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Evaluation of the Locally and Single Dose Teriparatide Effect on Masseter Muscle Thickness and Early Mandibular Bone Healing

Lokal ve Tek Doz Uygulanan Teriparatidin Masseter Kası Genişliği ve Erken Dönem Mandibular Kemik İyileşmesi Üzerine Olan Etkisinin Değerlendirilmesi

Cansu Gül Koca[1*], Meryem Kosehasanogullari[2], Bengisu Yıldırım[3], Ilhan Kaya[1], Esra Yüce[4], Muhammet Fatih Çiçek[1]

[1]Uşak Üniversitesi Diş Hekimliği Fakültesi Ağız, Diş ve Çene Cerrahisi Anabilim Dalı
[2]Uşak Eğitim Araştırma Hastanesi Fizik Tedavi ve Rehabilitasyonu Kliniği
[3]Uşak Üniversitesi Diş Hekimliği Fakültesi Protetik Diş Tedavisi Anabilim Dalı
[4]Istanbul Aydın Üniversitesi Diş Hekimliği Fakültesi Ağız, Diş ve Çene Cerrahisi Anabilim Dalı

ABSTRACT

Objective: Bone repair is a multifactorial mechanism involving a large number of cells, molecules and growth factors. In this healing period, muscle tissue has an important role. The aim of the study was to evaluate the effect of single dose and locally administered teriparatide on mandibular bone healing and masseter muscle thickness.

Materials and Methods: In this study, 24 Sprague-Dawley male rats were used and the experimental animals were divided into 3 groups. Groups were defined in the following way: Group-1 had empty defect, Group-2 received 20 µg of TP, and Group-3 received 40 µg of TP. Before surgery and postoperative 4th week, masseter muscle thickness was measured with the same ultrasound imaging system. This was followed by histomorphometric evaluation that was performed for the measurement of mandibular bone healing.

Results: A statistically significant difference had been found in terms of the amount of bone ossification area between Group-1 and Group-2 and between Group-1 and Group-3 ($p<0.01$), but there was no statistically significant difference between Group-2 and Group-3 ($p>0.01$). Increase in the masseter muscle thickness in the postoperative period was statistically significant in all groups ($p<0.05$). On the other hand, increasing in the masseter muscles thickness was higher in Group-2 and Group-3 than Group-1 but not statistically significant ($p>0.05$).

Conclusion: As a result of this study, locally and single dose administered TP improved bone healing postoperative 4th week. On the other hand, TP did not have a significant effect on the increase of masseter muscle thickness.

Key Words: Bone healing, masseter muscle, teriparatide ultrasound

ÖZET

Amaç: Kemik iyileşmesi pek çok hücre, molekül ve büyüme faktörünün katıldığı kompleks bir olaydır. İyileşme periyodunda kas dokusu önemli bir yere sahiptir. Bu çalışmada, lokal ve tek doz uygulanan teriparatidin, mandibular defekt iyileşmesi ve masseter kas kalınlığı üzerine olan etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Cerrahi işlem öncesi kas kalınlığı ultrasonik görüntüleme tekniği ile ölçülmüştür. Mandibular defekt tam kalınlık ve 3 mm çapında olacak şekilde oluşturulmuştur. Sıçanlar her grupta 8 adet olacak şekilde negatif kontrol grubu (Grup 1), 20 µg teriparatid kullanılan grup (Grup 2) ve 40 µg teriparatid kullanılan grup (Grup 3) olmak üzere rastgele 3 gruba ayrılmıştır. Masseter kası ultrason ölçümleri aynı teknik kullanılarak 4 hafta sonra sakrifikasyondan hemen önce tekrarlanmıştır. Mandibular kemik iyileşmesi bütün gruplarda histomorfometrik teknik kullanılarak değerlendirilmiştir.

