

# **RESEARCH ARTICLE**

# THE EFFICACY OF STRONTIUM RANELATE IN THE MANAGEMENT OF ALVEOLAR BONE LOSS (CLINICAL AND RADIOGRAPHIC STUDY).

## Omar H. khashaba<sup>1</sup>, A. Nabil Nasser<sup>2</sup> and M. M. Bazed<sup>3</sup>.

- 1. Professor of Oral medicine and Pereiodontology, Department of Oral medicine and periodontology, Faculty of Oral and Dental Medicine, Mansuora university, Egypt.
- 2. B.D.S, Faculty of Oral and Dental Medicine, Mansuora university, Egypt.
- Lecturer of Oral medicine and Pereiodontology, Department of Oral medicine and periodontology, Faculty of Oral and Dental Medicine, Mansuora university, Egypt.

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## Abstract

**Objective:** The aim of the present study is to evaluate the efficacy of strontium ranelate as a bone graft substance in correction of alveolar bone loss associated with periodontal disease .

**Materials and methods:** A split-mouth study were used in 20 patients suffering from periodontal disease with alveolar bone loss. After scalling, root planning (SRP) and depridement of granulation tissue in the depth of the periodontal pocket , a full thickness flap was done and a mix of strontium ranelate 2gm (Protelos) with sterile saline was delivered in a putty form on the alveolar bone untill the bone defect is filled, and the other side was subjected only to SRP and depridement of granulation tissue. At first Periodontal health statue will be assessed by measuring specific indices such as: Gingval index (GI), Periodontal pocket depth (PPD) ,Bleeding on probing (BOP) and Plaque index (PI). At baseline, digital panoramic radiograph was taken, patients were recalled for follow up and rescoring of all indices after 2, 6 and 8 weeks, and a panoramic radiographs were taken again after 12 weeks for radiographic assessement .

**Results:** Comparing the PPD between the 2 sides showed that there was much improvement in the scores in the side of the strontium ranelate(applied side) and (p value <0.05), so the difference between 2 sides considered statistically significant.

Panoramic xrays results: comparing two sides showed increase nearly about 0.5-1.1 mm in the hight of the alveloar bone in the side of strontium ranelate (applied side) while the other side(control side) remained without any progression in the height of the alveolar bone.

**Conclusion:** clinical and radiographic results obviously showed statistically significant and provides evidence that strontium ranelate can be used for management of alveolar bone loss associated with periodontal diseases.

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## Corresponding Author:- Omar H. khashaba.

Address:- Professor of Oral medicine and Pereiodontology, Department of Oral medicine and periodontology, Faculty of Oral and Dental Medicine, Mansuora university, Egypt.

## Introduction:-

Periodontal disease is a localized inflammatory disorder in which periodontal pathogens escape the host immunological defense system, leading to tissue destruction and bone loss <sup>1</sup>. Diagnosis of periodontal disease is dependent to a great extention on clinical parameters such as probing pocket depth, clinical attachment loss,tooth mobility, furcation involvement,bleeding on probing, plaque index and radiographic quantification of marginal bone loss <sup>2</sup>.

Alveolar Bone loss is the consequence of periodontal diseases or trauma from occlusion. Regeneration of the lost bone is crucial for the patient rehabilitation of function, phonetics and aesthetics.. in recent years, there have been developments in the field of treatment of bone loss which integrates the use of different bone grafts <sup>1,3</sup>.

The uses ofperiodontal bone grafts are: reduction of probing depth , clinical attachment gain, bone fill of the osseous defect and regeneration of new bone <sup>4</sup>.Several methods ,materials and techniques have been used for bone grafting.Grafting material used for bone augmentation may be ;autogenous bone graft harvesting from one site to another within the same individual, allograft transferred between members of the same species, xenografts from different species, and alloplast which are synthetic in origin<sup>5</sup>. Allografts are osteoconductive and may be osteoinductive. Xenografts are osteoconductive but have a very slow resorption rate. The synthetic materials are inert with little osteoinductive activity <sup>5</sup>.

Recently a new material has been used for replacement of bone loss, this material is called stroniumranelate.Strontiumranelate is a used in the treatment of osteoporosis, Strontium ranelate is composed of two atoms of stable strontium (Sr) combined with ranelic acid, which acts as carrier , unlike any other drug, has a dual effect on bone remodelling, being able to stimulate bone formation by osteoblasts, a property shared with bone-forming agents, and to inhibit bone resorption by osteoclasts, as do anti-resorptive agents<sup>6,7</sup>.

