Journal of Cranio-Maxillo-Facial Surgery 47 (2019) 120–126

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Evaluation of teriparatide effect on healing of autografted mandibular defects in rats

Mohammad Zandi [a, b], Arash Dehghan [c], Faezeh Gheysari [a, *], Leila Rezaeian [b], Naser Mohammad Gholi Mezerji [d]

[a] Department of Oral and Maxillofacial Surgery, Hamadan University of Medical Sciences, Hamadan, Iran
[b] Dental Research Center, Hamadan University of Medical Sciences, Hamadan, Iran
[c] Department of Pathology, Hamadan University of Medical Sciences, Hamadan, Iran
[d] Department of Biostatistics and Epidemiology, Hamadan University of Medical Sciences, Hamadan, Iran

ARTICLE INFO

Article history:
Paper received 21 July 2018
Accepted 16 November 2018
Available online 23 November 2018

Keywords:
Teriparatide
Bone defect
Autologous graft
Healing
Animal study

ABSTRACT

Objective: To evaluate the effects of short-term teriparatide administration on healing of autologous bone graft in mandibular critical-size defects.

Subjects and methods: A 5-mm mandibular bone defect was created and iliac bone graft was harvested in 135 rats. Rats were randomly divided into 3 groups of negative control (NC), control (C), and study (S). In groups S and C, iliac graft was placed in defect and 2 μg/kg/day teriparatide or saline, respectively, was administered for 20 days. In group NC, iliac graft was not transferred to the defect and saline was injected for 20 days. Twenty, 40, and 60 days after surgery, 15 rats in each group were euthanized and the healing process was histologically evaluated and scored using a grading system (1–6).

Results: In group NC, defects did not heal or were predominantly filled with fibrous tissue. At day 20, bone defects in both C and S groups contained a large area of graft particles, numerous collagen fibers and some areas of new trabeculae. At the day 40, defects in group S showed a larger bone graft area, more new bone formation, smaller connective tissue area, and a higher healing score compared to group C ($P < 0.05$). At day 60, most of the defect in group S was filled with graft particles and mature bone while in group C, new trabecular bone formation was still underway ($P < 0.05$).

Conclusion: Teriparatide therapy improves healing of bone defects reconstructed with autograft by reducing bone graft resorption and enhancing new bone formation and maturation.

1. Introduction

Defects of the facial bones have a variety of causes, such as extensive trauma, eradication of pathologic lesions, infections, and congenital musculoskeletal deformities. Management of large maxillofacial bone defects represents a great challenge in reconstructive surgery. Despite the great advances in bone reconstruction, autogenous bone grafting remains the gold standard for maxillofacial reconstruction. Autogenous bone graft possess all of the characteristics required for new bone formation including osteogenesis, osteoinductivity, and osteoconductivity and does not cause problems such as compatibility and disease transmission (Giannoudis et al., 2005; Khan et al., 2005; Drosos et al., 2007). A major problem associated with the use of autologous bone graft in reconstructive surgery is the anticipated graft resorption. The mechanism of bone resorption after bone grafting is not well understood. It has been shown that the surgically augmented height with an autologous bone graft decreased to 60% after 10 months (Toker et al., 2012; Li et al., 2016). The rate of bone resorption primarily depends on uncoupling of bone resorption and bone formation due to differential activity of osteoblasts and osteoclasts in the recipient bed and graft (Gordt and Alberius, 1999; Altundal et al., 2007). To enhance bone formation and minimize bone resorption in grafted bone defects, a variety of growth factors, pharmacological agents, and hormones such as bone morphogenetic proteins (BMPs), parathyroid hormone (PTH), interferon- γ, bisphosphonates, and platelet rich plasma (PRP) has been used and evaluated (Altundal et al., 2007; Marukawa et al., 2011; Toker et al., 2012; Li et al., 2016).

* Corresponding author. Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Hamadan University of Medical Sciences, Shahid Fahmideh Street, Hamadan, Iran. Fax: +98 8138354220.
E-mail address: F.gheisary@outlook.com (F. Gheysari).

https://doi.org/10.1016/j.jcms.2018.11.015
1010-5182/

Teriparatide is the synthetic form of human PTH consisting of the first 1-34 N-terminal amino acids, which is the bioactive portion of the hormone (Inomata et al., 1995). Teriparatide is the only anabolic agent approved by the Food and Drug Administration (FDA) for the treatment of osteoporosis (Rubin and Bilezikian, 2005; Esbrit and Alcaraz, 2013). It has been shown that intermittent administration of teriparatide promotes maturation of circulating osteoblast precursors, induces differentiation and proliferation of osteoblasts, and stimulates new bone formation by these cells. It also reduces osteoblast and osteocyte apoptosis (D'Amelio et al., 2012; Zandi et al., 2017). Several studies demonstrated that intermittent administration of teriparatide improves fracture healing rate and mechanical strength of bone at the fracture site in animal models (Jahng and Kim, 2000; Nakajima et al., 2002). Other studies also have shown that intermittent administration of teriparatide enhances and accelerates graft bone healing in the spinal fusion rat model (Qiu et al., 2013; Sugiura et al., 2015; Kaito et al., 2016).