Bulgular: Kemik iyileşmesi açısından Grup 1 ile Grup 2 ve Grup 1 ile Grup 3 arasında istatistiksel olarak anlamlı farklılık olduğu görülmüştür ($p<0.01$). Bununla birlikte defekt alanında oluşan yeni kemik miktarı açısından, Grup 2 ile Grup 3 arasında istatistiksel olarak anlamlı farklılık görülmemiştir ($p>0.01$). Masseter kası kalınlığındaki artış bütün gruplarda istatistiksel olarak anlamlıdır ($p<0.05$). Bununla birlikte Grup 2 ve Grup 3'te kas kalınlığında görülen artışın Grup 1'e göre istatistiksel olarak anlamlı olmasa da daha fazla olduğu görülmüştür ($p>0.05$).

Sonuç: Sonuç olarak tek doz ve lokal uygulanan teriparatidin, kemik iyileşmesini postoperatif 4. haftada arttırdığı, bunun yanı sıra masseter kası kalınlığının artışında anlamlı bir etkisinin olmadığı görülmüştür.

Anahtar Kelimeler: Teriparatid, kemik iyileşmesi, masseter kası, ultrason

***Sorumlu Yazar:** Cansu Gül. Koca, Uşak University, Dentistry Faculty, Department of Oral and Maxillofacial Surgery
E-mail: cansu.koca@usak.edu.tr Phone: 0 (276) 221 2121/ 0543 806 9991 Fax: 0 (276) 221 2232
ORCID ID: Cansu Gül Koca: 0000-0002-2106-8819, **Meryem Kosehasanogullari:** 0000-0001-5893-0823, **Bengisu Yıldırım:** 0000-0002-9208-5827, **Ilhan Kaya:** 0000-0002-6505-9658, **Esra Yüce:** 0000-0002-8026-9522, **Muhammet Fatih Çiçek:** 0000-0001-9446-3433
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Introduction

Bone tissue is a special tissue with the ability to repair itself (1). Pathologic lesions, congenital deformities and infections may disrupt integrity of bone (1). Bone repair is a multifactorial event involving a large number of cells, molecules and growth factors (2). Ideal graft materials and/or biomaterials should provide appropriate bone healing as well as accelerate healing process (3). Therefore, various biomaterials and/or graft materials are currently evaluated today. Teriparatide (TP), which is used in osteoporosis treatment, has recently been favored in dentistry due to its effect on bone healing (4). TP is a recombinant human protein composed of the first 34 amino acid fragments from the parathyroid hormone. It was originally formed by Eli Lilly in 2002 and is the only type of drug approved by the Food and Drug Administration that has an anabolic effect when used in the treatment of osteoporosis (4). There are numerous studies about the effect of TP on bone healing in literature, however, a study evaluating the effect of TP on masseter muscle has not been carried out yet.

Muscle tissue with growth factors, vascular support and stem cell potency has an important effect on bone healing (2, 5). Measurements of muscle thickness are evaluated with various imaging techniques (6). Ultrasound imaging is a suitable technique for imaging soft tissues (6). It offers numerous advantages compared to computerized tomography and magnetic resonance imaging. First of all, ultrasound imaging does not use ionizing radiation and it is a non-invasive, economical and simple technique for diagnosis.

The aim of the study was to evaluate the effects of locally at different doses TP, applied in the mandibular defect area, on bone healing and muscle thickness in postoperative 4th week. There are no studies in the literature evaluating the effect of single dose and locally administered TP on bone healing and muscle thickness. Therefore, it can be stated that this study is unique one in this regard.

Material and Method

Animals and Experimental Groups: The protocol of this study was approved by the Experimental Ethics Committee of Afyon Kocatepe University. The study included 24 four-month-old male Sprague-Dawley rats weighing 350-400 grams, which had completed their skeletal development. There were 3 groups, and each group contained 8 rats. All of the animals were randomly selected and grouped at the time of the experiment, which was defined as Table 1.

