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The Effectiveness of Teriparatide Therapy for Medication Induced Osteonecrosis of The Jaw (Mronj) in Rats -A Systematic Review

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Abstract

Background: Medication induced osteonecrosis of the jaw (MRONJ) is caused due to various medications such as antiresorptive agents like bisphosphonates. Conservative treatment options are available, but surgical treatment is regarded as successful. Recently, researchers have said that Teriparatide is effective in treating medication related osteonecrosis of the jaw (MRONJ) patients as it has anabolic effects on bone. Teriparatide is a human biosynthetic parathyroid hormone which is now being used in the treatment of MRONJ.

Aim: To assess the effectiveness of Teriparatide therapy for medication induced osteonecrosis of jaw.

Study design: A systematic review of randomised controlled trials of teriparatide therapy for medication induced osteonecrosis of jaw was performed. The records obtained were 1247 out of which 24 were full text articles. The interventions and outcomes were assessed and results were obtained.

Result: 5 studies that were randomised controlled trials were included. The studies were performed only on animal models. Among the 5 studies, all of them were found to be statistically significant, but further studies must be done to prove the effectiveness of Teriparatide in treating medication induced osteonecrosis of the jaw.

Conclusion: There are very few randomised controlled trials done on human models which lead to lack of evidence to prove the effectiveness of Teriparatide therapy in treatment of osteonecrosis of the jaw.

Keywords: Teriparatide therapy, osteonecrosis, medication induced osteonecrosis of jaw, bisphosphonate induced osteonecrosis.

INTRODUCTION

Teriparatide (TPTD) is a biosynthetic human parathyroid hormone which has anabolic effects on bone. It acts by increasing bone formation by stimulating the number of osteoblasts, promoting osteogenic differentiation of bone mesenchymal stem cells and improving cell survival [11].

Teriparatide (TPTD) was approved by the FDA in the year 2002 for use in post-menopausal women and men with osteoporosis with increased risk of fracture and in patients with glucocorticoid induced osteoporosis [2].It increases the mechanical strength of the bone [7]. Teriparatide has now been used in the treatment of osteonecrosis and its rationale is the mechanism of action and regulatory function of parathyroid hormone [10]. Mechanism of Teriparatide includes increase in the number of remodelling units which leads to increased bone formation which thereby promotes healing and removes the damaged bone.

Osteonecrosis of the jaw (ONJ) is caused due to various factors of which medications play a major role. Bisphosphonates have been used for the treatment of a large number of metabolic diseases ranging from osteoporosis to cancer related alterations to oral bone loss [14]. Osteonecrosis of the jaw has emerged as a rare but significant condition associated with bisphosphonate treatment [1] especially in patients consuming the drug for at least 12 months of duration. Antiresorptive agents like bisphosphonates include alendronate, risedronate, ibardronate, zoledronic acid and denosumab which decrease the risk of skeletal related events in patients with cancer and metabolic bone diseases. The risk is high when administered intravenously and low when given orally. Researchers have discovered thatother potent remodelling agents have also been associated with medication induced osteonecrosis of the jaw. Hence, recent advances have led to the efficient use of teriparatide in reversing oral cavity bone loss [4]. Teriparatide (TPTD) activates the turnover of living bone which causes sequestrum separation followed by normal mucosal coverage of exposed bone [15]. Thus teriparatide therapy is proved to be efficient in treating medication induced osteonecrosis of the jaw (MRONJ).

OBJECTIVES:

To assess the effectiveness of Teriparatide therapy in the treatment of medication induced osteonecrosis of the jaw.

MATERIALS AND METHODS:

STUDY DESIGN:

Systematic review of randomised controlled trials of teriparatide therapy for medication induced osteonecrosis of the jaw.

ELIGIBILITY CRITERIA:

Inclusion criteria:

- Randomised controlled trials of any duration used for both prevention and treatment outcomes were included.
- Studies published in English were included.
- Studies depicting adjunctive treatment options were also included.
- Randomised controlled trials on animals alone and were included.