So far, there is no information in the published literature about the effects of intermittent teriparatide administration on healing of mandibular critical-size defects reconstructed with autologous bone graft. Because maxillofacial bones are derived from distinct cell lineage during embryonic development and their reparative and regenerative capacities are different from other skeletal bones, the effects of teriparatide therapy on graft healing of maxillofacial bone defects need to be evaluated exclusively (Zandi et al., 2017).

The present experiment was done to evaluate the effects of short-term teriparatide therapy on healing of mandibular critical-size defects reconstructed with autologous iliac bone graft.

2. Material and methods

The protocol of this study was reviewed and approved (IR.UMSHA.REC.1396.179) by the Ethics Committee of the Hamadan University of Medical Sciences.

2.1. Animals and experimental groups

The animals used in the present study included 135 naïve male 5-month-old Wistar albino rats weighing 325 ± 25 g, bred at the Hamadan University of Medical Sciences. The animals were housed at 4 rats per cage, in a temperature- and humidity-controlled environment with food and water supplies ad libitum from two weeks before the start of the experiment. The rats were randomly divided into 3 experimental groups of 45 rats each: negative control (NC) group, control (C) group, and study (S) group.

In each of 135 rats, a 5-mm through and through bone defect was generated in the body of the mandible and an autologous bone graft was harvested from the iliac crest. For rats in the S group, the harvested graft was placed in the mandibular defect and subcutaneous injection of 2 μg/kg/day teriparatide (Cinnopar, Cinnagen, Iran) was started on the day of the surgery and continued for 20 days. The rats in the C group underwent the same surgical procedure as S group but received normal saline for 20 days. For the rats in the NC group, iliac graft was harvested but was not placed in the mandibular defect and normal saline was injected for 20 days.

2.2. Surgical procedures

All surgical procedures were performed under intraperitoneal general anesthesia using 75 mg/kg of Ketamine hydrochloride (Rotexmedica, Trittau, Germany) and 7.5 mg/kg of midazolam (Midazolex, Exir, Iran). The iliac crest was the donor site and the body of the mandible was the recipient site (operation side was randomly selected). Following anesthesia, the hair around the donor and recipient areas was shaved and then vigorously disinfected using a 10% povidone iodine solution. A 15 mm linear submandibular incision was made through the skin parallel to the inferior border of the mandible. After soft tissue dissection, the periosteum was carefully elevated to expose the mandibular bone. With a surgical trephine used in a low-speed handpiece and under continuous irrigation with saline solution, a 5 mm diameter through and through critical size defect was created in the body of the mandible just distal to the roots of the last molar tooth (Fig. 1). After preparation of the recipient site, an approximate 20-mm long dorsal skin incision was used to expose the iliac crest bone. Using a rongeur, autologous bone graft was harvested from the iliac crest and ground with a manual bone crusher and tightly placed into the mandibular defect (only for rats in groups S and C). Then, the wounds were sutured in layers. To prevent post-surgical infection and to control pain, all of the rats received 25 mg/kg cefazolin (Ancef; Kefzol, 1gr, Razi, Iran) for 7 days, analgesics, and appropriate basic care. Twenty, 40, and 60 days after surgery, 15 rats in each group were euthanized using an intraperitoneal injection of 200 mg/kg sodium pentobarbital.

2.3. Histologic processing

Following euthanasia, the hemimandible with bone defect was harvested and the surrounding soft tissues were dissected and removed, with care taken not to damage the bone. The 135 harvested hemimandibles were fixed in 10% formalin solution, demineralized with EDTA, and embedded in paraffin to obtain sagittal serial sections 4 μm thick. The sections were stained with haematoxylin-eosin (H&E) and two sections from the central area were selected for histological analysis under light microscopy.

A pathologist who was unaware of group assignments measured the percentage of connective tissue and regenerated bone and/or remained graft (RBRG) areas within the confines of the total surgical defect area using a 10 mm × 10 mm eyepiece grid reticule. The healing process in the defect was scored using the following histological grading system: Grade 1, no healing or healing with connective tissue; Grade 2, mostly connective tissue with some RBRG; Grade 3, comparable amounts of connective tissue and RBRG; Grade 4, predominantly RBRG with some connective tissue; Grade 5, entirely RBRG and defect distinguishable from surrounding uninjured bone; Grade 6, complete repair (defect area indistinguishable from surrounding uninjured bone).

2.4. Statistical methods

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) version 16.0.

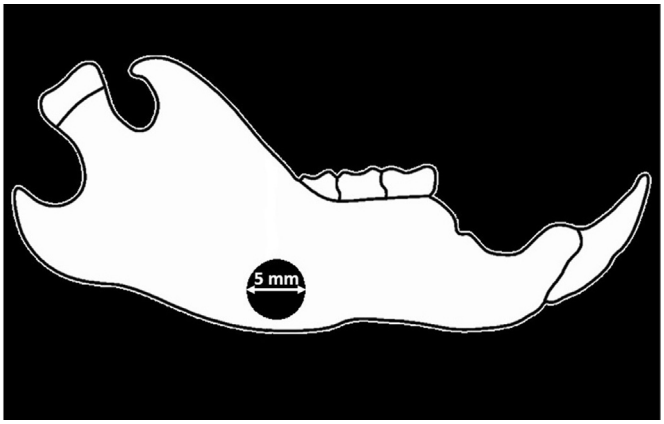

Fig. 1. Design of the through and through critical size defect in mandibular bone.