Ultrasound Measurement, Surgical Procedure, Postoperative Care and Medication: All rats were administered 90 mg/kg ketamine hydrochloride (Alfamine®, Ege-Vet, Turkey), and 10 mg/kg xylazine (Alfazyne®, Ege-Vet, Turkey) intraperitoneally for induction of general anesthesia. The depth of the anesthesia was measured by the loss of pedal reflex. Ultrasound measurements were made and noted blindly by another researcher. All measurements were made by the same researcher extraorally by keeping the rats' mouths closed. While doing measurements of right masseter muscles, probe was positioned perpendicular to the anterior border of the muscle and removed along inferior border of the mandible to anterior edge of the ramus. The measurements were done with minimum pressure imaging of the muscle. From the basis mandible, the widest area was selected due to standardization. Examinations were performed using a transvaginal probe, B-mode sonography, with Mindray Ultrasound System (Mindray DC-40, China). After the ultrasound measurements had been completed, surgical procedure was started on all rats. Before the procedure, the surgical area in all animals, and skin tissue was shaved and disinfected with iodine solution. 13-mm longitudinal skin incision was performed parallel to the lower edge of the mandible. Bone tissue was reached following the blunt dissection of the masseter muscle and the elevation of periosteum. A full thickness 3-mm defect was created under continuous serum physiological irrigation in the distal portion of the last molar tooth (Figure-1). Following the creation of the defect, bleeding control was ensured and TP (Forsteo®, Eli Lilly and Company, France) were dropped to the defect areas according to the groups or the defect was left empty. The muscle and skin were sutured separately with 4/0 vicryl polyglactin using the continuous locking suture technique. All operations were performed by the same surgeon.

In order to prevent infection on the day of the surgical operation and the post-operative 2 days, intramuscular 5 mg/kg/day amikacin sulfate antibiotics (Amikozit®, Eczacıbaşı, Istanbul, Turkey) and intraperitoneal ketoprofen analgesics (Profenoid®, Senofi Aventis, Istanbul, Turkey) were administered.

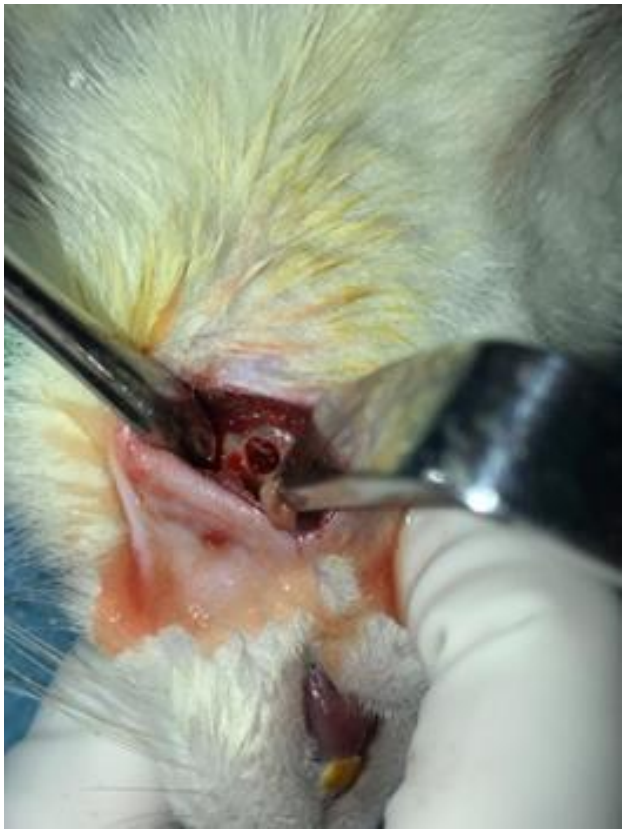

Fig. 1. Creating of 3 mm diameter defect area in rat mandible

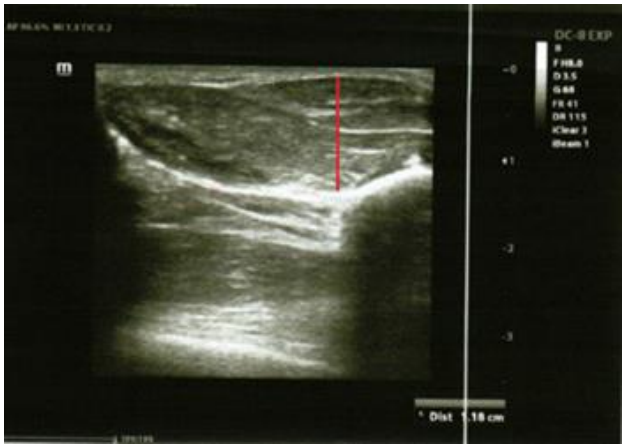

Fig. 2a. Preoperative ultrasound measurement of the rat masseter muscle thickness in Group 1