Exclusion criteria:

- Case reports and review articles were excluded.
- Studies published in languages other than English were excluded.

- Studies having access to only abstracts were excluded.
- Randomised controlled trials on humans were excluded.

SEARCH STRATERGY:

The articles were searched from various recognised databases. Additional records were also searched from other sources. A literature search to collect relevant data was performed using the MesH terms, "Teriparatide", "osteonecrosis", "Bisphosphonates", "medication", "randomised controlled trial". The various sources include:

- PubMed
- Wiley online library
- Elsevier Science direct
- Cochrane
- Jama network
- Prospero
- Med page today
- Sage journals

RESULTS:

The search resulted in 1247 articles among which the duplicates were removed and the rest of the articles were screened. Based on the inclusion and exclusion criteria, a total of 24 full text articles were assessed individually, from which 5 articles were included in quality analysis. The flow diagram of the reports that were identified, screened, assessed for eligibility, excluded and included in the review is shown in figure 1.

The various characteristics of the intervention in the included studies are shown in Table 1. The table included 5 studies that depicted the effectiveness of Teriparatide therapy for the treatment of medication induced osteonecrosis of jaw by comparing with experimental and control groups. Each study differed from each other by their sample size, type of population and duration of intervention. The trials were performed in rat models in which osteonecrosis was induced using medications and was then treated with teriparatide. Two of the trials were done for 8 weeks, one for 4 weeks, and one trial for 10 weeks and the other for 16 weeks. The rat models were divided into experimental and control groups based on various criteria as described in Table 1.

The outcome data of the included studies is shown in Table 2. It describes in detail regarding the effects of teriparatide therapy on rat models. The *p* values of various studies were also mentioned in the table.

The bias analysis is shown in Table 3. The bias was categorised according to the Cochrane risk of Bias for Randomised controlled trials. The bias was mentioned as high risk, low risk and unclear according to each study. The bias analysis yielded mixed results that stated that most of the studies did not mention various criteria under bias analysis and so there was a need for further studies and research to prove the effective teriparatide therapy for osteonecrosis of jaw.