Data were expressed as means and standard deviation. After applying the Kolmogorov–Smirnov test to check the normality assumption, a one-way analysis of variance followed by Tukey post hoc comparisons was made to assess the significance of differences between the groups. A p-value less than 0.05 was considered as significance.

3. Results

All 135 rats tolerated the experiment well and no postoperative complication was observed.

The percentage of various tissues and healing score in bone defect among groups at 20, 40, and 60 postoperative days are presented in Table 1.

3.1. Day 20 after surgery

In histological evaluation of the mandibular bone defects in the NC group, either an empty defect or a defect filled with fibrous connective tissue was seen. Presence of mild bone resorption at the margin of the defect was a common finding (Fig. 2A). Histological evaluation of the grafted bone defects in the C and S groups revealed areas of remaining bone graft particles (39.33% ± 7.76% and 44.00% ± 9.67%, respectively) among numerous collagen fibers (53.67% ± 8.76% and 43.00% ± 17.20%, respectively), and some areas of newly formed trabecular bone (7.00% ± 4.55% and 13.00% ± 10.49%, respectively) (Fig. 2B). Statistical analyses showed that the percentage of connective tissue, remaining bone graft, and newly formed trabecular bone and the score of healing in the NC group were significantly ($P < 0.05$) different from those in groups C and S. However, no significant difference between groups C and S was observed.

3.2. Day 40 after surgery

In the NC group, histological findings of the surgical defect at day 40 after surgery were nearly the same as those observed at day 20; only a negligible newly formed trabeculae was projected from the defect margin (Fig. 3A). Histological assessment of the mandibular defect in group C at day 40 showed smaller areas of remaining bone graft particles (29.67% ± 9.35%), more new bone formation (22.00% ± 6.21%), and nearly the same amounts of connective tissue (48.33% ± 10.63%) and the same healing score (3.20 ± 0.68) compared with group C at day 20 (Fig. 3B). Histological evaluation of group S at day 40 showed a larger area of remaining bone graft (46.67% ± 13.05%), more new bone formation (34.67% ± 10.08%), smaller area of connective tissue (18.67% ± 17.67%), and higher healing score (4.00 ± 0.76) compared to group C at day 40 (Fig. 3C). All differences were statistically significant ($P < 0.05$).

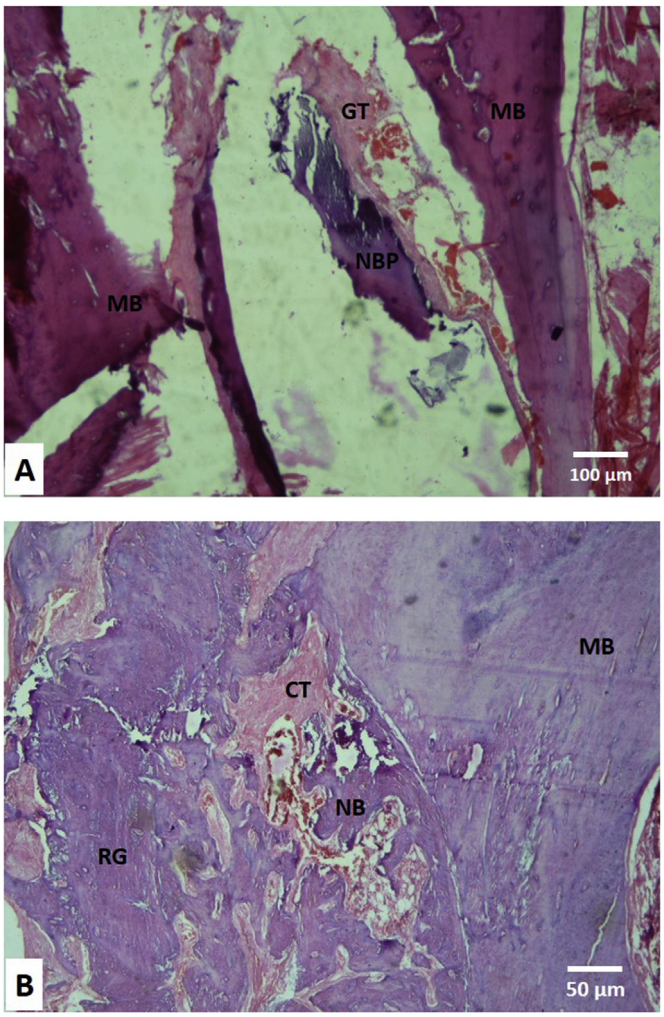

Fig. 2. Histological findings of bone defects at day 20 after surgery. A, in the negative control group, impaired bone healing and presence of granulation tissue (GT) and necrotic bone particles (NBP) within the mandibular bone (MB) defect are seen. B, in the study group (similar to the control group), areas of remaining bone graft (RG) and connective tissue (CT) and new bone (NB) formation within mandibular bone (MB) defect are seen. Sections were stained with haematoxylin and eosin.