All rats were sacrificed after 4 weeks and the same procedures were repeated for the measurement of the masseter muscle thickness with ultrasound before taking mandible samples (Figure 2-4).

Histomorphometric Processing: The animals were sacrificed at postoperative 4th week. After the mandible had been removed as a single piece from the muscle and skin tissue, it was divided into two parts from the side of symphysis. The operated side was fixed in 10% buffered formaldehyde to perform histomorphometric analysis for a period of 1 week. Following the

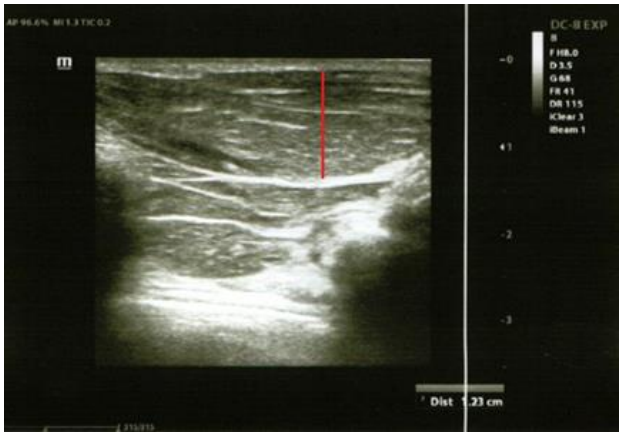

Fig. 2b. Postoperative ultrasound measurement of the rat masseter muscle thickness in Group 1

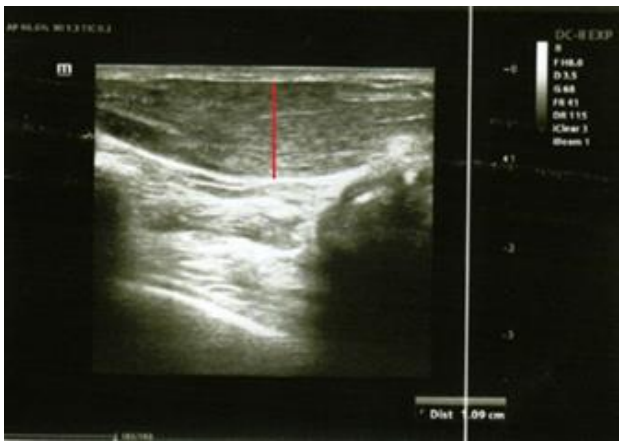

Fig. 3a. Preoperative ultrasound measurement of the rat masseter muscle thickness in Group 2

fixation, all materials were decalcified in a solution prepared with 1 scale of 50% formic acid and 20% sodium citrate solutions. After the decalcification process had been completed, the bone tissue samples were washed in running tap water, then passed through increasing series of ethanol (50%-99%) and xylene, and embedded in paraffin blocks following melted paraffin infiltration at 62°C. Sections with a width of 5-7 µm were taken with microtome (Leica RM2245) from the paraffin blocks and placed on glass slides. These sections were stained with hematoxylin-eosin staining method and assessed. The stained sections were studied with a Nikon Ci-S light microscope, Nikon DS-Fi3 camera and NIS-Elements D image analysis system (Nikon Corporation, Tokyo, Japan) and photographed. Histomorphometric examinations were performed blindly by one pathologist for two times (Figure 5-7).

Statistical Analysis: NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis.

