling stages. On the other hand, as osseointegration of dental implants involves three phases (homeostasis, bone formation, and bone remodeling), the effect of this class of drugs on two stages of this process has been confirmed and the success of the implantation is dependent on complete conduction of osseointegration process without any defects. Therefore, the use of these drugs could be associated with an increased risk of dental implant failure.

One of the limitations of this study was the selection of the minimum number of samples due to ethical considerations.

The present study is the first study conducted in a prospective manner in order to investigate the association of PPIs with osseointegration in dog jaw as an animal model comparable to humans. Therefore, the possibility of generalizing the results of the study to human groups can be considered. However, future clinical studies will have to be performed to validate these outcomes on humans.

CONCLUSION

The results of this study showed that systemic administration of omeprazole could have a negative effect on BIC and therefore might interfere with osseointegration of dental implants. The results of this study can reduce the unwanted effects of this class of drugs on the implant treatment results by limiting the prescription and arbitrary use of PPIs.

Conflicts of interest
The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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