3.3. Day 60 after surgery

The histological features of surgical defect in the NC group at day 60 after surgery were nearly similar to those observed at days 20 and 40, although a narrow band of new bone formation at the edge

Table 1
Percentage of various tissues and healing score in bone defect among groups at 20, 40, and 60 postoperative days.

Group	No.	Connective Tissue (Mean ± SD)	Remaining graft and mature bone (Mean ± SD)	Newly formed trabeculae (Mean ± SD)	Healing score (Mean ± SD)
NC20	15	97.00 ± 8.02	0.00 ± 0.00	3.00 ± 8.02	1.40 ± 0.51
NC40	15	87.67 ± 11.93	0.00 ± 0.00	12.33 ± 10.43	1.67 ± 0.49
NC60	15	85.00 ± 9.82	0.00 ± 0.00	15.00 ± 9.82	1.87 ± 0.35
C20	15	53.67 ± 8.76[a]	39.33 ± 7.76[a]	7.00 ± 4.55[a]	2.67 ± 0.49[a]
C40	15	48.33 ± 10.63[a]	29.67 ± 9.35[a]	22.00 ± 6.21[a]	3.20 ± 0.68[a]
C60	15	19.00 ± 9.10[a]	28.67 ± 12.31[a]	52.33 ± 13.87[a]	4.00 ± 0.65[a]
S20	15	43.00 ± 17.20[a]	44.00 ± 9.67[a]	13.00 ± 10.49[a]	3.27 ± 0.80[a]
S40	15	18.67 ± 17.67[ab]	46.67 ± 13.05 [ab]	34.67 ± 10.08[ab]	4.00 ± 0.76[ab]
S60	15	3.67 ± 5.81[ab]	81.33 ± 19.22 [ab]	15.00 ± 15.12[b]	5.07 ± 0.59[ab]

[a] Statistically significant difference compared with NC group at the same time point ($P < 0.05$).
[b] Statistically significant difference compared with C group at the same time point ($P < 0.05$).

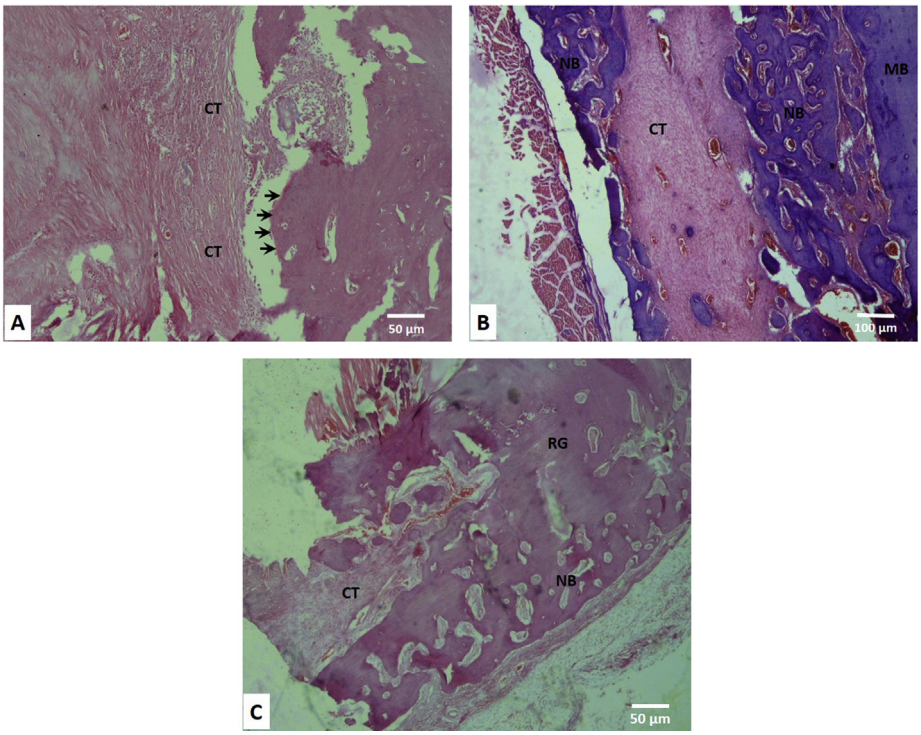

Fig. 3. Histological findings of bone defects at day 40 after surgery. A, in the negative control group, bone defect is mostly filled with fibrous connective tissue (CT), and a negligible new trabeculae (arrows) is formed adjacent to defect margin. B, in the control group, defect of mandibular bone (MB) is mostly filled with newly formed bone (NB) and connective tissue (CT). C, in the study group, relatively larger area of remaining graft (RG) and newly formed bone (NB), and smaller area of connective tissue (CT) are present in the bone defect, Sections were stained with haematoxylin and eosin.

of the defect was observed. Histological examination of the bone defect in group C showed that most of the connective tissue inside the defect was replaced by newly formed trabecular bone. Areas of remaining graft particles were observed within the defect (Fig. 4A). Histological examination of the bone defect at day 60 after surgery showed less connective tissue and new trabecular bone, larger area of remaining graft particles/mature bone, and higher healing score in group S (3.67% ± 5.81%, 15.00% ± 15.12%, 81.33% ± 19.22%, and 5.07 ± 0.59, respectively) compared to group C (19.00% ± 9.10%, 52.33% ± 13.87%, 28.67% ± 12.31%, and 4.00 ± 0.65, respectively) (Fig. 4B). All differences were statistically significant ($P < 0.05$).