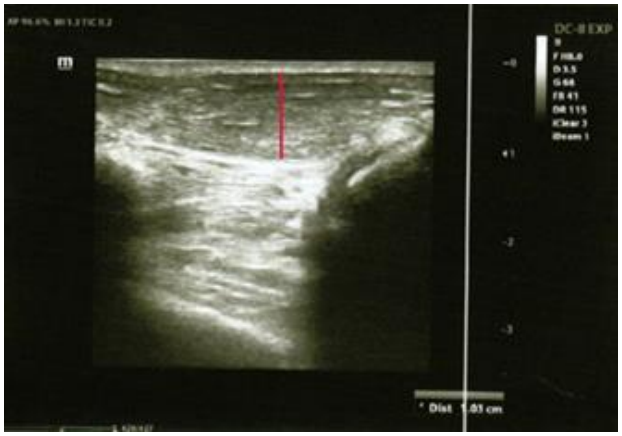

Fig. 3b. Postoperative ultrasound measurement of the rat masseter muscle thickness in Group 2

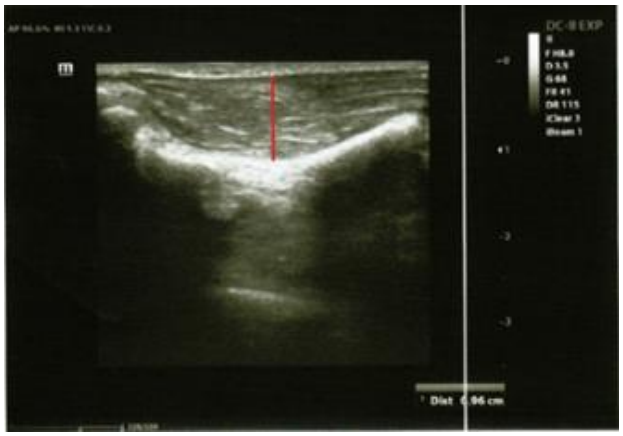

Fig. 4a. Preoperative ultrasound measurement of the rat masseter muscle thickness in Group 3

Descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Ratio, Minimum, Maximum) were used to evaluate the data of the study. The distribution of the data was evaluated by Shapiro-Wilks test. Kruskall-Wallis test was used for comparison of three independent groups that did not show normal distribution, and Mann-Whitney U test was used for comparison of two groups. Wilcoxon Test was used for comparison of two dependent groups. P values below 0.05 were considered statistically significant.

Results

During the study, no complications, such as wound infections or mandible fractures, developed that would lead to the exclusion of the animals.

Comparison of new bone area between groups: Post-operative bone healing was observed in all groups. A statistically significant difference was found in terms of the amount of bone ossification area between Group-1 and Group-2 and between

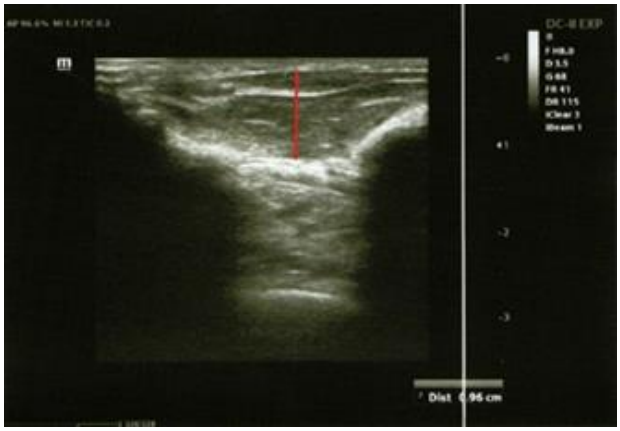

Fig 4b. Postoperative ultrasound measurement of the rat masseter muscle thickness in Group 3.