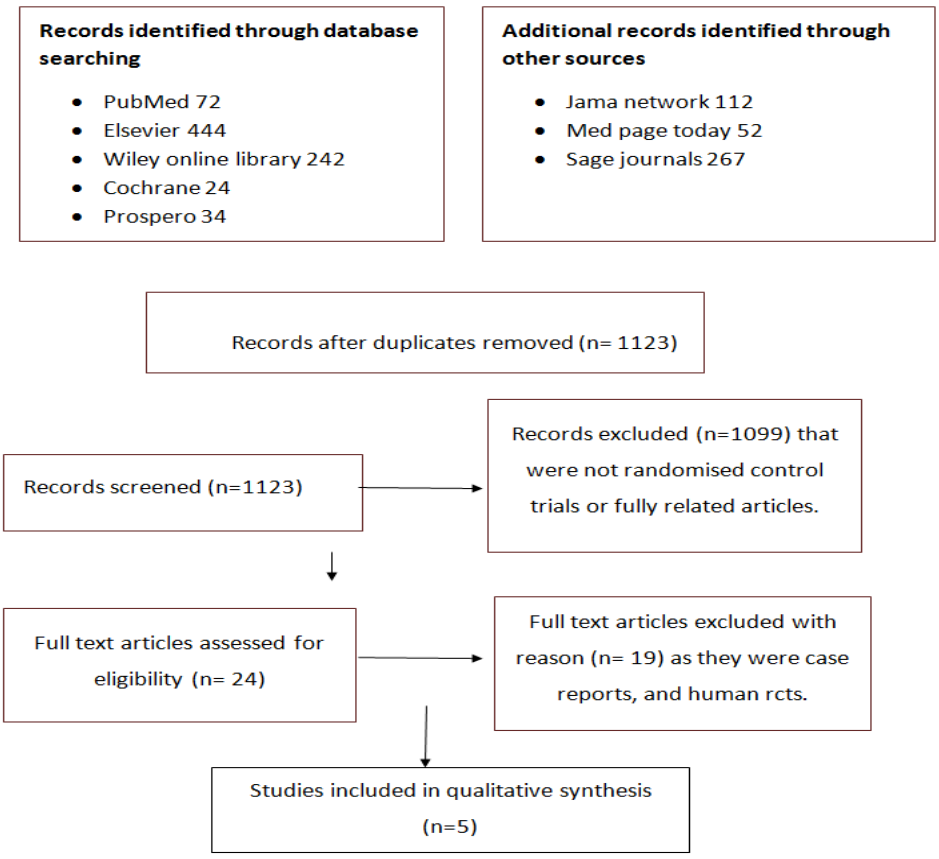

FIGURE 1: PRISMA (DIAGRAM SHOWING THE NUMBER OF STUDIES IDENTIFIED, SCREENED, ASSESSED FOR ELIGIBILITY, EXCLUDED AND INCLUDED IN THE SYSTEMATIC REVIEW

I.CHARACTERISTICS OF THE INTERVENTIONS IN THE INCLUDED STUDIES

AUTHOR NAME	YEAR	SAMPLE SIZE	CHARACTERISTICS	DURATION	NUMBER[CASE/CONTROL] µg - microgram mg-milligram kg- kilogram
N Ersan et al	2014	30	Healthy, female Sprague- Dawley rats, aged between 10 weeks and 12 weeks	8 weeks	3 GROUPS : Group I—zoledronic acid (ZA) (n=10) Group II—ZA and teriparatide (n=10) Group III—control group(n=10)
E. H. Dayisoylu et al	2013	36	female Sprague–Dawley rats	16 weeks	4 GROUPS: Group I- sterile saline(SS) group Group II- Zoledronic acid (ZA) group Group III-Zoledronic acid + Extraction group Group IV-Zoledronic acid +Extraction + Teriparatide therapy group
Aydin Keskinruzgar et al	2016	80	Rats that had been injected intraperitoneally with zoledronic acid for 7 weeks were used.	10 weeks	3 GROUPS : Preoperative Group: Before the tooth extraction procedure, teriparatide was injected subcutaneously for 3 weeks (0.04 mg/ kg twice a week) to prevent osteonecrosis (at weeks 5, 6, and 7). Postoperative Group: After the tooth extraction procedure, teriparatide was injected subcutaneously for 3 weeks (0.04 mg/ kg twice a week) to prevent osteonecrosis (at weeks 8, 9, and 10). Osteonecrosis Group: After MRONJ had occurred, teriparatide was injected subcutaneously for 3 weeks (0.04 mg/kg twice a week) for the treatment of osteonecrosis (at weeks 15, 16, and 17), and the osteonecrosis group was sacrificed at 17 weeks (O-17, n = 8). (O-17, n = 8).
Mohammad Zandi et al	2017	120	Wistar rats that had been affected with MRONJ(after six weekly zoledronate injections and tooth extraction)	8 weeks	4 GROUPS: C-control group, L-low group, M-medium group, H-high group. The subgroups included: C4(n=15), C8(n=15) L4(n=15), L8(n=15) M4(n=15), M8(n=15) H4 (n=15), H8 (n=15).
Mohammad Zandi et al	2016	100	male Wistar rats	4 weeks	2 GROUPS: Protocol A: 25 TPD treated (AT) and 25 controls (AC) rats ,received 5 weekly injection of 0.06 mg/kg zoledronate after which extraction of bilateral mandibular first molars was performed for all rats, and 4-week TPD (20 µg/kg/day) and saline therapy was started. Protocol B: 25 TPD-treated (BT) and 25 control (BC) rats received 5 weekly injection of 0.06 mg/kg zoledronate. One week later, 4-week TPD and saline therapy was started.