A comparison of healing process in mandibular bone defect during the 60 days of study between NC, C, and S groups is presented in Fig. 5.

4. Discussion

In the present study, the effect of teriparatide on healing of autologous bone grafted mandibular critical-size defects was investigated in a rat model and promising results were obtained. It was demonstrated that the administration of teriparatide for a short period of time not only reduced the amount of graft resorption but also enhanced the formation of new bone in mandibular defects reconstructed with autogenous bone graft. Histological examination of bone defects 40 days after bone grafting showed less graft resorption and more new bone formation in teriparatide-treated rats compared to control rats. Teriparatide is the only FDA approved anabolic agent currently approved for treatment of osteoporosis (Rubin and Bilezikian, 2005; Esbrit and Alcaraz, 2013). Preclinical studies evaluating the effects of teriparatide therapy on graft healing showed that this agent increased the strength and bone mineral content of the various bone grafts (Abe et al., 2007; Hashimoto et al., 2007; Reynolds et al., 2011). Increased bone formation following teriparatide therapy might be primarily due to inducing the maturation of circulating osteoblast precursors and differentiation of lining osteoblasts leading to an increase in osteoblast number, prevention of osteoblast apoptosis, enhanced mineral apposition rate and osteoblast activity, and improvement of bone microarchitecture (Dobnig et al., 1995; Schmidt et al., 1995; Jilka et al., 1999; Pettway et al., 2008; Sugiura et al., 2015). Continuous versus intermittent administration of PTH has different effects on osteogenesis and osteoclastic activity; while the former results in net bone resorption, the latter causes a net increase in bone deposition. In the same line, several in vitro studies have shown that intermittent PTH inhibits osteoblast apoptosis but has no effect on osteoclast numbers. In contrast, continuous elevation has no effect on osteoblast apoptosis but actually increases osteoclast numbers. PTH also affects cortical and cancellous bone differently. It has a greater anabolic effect on cancellous bone than on cortical bone (Jilka et al., 1999; Bellido et al., 2003; Skripitz and Aspenberg, 2004; Rowshan et al., 2010).

The effects of teriparatide on healing of bone graft have only recently been investigated. Several studies have shown that intermittent administration of teriparatide in animal models of spinal fusion led to an enhanced quantity of the fusion callus and acceleration of spinal fusion (Ming et al., 2012; Qiu et al., 2013; Sugiura et al., 2015). However, the dose of teriparatide used in previous bone graft and fracture healing preclinical studies was tens or hundreds of multiples of the clinical doses (20 μg/day) in indicated and off-label uses. Those studies suggested that only high doses of teriparatide were effective in enhancing fracture repair, graft osseointegration and biomechanics in rodents while the lower doses did not provide any benefit (Andreassen et al., 1999; Komatsubara et al., 2005; Takahata et al., 2012).

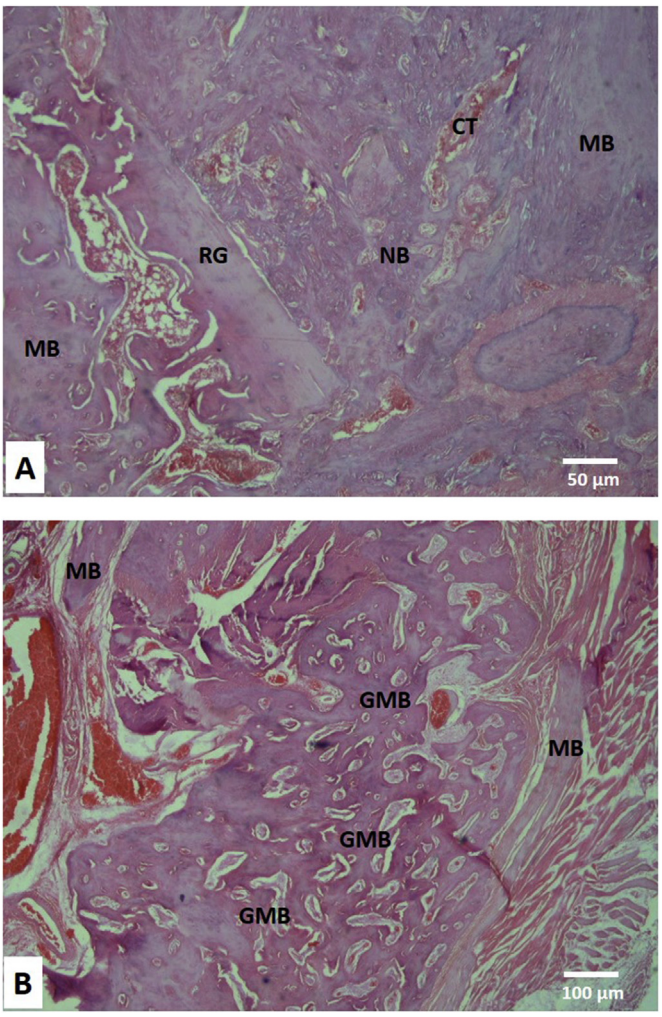

Fig. 4. Histological findings of bone defects at day 60 after surgery. A, in the control group, a large area of newly formed trabecular bone (NB) and small areas of remaining graft (RG) and connective tissue (CT) are observed within the defect of mandibular bone (MB). B, in the study group, defect of mandibular bone (MB) is mostly occupied with grafted and mature bone (GMB). Sections were stained with haematoxylin and eosin.