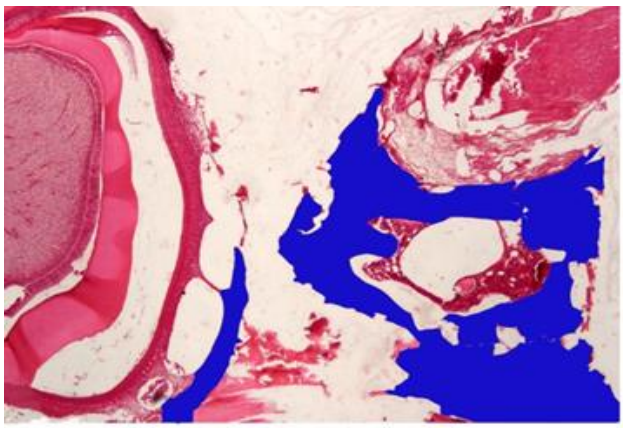

Fig. 5. Histomorphometric analysis image of bone healing area in Group 1. Blue areas indicate newly ossified areas

Group-1 and Group-3. In other words, the difference between the ossification area with empty defect and TP-administered defect groups was found to be statistically significant ($p<0.05$) (Table 2).

There was no statistically significant difference between Group-2 and Group-3 in terms of the amount of the new bone tissue formed in the defect area. In other words, the newly formed bone amount was higher in the group in which 40µg TP was used than the group in which 20µg TP was used; however, this difference was not statistically significant (Table 2) ($p>0.05$).

Comparison of masseter thickness differences between groups: Table-3 showed no statistically significant difference according to preoperative measurements of rat masseter muscle thickness among groups ($p>0.05$).

There was a difference between preoperative and postoperative measurements. The difference between preoperative and postoperative measurements of masseter muscle thickness showed a statistically significant increase within

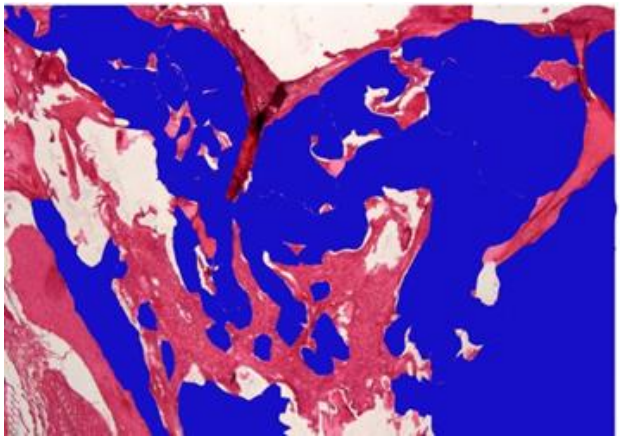

Fig. 6. Histomorphometric analysis image of bone healing area in Group 2. Blue areas indicate newly ossified areas

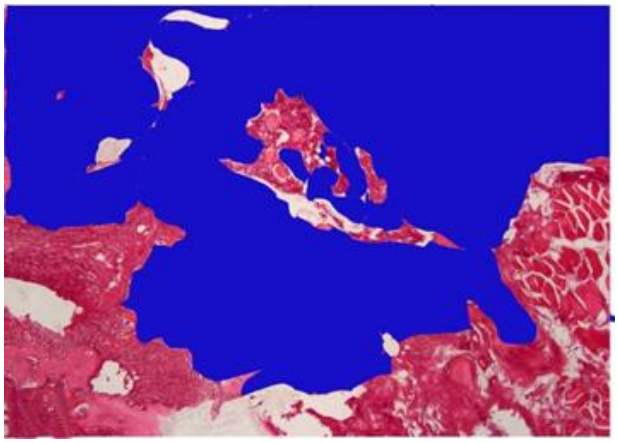

Fig. 7. Histomorphometric analysis image of bone healing area in Group 3. Blue areas indicate newly ossified areas

each group itself. In other words, the increase in masseter muscle thickness was significantly observed in Group-1, Group-2 and Group-3 after postoperative measurements ($p<0.05$) (Table-4). Nevertheless, there was no statistically significant difference among Group-1, Group-2 and Group-3 with regard to the increase in masseter muscles thickness ($p>0.05$) (Table-5).

Discussion

The present study is the first to evaluate the effect of single dose and locally administered TP on mandibular healing and thickness of masseter muscle in rats. According to the results, the healing rates of the bone in Group-2 (20 μg TP used group) and Group-3 (40 μg TP used group) were significantly higher than Group-1 (empty defect group).