Strontium ranelate enhances the replication of pre-osteoblasts and increases collagen type I synthesis <sup>8</sup>. Strontium ranelate promotes bone nodule formation by increasing the differentiation from early progenitor cells to mature osteoblasts <sup>9</sup>.

There is growing evidence that strontium influences bone remodeling by affecting both bone resorption and bone formation. In vitro, strontium inhibits bone resorption<sup>8</sup>, and stimulates bone formation<sup>10</sup>. In vivo, the administration of strontium at low concentrations inhibits bone resorption<sup>11,12</sup>, and stimulates bone formation, as evaluated by bone histomorphometry in osteoporotic patients<sup>13</sup>.

It has been shown that strontium ranelate improves bone mass in an experimental model of osteopenia in rats. These histomorphometric data in estrogen-deficient rats suggest that strontium ranelate has an uncoupling effect between bone resorption and bone formation <sup>14</sup>.

Indeed, in vitro studies have shown that strontium ranelate inhibits osteoclast activity <sup>15</sup>, and stimulates osteoblast proliferation and collagen synthesis <sup>10</sup>. These findings raise the possibility that strontium ranelate may have beneficial effects on bone remodeling in large mammals by decreasing bone resorption while maintaining bone formation.

## Materials and methods:-

## Patient selection:-

The present study was carried out on 20 patients, seeking a periodontal treatment at Department of Oral medicine and Periodontology, Faculty of Dentistry, Mansoura University.

Periodontal health state was assessed for each patient clinically and radiographically.

## Inclusion criteria:-

The included patients in this study were:

- Free from any systemic disease and no history of using systemic antibiotics in the last three months.
- Dental history: No periodontal treatment for at least three months before starting the study.
- Non-alcoholic.

- Non-smoker.
- Between 25 to 45 years in age

## Exclusion criteria:-

The excluded patients from this study were:

- Have systemic disease that may influence the severity or progression of periodontitis such as HIV infection or diabetes mellitus type 1 &2.
- Receiving medications that may influence the periodontium (e.g., phenytoin, nifedipine, or non-steroidal antiinflammatory drugs)
- Received systemic administration or local application of antibiotics within the previous 6 months
- Pregnant or lactating female patients

## Study design:-

A randomized split-mouth study was be used in all patients suffering from periodontal disease with alveolar bone loss. After scalling and root planning, a surgical flap (full thickness flap) was be done and a mix of strontium ranelate (Protelos 2gm) with sterile saline will be delivered in one side untill the bone defect is filled, and the other side was subjected only to scalling and root planning and depridement of granulation tissue.

## Clinical measurements:-

Proper case history was obtained from each patient taking into consideration the history of the present chief complain , onset and duration of the patients periodontal manifestations as well as any past dental treatment . Each patient was thoroughly examined clinically to assess the gingival tissue health in terms of color, size, texture and contour. Patients were evaluated at the baseline and after 2 ,6 , 8 and 12 weeks . Clinical evaluation was performed using the following clinical parameters:

## Plaque index<sup>98</sup> (PI):-

This index was used to assess the thickness of plaque at the gingival area of the tooth .The evaluation or scoring was done on selected teeth (upper right 6, upper right 2, upper left 4, lower left 6, lower left 2, lower right 4) .The surfaces examined were the four gingival areas of the tooth: the distofacial, facial, mesiofacial and lingual/palatal surface. Mouth mirror, light source, periodontal probe and air drying of the teeth and gingival were used in the scoring of this index

Scoring criteria:

- 0- No plaque
- 1- A film of plaque adhering to the free gingival margin and adjacent area of the tooth .The plaque was recognized only by running a probe across the tooth surface
- 2- moderate accumulation of soft deposits within the gingival margin and/or adjacent tooth surface that could be seen by naked eye
- 3- Abundance of soft matter within the gingival pocket and /or on the gingival margin and adjacent tooth surface

## Gingival index<sup>99</sup> (GI):-

This index will be used to assess the severity of gingivitis and its location in four possible areas .The severity of gingivitis will scored on all surfaces of selected teeth (upper right 6, upper right 2, upper left 4, lower left 6, lower left 2, and lower right 4).

The surfaces will be examined are the four gingival areas of the tooth: the distofacial papilla, facial margin, mesiofacial papilla and entire lingual gingival margin .A periodontal probe will be used for recording the scores Scoring criteria:

- 0- No inflammation / normal
- 1- Mild inflammation / slight color change and edema, no bleeding elicited on probing
- 2- Moderate inflammation, redness, edema, bleeding on probing
- 3- Severe inflammation, marked redness and edema, ulceration, spontaneous bleeding

For each index, the score of the tooth will be obtained by adding the four scores per tooth and dividing it by four .The index score for the person will be obtained by adding the index scores per tooth and dividing it by the number of teeth examined.