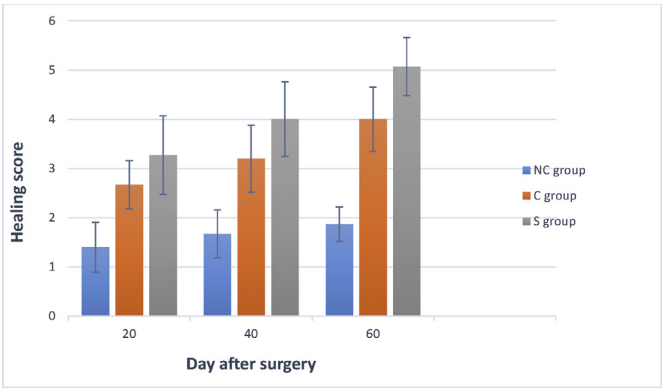

Fig. 5. Comparison of healing process in mandibular bone defect between groups during 60 days after surgery. The healing score was significantly ($P < 0.05$) different between all groups except between C and S groups at the day 20 after surgery.

In the current experiment, a dose of 2 µg/kg/day of teriparatide was administered to rats, which closely approximates the human therapeutic dose rate for treatment of osteoporosis (Zandi et al., 2018). The rationale for choosing 2 µg/kg/day dose of teriparatide in the present experiment was based on the findings of previous studies demonstrating that teriparatide doses of 5 µg/kg in rats resulted in three time the systemic exposure seen with a clinical dose of 20 µg (Eli Lilly and Co, 2002). Because the embryonic origin, bone turnover, and mechanism of healing and regeneration in mandibular bone is different from other skeletal area, their response and sensitivity to teriparatide therapy might be different. This may explain why lower doses of teriparatide enhanced graft healing in the current study but was reported to be ineffective in the orthopedic literature. Similarly, a study by Rowshan et al. (2010) showed evidence that a low dose of PTH administration might improve the healing process in a rat mandibular fracture model.

In the present study, histological evaluation of grafted bone defect at day 60 after surgery showed that the defect area in teriparatide-treated rats was completely filled with grafted particles and mature bone while the bone defect in control rats was mostly occupied with new trabecular bone and some connective tissue. This finding indicated that intermittent teriparatide administration influenced both modeling and remodeling of newly formed bone leading to an accelerated graft repair and a reduced healing time, which was in agreement with the results of spinal fusion animal studies (Ming et al., 2012; Qiu et al., 2013; Sugiura et al., 2015; Kaito et al., 2016).

In the present investigation, histological examination of grafted bone defect at 20 days following surgery revealed no difference in healing process between teriparatide-treated and control rats while at days 40 and 60 after surgery, the rats receiving teriparatide had more enhanced and accelerated bone healing compared with the control group. Similarly, an experimental study by Nakajima et al. (2002) evaluating the effect of low-dose teriparatide therapy on femoral fracture healing in rats demonstrated that in the early stages of fracture healing, PTH promoted osteoclastogenesis in hard callus. It was only at the later stages of fracture healing that an increase in mechanical strength of the callus was observed. In an animal study by Alkhiary et al. (2005), the effects of both low and high doses of teriparatide on femoral fracture healing in rats were evaluated. In that study, only the rats treated with a high dose of teriparatide showed a significant increase in bone mineral content and density and total osseous tissue volume at 21 days after femoral fracture; the positive effect of low-dose teriparatide on fracture healing was observed later at day 35 postfracture.

The findings of present and past studies indicate that the anabolic effects of teriparatide depend on the dose, frequency and duration of administration (Komatsu et al., 2018). Although the administration of higher doses of teriparatide has a more pronounced and early effect in enhancement of healing process and shortening the healing time, the high doses combined with long treatments have been linked to a high incidence of osteosarcoma in rats (Tashjian and Gagel, 2006; Takahata et al., 2012). The timing of the commencement and withdrawal of teriparatide therapy is important, as it will likely dictate the cell population that responds to the drug during various stages of bone healing (Reynolds et al., 2011).

The strengths of the present study were the randomized controlled experimental design having both negative control and control groups, administration of a low-dose teriparatide which was very close to the recommended clinical dose, and histological evaluation of the outcomes at 3 different time-points after surgery.