Bone tissue is a special tissue with the ability to repair itself. When bone integrity is disrupted by any factor, a series of complex reactions occur, inducing bone healing. TP was the only drug used in osteoporosis, and had an anabolic effect on bone that had been approved by the Food and Drug Administration (4). Although TP is actually used in the treatment of osteoporosis, it has been used in different branches of dentistry in recent years. Numerous studies are available in the literature about the effects of TP on the healing of long bones (ossified by endochondral ossification) and craniofacial bones (ossified by intramembranous ossification) (7-9). The effect of TP depends on the frequency and dosage of administration (10). Intermittent administration of TP causes anabolic effect, while continuous administration of TP causes catabolic effect on bone metabolism (11). Anabolic effect of TP provides osteoblastic maturation, differentiation from stem cells and blocking apoptosis of osteoblasts. However, intermittent administration of TP not only causes an anabolic effect, but also causes a non-anabolic effect on bone metabolism, depending on the nature of the carrier material which is used in combination with (12). Combined use of TP with allograft provides angiogenesis by increasing angiopoietin-1 and preventing arteriogenesis by reducing angiopoietin-2, thereby achieving non-anabolic effect (12). Another factor that determine the effectiveness of TP is dosage of administration. In clinic studies, administration dose is about 20-40 μg/day, but there is no consensus about TP dosage in preclinic studies (4, 8).

In the present study, 20 μg and 40 μg TP were administered locally and as single dose in mandibular defect side, and at postoperative 4th week, bone healing was statistically significant in TP groups compared to the empty group. Although these results are consistent with the findings of many studies on the effect of TP on bone healing in the literature, there are some differences as well. (8, 9). The first difference was that the authors often created critical dimensional defects in the bone to assess the effect of biomaterials and/or graft materials in the literature. In the present study, the authors didn't create critical-sized defects in rat mandible to compare bone healing mechanism of the body and effect of TP on bone healing mechanism. The second difference is that the studies in the literature where TP is administered locally always used a carrier, while in the present study, TP was locally administered to the surgical area without a carrier.

Table 1. Classification of Groups

Experimental Groups	Classification of Groups
1st Group	Empty defect
2nd Group	20μg TP
3rd Group	40μg TP

Table 2. Comparison Parameters According To The Healing of Bone Defect

		N	Mean±St.Dv.	Min-Max (Median)	p
Groups	Empty	8	0,31±0,1	0,2-0,55 (0,29)	0,001**
	TP 20 μg	8	0,59±0,18	0,33-0,79 (0,63)	
	TP 40 μg	8	0,66±0,14	0,44-0,81 (0,67)	

N: number of rats, St. Dv: Standard Deviations, Min-Max: Minimum-Maximum, p: p value

Table 3. Comparison Preoperative of Masseter Muscle Width In All Groups

		N	Mean±St.Dv.	Min-Max (Median)	p
Masseter Muscle Width	Empty	8	0,66±0,02	0,63-0,68 (0,66)	0,214
	TP 20 μg	8	0,68±0,03	0,64-0,72 (0,68)	
	TP 40 μg	8	0,67±0,02	0,64-0,7 (0,67)	

N: number of rats, St. Dv: Standard Deviations, Min-Max: Minimum-Maximum, p: p value

The actual question that should be asked is whether TP, when administered as a single dose, can induce these effects. Shiraki et al. (13) evaluated the effect of a single-dose injection of TP on the bone turnover markers and calcium mechanism in postmenopausal women. It has been reported that a single dose injection activates calcium metabolism and results in certain changes in bone formation/resorption markers. In particular, a rapid increase in the resorption markers and a decrease in formation markers were observed on days 1–2, while a rapid increase in bone formation markers and a decrease in resorption markers were observed on days 2–14 (13). The fact that a single dose TP led to a significantly high amount of bone tissue formation in the postoperative 4th week in the present study can be explained with the study by Shiraki et al (13). In light of this information, the authors are of the opinion that the locally administered single-dose TP in the present study allowed for a greater possibility of increasing the osteoclastic and osteoblastic activities.