II.OUTCOME DATA AS REPORTED IN INCLUDED STUDIES

AUTHOR NAME	YEAR	OUTCOME	RESULTS
N Ersan et al	2014	Micro CT examination , histopathological examinations and TRAcP enzyme histochemistry were performed which stated that bone formation was more in ZA1TP group than in ZA group.	The newly formed bone in the extraction socket was less in ZA group than in ZA1TP ($p<0.05$), also the number of osteoclasts and necrotic bone area were higher in ZA group.
E. H. Dayisoylu et al	2013	Intergroup analysis was performed which stated that the number of osteoblasts, osteoclasts and fibroblast were more in groups III and IV whereas their activity was vice versa. BRONJ was observed in 66% of the subjects in group III and 22% of the subjects in group IV.	BRONJ was statistically significant in group III than in groups I and II ($p<0.01$). No difference was observed in group IV than in groups I and II ($p>0.01$)
Aydin Keskinruzgar et al	2016	The osteoclast numbers and the inflammatory phase of bone healing was more in experimental groups than in control groups. The osteoblast numbers and osteonecrotic bone areas were similar in both control and experimental groups.	a statistically significant difference in osteoblast numbers was detected between the control group and preoperative groups ($P = .043$). Also ,a significant difference was seen in osteoclast numbers was detected between the control and preoperative groups ($P = .037$) and between the control and postoperative groups ($P = .009$).
Mohammad Zandi et al	2017	72.2%, 61.5%, and 40% of the experimental rats with stage I, II, III MRONJ showed clinical improvement of the disease after Teriparatide therapy.	Statistical analysis stated that the experimental subgroups had a significant improvement ($p<0.05$) clinically and histologically compared to control groups.
Mohammad Zandi et al	2016	Clinical examination of the rats in group A revealed osteonecrotic lesion in 20% of the TPD treated and 78% of the control groups. And in study group B, osteonecrotic lesion occurred in 14% of the TPD treated and 78% of the control groups.	The differences between AT and AC and between BT and BC based on Incidence of bone exposure/fistula and mean numbers of osteocytes and empty lacunae were statistically significant ($P<0.001$).

BIAS ASSESSMENT AS INCLUDED IN THE STUDIES

The bias is assigned as low risk (+), high risk (-) and unclear (?)

Author name, year	Random sequence generation	Allocation concealment	Blinding of outcome	Incomplete outcome data	Blinding of participants and personnel	Selective reporting	Judgemental bias
N Ersan et al	?	-	?	+	+	-	+
E.H.Dayisoylu et al	-	-	?	+	+	?	+
Aydin Keskinruzgar et al	-	-	?	?	+	+	-
Mohammad Zandi et al	?	-	?	+	+	+	+
Mohammad Zandi et al	+	?	+	+	+	+	-

DISCUSSION:

The systematic review has yielded positive results regarding the effect of Teriparatide therapy on medication induced osteonecrosis of the jaw. The search resulted in several studies but some were excluded as they were not fully related articles, case reports or non-randomised controlled trials. Hence studies depicting randomised controlled trials in animal models alone were included. In the above studies, teriparatide therapy was used as one of the interventions to treat medication induced osteonecrosis of the jaw. All the studies concluded that Teriparatide was highly effective for the treatment of medication induced osteonecrosis of the jaw. Due to the lack of trials in human models, further studies are needed for efficient use of teriparatide in the successful treatment of the same [13].

Based on this systematic review, the effect of teriparatide therapy has been reported for the treatment of medication induced osteonecrosis of jaw in various studies. In a periodontal disease induced BRONJ rat model, Aghaloo et al reported increased periosteal new bone formation and wider alveolar bone on micro CT images. Increase in alveolar bone formation in rats was also induced by intermittent parathyroid hormone administration. Also, the alveolar bone width of the ZA (Zoledronic acid) group was found to be greater than that of the control group. The ZA1TP (Zoledronic acid and Teriparatide) group had the largest alveolar bone width of the extraction site. The use of Teriparatide on refractory BRONJ lesions was first defined by Harper and Fung, who observed soft-tissue healing in a patient with a 3 month Teriparatide administration. [1]