The present experiment had several drawbacks: first, an animal model with different physiology, drug metabolism, bone

turnover and probably bone healing process compared to humans was used. Second, only the effects of a single dose (2 μg/kg/day) and a 20-day period of teriparatide administration were evaluated and no comparison with the effects of other doses and durations of teriparatide therapy on bone healing was made. Third, long-term (more than 2 months) effects of teriparatide on bone healing was not assessed. Therefore, further experiments using large animals and also clinical trial studies evaluating the effects of different doses and durations of teriparatide therapy and its long-term effects on healing of grafted craniofacial defects are recommended.

5. Conclusion

The present study demonstrated that daily administration of a low-dose teriparatide for a period of 20 days enhanced and accelerated the healing process of grafted mandibular critical-size defects in rats. Bone defects in teriparatide-treated rats had more new bone formation and bone maturation and shorter healing time compared to those in the control rats. It was also found that the beneficial effects of low-dose teriparatide therapy appeared only at late stages of bone healing.

Ethical approval

Hamadan University of Medical Sciences Ethics Committee.

Funding

The study was funded by Vice-chancellor for Research and Technology, Hamadan University of Medical Sciences (No. 9603091543).

Conflicts of interest

None declared.

Acknowledgements

This study has been adapted from an MSc thesis at Hamadan University of Medical Sciences.

I wish to make a special note of thanks to Mr. Eilia Zandi for his kind help and assistance at the animal house.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2018.11.015.

References

Abe Y, Takahata M, Ito M, Irie K, Abumi K, Minami A: Enhancement of graft bone healing by intermittent administration of human parathyroid hormone (1–34) in a rat spinal arthrodesis model. Bone 41: 775–785, 2007

Alkhiary YM, Gerstenfeld LC, Krall E, Westmore M, Sato M, Mitlak BH, et al: Enhancement of experimental fracture-healing by systemic administration of recombinant human parathyroid hormone (PTH 1-34). J Bone Jt Surg Am 87: 731–741, 2005

Altundal H, Sayrak H, Yurtsever E, Göker K: Inhibitory effect of alendronate on bone resorption of autogenous free bone grafts in rats. J Oral Maxillofac Surg 65: 508–516, 2007

Andreassen TT, Ejersted C, Oxlund H: Intermittent parathyroid hormone (1–34) treatment increases callus formation and mechanical strength of healing rat fractures. J Bone Miner Res 14: 960–968, 1999

Bellido T, Ali AA, Plotkin LI, Fu Q, Gubrij I, Roberson PK, et al: Proteasomal degradation of Runx2 shortens parathyroid hormone-induced anti-apoptotic signaling in osteoblasts: a putative explanation for why intermittent administration is needed for bone anabolism. J Biol Chem 278: 50259–50272, 2003

D'Amelio P, Tamone C, Sassi F, D'Amico L, Roato I, Patanè S, et al: Teriparatide increases the maturation of circulating osteoblast precursors. Osteoporos Int 23: 1245–1253, 2012

Dobnig H, Turner RT: Evidence that intermittent treatment with parathyroid hormone increases bone formation in adult rats by activation of bone lining cells. Endocrinology 136: 3632–3638, 1995

Drosos GI, Kazakos KI, Kouzoumpasis P, Verettas DA: Safety and efficacy of commercially available demineralized bone matrix preparations: a critical review of clinical studies. Injury 38: S13–S21, 2007

Esbrit P, Alcaraz MJ: Current perspectives on parathyroid hormone (PTH) and PTH-related protein (PTHrP) as bone anabolic therapies. Biochem Pharmacol 85: 1417–1423, 2013

Giannoudis PV, Dinopoulos H, Tsiridis E: Bone substitutes: an update. Injury 36: S20–S27, 2005

Gordt M, Alberius P: Some basic factors essential to autogeneic nonvascularized onlay bone grafting to the craniofacial skeleton. Scand J Plast Reconstr Hand Surg 33: 129–146, 1999

Hashimoto T, Shigetomi M, Ohno T, Matsunaga T, Muramatsu K, Tanaka H, et al: Sequential treatment with intermittent low-dose human parathyroid hormone (1–34) and bisphosphonate enhances large-size skeletal reconstruction by vascularized bone transplantation. Calcif Tissue Int 81: 232–239, 2007

Inomata N, Akiyama M, Kubota N, Jüppner H: Characterization of a novel parathyroid hormone (PTH) receptor with specificity for the carboxyl-terminal region of PTH-(1-84). Endocrinology 136: 4732–4740, 1995

Jahng JS, Kim HW: Effect of intermittent administration of parathyroid hormone on fracture healing in ovariectomized rats. Orthopedics 23: 1089–1094, 2000

Jilka RL, Weinstein RS, Bellido T, Roberson P, Parfitt AM, Manolagas SC: Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. J Clin Invest 104: 439–446, 1999

Kaito T, Morimoto T, Kanayama S, Otsuru S, Kashii M, Makino T, et al: Modeling and remodeling effects of intermittent administration of teriparatide (parathyroid hormone 1-34) on bone morphogenetic protein-induced bone in a rat spinal fusion model. Bone Rep 5: 173–180, 2016

Khan SN, Cammisa Jr FP, Sandhu HS, Diwan AD, Girardi FP, Lane JM: The biology of bone grafting. J Am Acad Orthop Surg 13: 77–86, 2005