As already mentioned, bone healing is a complex and multifactorial event. Therefore, muscle tissue which supply bone with vascularization, stem-cells and growth factors should be considered (2). It was specified in the literature that ectopic bone formation could be seen in muscle tissue after orthopedic surgery or trauma (14, 15). In other words, bone formation within the muscle tissue can be achieved if a suitable environment is created. In the present study, there was an increasing in thickness of masseter muscles in all groups. On the other hand, there were not any statistically significant differences among groups according to increasing thickness of masseter muscles.

In the literature, authors focused on 4 factors, insulin growth factor-1 (IGF-1), bone morphogenic protein (BMP), myostatin and osteonectine, about bone-muscle interactions during muscle and bone healing period (2). In the present study, variations in muscle thickness in all groups can be explained by these factors.

It is emphasized that IGF-1 is a particularly important factor regarding the increase of muscle mass and acceleration of bone healing after trauma. There are also studies evaluating the relationship between IGF-1 and PTH. Pfeilschifter et al. (16) and Watson et al. (17) reported that PTH was a key hormone in regulating IGF-1, and that it increased IGF-1 level (16, 17). Lombardi et al. (18) suggested that there was a positive interaction between PTH and IGF-1, and that IGF-1 was a mandatory factor for PTH anabolic function (18). In addition to this, it is known that PTH increases in cellular calcium and has negative effects on bone structure and metabolism (19, 20, 21). Although intravenously administered PTH had such negative effects, locally administered single-dose TP did not have such negative effects in early bone healing period as the present study showed. In the

Table 4. Preoperative and Postoperative Measurements of Masseter Muscle Width

		Mean±St.Dv Min-Max (Median)	Difference	bp
Empty	Preoperative Measurement (n=8)	0,65±0,02 0,62-0,67 (0,65)	0,01±0,0001	0,046*
	Postoperative measurements (n=8)	0,66±0,02 0,63-0,68 (0,66)		
TP 20 μg	Preoperative Measurement (n=8)	0,66±0,02 0,63-0,7 (0,66)	0,01±0,01	0,023*
	Postoperative measurements (n=8)	0,67±0,03 0,64-0,72 (0,68)		
TP 40 μg	Preoperative Measurement (n=8)	0,65±0,01 0,63-0,67 (0,66)	0,01±0,01	0,014*
	Postoperative measurements (n=8)	0,66±0,02 0,64-0,70 (0,67)		

N: number of rats, St. Dv: Standard Deviations, Min-Max: Minimum-Maximum, p: p value

Table 5. Comparison of Increasing of Muscle Width In All Groups

		N	Mean±St.Dv.	Min-Max (Median)	p
Width	Empty	8	0,01±0,01	0-0,01 (0,01)	0,148
	TP 20 μg	8	0,01±0,01	0-0,02 (0,01)	
	TP 40 μg	8	0,01±0,01	0-0,03 (0,01)	

N: number of rats, St. Dv: Standard Deviations, Min-Max: Minimum-Maximum, p: p value

present study the surgeon created the blunt dissection of the muscle tissue cause of reaching lateral wall of the mandible. In this way it was caused trauma to muscle tissue. It was possible that trauma to the muscle and bone might have caused IGF-1 to be released above the normal level. However, TP had no significant effect on increasing the width of masseter muscles in early period of bone healing.

There are no studies in the literature evaluating the effect of single-dose and locally administered TP on bone healing and muscle thickness. This fact adds a unique value to the study and gives the opportunity to evaluate the effect of TP on muscle thickness and bone healing together. As a result of the present study, locally administered single-dose TP improved bone healing after 4 weeks from the surgery. On the other hand, locally applied single dose TP had an effect on increasing the masseter muscle thickness but it was not significant. According to the findings of the study, the following points can be suggested:

1. The effects of TP on bone healing and muscle volume at different times may be compared to other graft materials and/or biomaterials in future studies.
2. The effect of locally administered single-dose TP on serum alkaline phosphotase, calcium and bone markers are assessable in future clinic and preclinic studies.

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