Ohbayashi et al demonstrated that bone regeneration was seen 6 months after Teriparatide therapy in a refractory BRONJ patient. Ma et al showed that Teriparatide reverses the inhibitory effects of antiresorptive drugs such as bisphosphonates [15]. In their study in ovariectomised rats, he concluded that alendronate suppressed the activation and formation of bone before teriparatide treatment, but 2 months after teriparatide treatment, there was an increase in bone formation and mineralisation [8]. A case report by Yoshiga et al stated that even weekly Teriparatide injections can result in resolution of stage 3 Bisphosphonate induced osteonecrosis of jaw (BRONJ) [9]. According to recent reports, Teriparatide enhanced angiogenesis which is beneficial for bone healing [12].

E. H. Dayisoylu et al stated that teriparatide increases the number of osteoblasts active in synthesizing new bone matrix at the cellular level. In addition, parathyroid hormone protects periosteal osteoblasts from apoptosis. Therefore, PTH increases periosteal bone formation with improved bone micro-architecture. The stimulation of osteogenic cell proliferation and differentiation in bone marrow-derived cells also contributes to the anabolic actions of intermittent PTH administration [2]. In a study by Kwon et al in 2013, 20 μg/day Teriparatide was given to 6 MRONJ patients for 1-3 months which resulted in bone healing [6].

Ni Ming et al. applied teriparatide 4 μg/kg per day and teriparatide 23 μg/kg per day subcutaneous injections for 4 weeks (5 days per week) after the spine fusion surgery in the rat model. They found that teriparatide showed anabolic skeletal effects and significantly enhanced spinal fusion rate in rats. However, some researchers also conduct the study with a follow up of 6–8 weeks. Longer course of treatment needed to be studied in further research [3].

Bashutski et al stated that teriparatide yielded positive effects on bone healing in the oral cavity. Teriparatide was reported to be effective in the healing of necrotic wounds in rats administered bisphosphonates and steroids [4]. In other studies, Kuroshima et al reported that teriparatide promotes healing of the tooth extraction socket. In a study associated with bisphosphonates and steroids, he reported that osteoblasts were considerably increased and osteoclasts and necrotic bone were decreased by teriparatide after bisphosphonate and steroid use. According to the results of this study, the number of osteoclasts was decreased in the control groups that were given BP without any treatment. Teriparatide administered before and immediately after tooth extraction might decrease the risk of developing osteonecrosis. But prospective randomized studies are needed to evaluate the long-term effectiveness of teriparatide [4].

Mohammad Zandi et al stated that short-term administration of resulted in improvement in both clinical and histological features of MRONJ. But antiresorptive therapy should be resumed only after complete resolution of MRONJ to minimize the chance of relapse of osteonecrosis. Doh et al stated that, long-term information and teriparatide administration is not recommended for more than 2 years [5]. Therefore, further studies are recommended to evaluate the effects of more prolonged teriparatide therapy on MRONJ. Thus similar reports of beneficial effects of TPD therapy regarding prevention and treatment of medication induced osteonecrosis of jaw have been documented in the literature. Limitation of the study includes teriparatide has been associated with the risk of osteosarcoma that is seen in rats undergoing Teriparatide therapy. Even though osteosarcoma was not reported in humans, Teriparatide treatment is not recommended for more than 2 years [6]. In patients with primary hyperthyroidism, the stimulation of osteoblasts is greater. Thus the dosage and duration of the therapy must be evaluated in both in vitro and in vivo models and the safety of the drug should be thoroughly evaluated. Another limitation of Teriparatide therapy is that not many human trials have been performed. Therefore further studies and research is needed in this field for better usage of Teriparatide in the treatment of medication induced osteonecrosis of jaw.

CONCLUSION:

Teriparatide therapy is proved to be one of the effective treatments for medication induced osteonecrosis of jaw. Since the study included in our review only included animal studies further review of search can be done to illustrate its effectiveness in human trails.

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