Komatsu J, Nagura N, Iwase H, Igarashi M, Ohbayashi O, Nagaoka I, et al: Effect of intermittent administration of teriparatide on the mechanical and histological changes in bone grafted with β-tricalcium phosphate using a rabbit bone defect model. Exp Ther Med 15: 19–30, 2018

Komatsubara S, Mori S, Mashiba T, Nonaka K, Seki A, Akiyama T, et al: Human parathyroid hormone (1–34) accelerates the fracture healing process of woven to lamellar bone replacement and new cortical shell formation in rat femora. Bone 36: 678–687, 2005

Li P, Honda Y, Arima Y, Yasui K, Inami K, Nishiura A, et al: Interferon-γ enhances the efficacy of autogenous bone grafts by inhibiting postoperative bone resorption in rat calvarial defects. J Prosthodont Res 60: 167–176, 2016

Lilly Eli, Co: United States Package Insert: forteo [teriparatide (rDNA origin) injection]. Indianapolis, IN; 2002

Marukawa E, Oshina H, Iino G, Morita K, Omura K: Reduction of bone resorption by the application of platelet-rich plasma (PRP) in bone grafting of the alveolar cleft. J Craniomaxillofac Surg 39: 278–283, 2011

Ming N, Cheng JT, Rui YF, Chan KM, Kuhstoss S, Ma YL, et al: Dose-dependent enhancement of spinal fusion in rats with teriparatide (PTH[1-34]). Spine 37: 1275–1282, 2012

Nakajima A, Shimoji N, Shiomi K, Shimizu S, Moriya H, Einhorn TA, et al: Mechanisms for the enhancement of fracture healing in rats treated with intermittent low-dose human parathyroid hormone (1-34). J Bone Miner Res 17: 2038–2047, 2002

Pettway GJ, Meganck JA, Koh AJ, Keller ET, Goldstein SA, McCauley LK: Parathyroid hormone mediates bone growth through the regulation of osteoblast proliferation and differentiation. Bone 42: 806–818, 2008

Qiu Z, Wei L, Liu J, Sochacki KR, Liu X, Bishop C, et al: Effect of intermittent PTH (1–34) on posterolateral spinal fusion with iliac crest bone graft in an ovariectomized rat model. Osteoporos Int 24: 2693–2700, 2013

Reynolds DG, Takahata M, Lerner AL, O'Keefe RJ, Schwarz EM, Awad HA, et al: Teriparatide therapy enhances devitalized femoral allograft osseointegration and biomechanics in a murine model. Bone 48: 562–570, 2011

Rowshan HH, Parham MA, Baur DA, McEntee RD, Cauley E, Carriere DT, et al: Effect of intermittent systemic administration of recombinant parathyroid hormone (1-34) on mandibular fracture healing in rats. J Oral Maxillofac Surg 68: 260–267, 2010

Rubin MR, Bilezikian JP: Parathyroid hormone as an anabolic skeletal therapy. Drugs 65: 2481–2498, 2005

Schmidt IU, Dobnig H, Turner RT: Intermittent parathyroid hormone treatment increases osteoblast number, steady state messenger ribonucleic acid levels for osteocalcin, and bone formation in tibial metaphysis of hypophysectomized female rats. Endocrinology 136: 5127–5134, 1995

Skripitz R, Aspenberg P: Parathyroid hormone—a drug for orthopedic surgery? Acta Orthop Scand 75: 654–662, 2004

Sugiura T, Kashii M, Matsuo Y, Morimoto T, Honda H, Kaito T, et al: Intermittent administration of teriparatide enhances graft bone healing and accelerates spinal fusion in rats with glucocorticoid-induced osteoporosis. Spine J 15: 298–306, 2015

Takahata M, Schwarz EM, Chen T, O'Keefe RJ, Awad HA: Delayed short-course treatment with teriparatide (PTH(1-34)) improves femoral allograft healing by enhancing intramembranous bone formation at the graft-host junction. J Bone Miner Res 27: 26–37, 2012

Tashjian Jr AH, Gagel RF: Teriparatide [human PTH(1–34)]: 2.5 years of experience on the use and safety of the drug for the treatment of osteoporosis. J Bone Miner Res 21: 354–365, 2006

Toker H, Ozdemir H, Ozer H, Eren K: Alendronate enhances osseous healing in a rat calvarial defect model. Arch Oral Biol 57: 1545–1550, 2012

Zandi M, Dehghan A, Amini P, Rezaeian L, Doulati S: Evaluation of mandibular fracture healing in rats under zoledronate therapy: a histologic study. Injury 48: 2683–2687, 2017a

Zandi M, Dehghan A, Mohammadi-Mofrad A, Amini P, Vahdatinia F: Short-term perioperative teriparatide therapy for the prevention of medication-related osteonecrosis of the jaw: a randomized, controlled preclinical study in rats. J Craniomaxillofac Surg 45: 275–280, 2017b

Zandi M, Dehghan A, Zandipoor N, Amini P, Doulati S: Effect of different doses and durations of teriparatide therapy on resolution of medication-related osteonecrosis of the jaw: a randomized, controlled preclinical study in rats. J Craniomaxillofac Surg 46: 466–472, 2018