## bleeding on probing index<sup>100</sup>(BOP):-

This index was used to assess both immediate evaluation of the patient's gingival condition and his motivation, based upon the actual bleeding tendency of the gingival papillae. A periodontal probe is inserted into the gingival sulcus at the base of the papilla on the mesial aspect, and then moved coronally to the papilla tip. This is repeated on the distal aspect of the papilla. The intensity of any bleeding is recorded as:

- 0- no bleeding;
- 1- A single discreet bleeding point;
- 2- Several isolated bleeding points or a single line of blood appears;
- 3- The interdental triangle fills with blood shortly after probing;
- 4- Profuse bleeding occurs after probing; blood flows immediately into the marginal sulcus.

## Probing Pocket Depth<sup>101</sup> (PPD):-

The evaluation was performed for teeth by Michigan (O) probe with Williams marking at (1, 2, 3, 5,7,8,9 and 10). Probing pocket depth (PPD) will be measured from gingival margin to the base of the pocket at six points (mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingual, distolingual) around each tooth. The mean probing depth will be obtained by all the measurements around the tooth and dividing by six. The mean probing depth of the patient will be obtained by totaling the mean probing depth of each tooth examined and dividing by the number of the teeth examined .

## Radioghraphic examination:-

Bone level for the tooth which was indicated in the surgery was measured by digital panoramic x-rays through image analysis programme as follow:

• Pre-operative bone defect (at baseline) [measured as the distance from contact point between the teeth to the base of intra-bony defect (IBD)].

• Postoperative bone fill (after 3 months) [measured by subtracting the preoperative bone defect from the distance between contact point between the teeth to the crest of the new bone level.].

## Informed concent:-

All patients were informed about the nature of the performed procedures. The patients were asked to read and sign an informed consent document which provide the patient with written information describing all aspects of the clinical trial and possible complications that might occur Fig(1).

Fig (1):- Consent from to surgical procedures.

Consent جراحية	to a Surgical Procedure إقرار موافقة لاجراء عملية ح
-I the undersigned hereby consent and	
, his assistants and team, to perform the Surgical Procedures:	
-The nature of the operation / has been ex me, and no warranty or guarantee has be to the results or cure.	<ul> <li>xplained to</li> <li>وقد تم شرح و توضيح طبيعة العملية / والإجراءات بالنسبة</li> <li>een made as</li> </ul>
Other risks of the procedures :	<ul> <li>مخاطر أخرى للاجراءات:</li> </ul>
I consent to the administration of genera conscious sedation, or local anesthesia a by my case. I understand that anesthesia and have been explained to me. -I authorize my physician / dentist and hi	s required من التخدير قد تصاحبه بعض المخاطر . و منبق شرحها لي . is team to do
any other additional procedures that his j may dictate during the course of the ope including the use of blood or blood prod needed in accordance with professional s -I have read and fully understand patient	لذ أى اجراءات اضافية تكون فى تقدير و لصالحى خلال العملية eration لا احتمال حاجتى لنقل الدم أو مشتقاته غند الحاجة وذلك طبقا hucts when standards. instructions
and have arranged for a responsible pers accompany me to and from the hospital -I also consent to any photography / vide	son to شخص مسئول لمرافقتي الى و من المستشفى otaping for
educational purposes as seen by my phy dentist. I also authorize the presence of during the surgical procedures.	Sician / Lyst ty the state is a second state of the second sta
Patient's Signature :	بع المريض :
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Physician :	

#### **Treatment procedures:-**

At the baseline, digital panoramic radiograph were be taken to access alveolar bone lost then all patients were be subjected to a full mouth supra and sub gingival scaling and root planning as basic full mouth treatment, using ultrasonic and hand instruments under local anesthesia Fig(2), one week later : Following adequate local anesthesia, buccal and lingual intrasulcular incisions were made using Bard-Parker blade no.15 Fig(3), and a full

thickness flap was reflected to expose the intrabony defects with care to preserve the interdental papilla Fig(4). After debridement of the osseous defects, the root surfaces were thoroughly scaled and root planed With Gracey curettes.



Fig (2):- full mouth scaling and root planning by using ultrasonic and hand instruments.



Fig (3):- buccal and palatal intrasulcular incisions were made.



Fig (4):- full thickness flap reflected to expose the intrabony defects with care to preserve the interdental papilla.

then strontium ranelate (Protelos 2gm) Fig(5), mixed with 4-6 drops of sterile saline to make putty form Fig(6), then carried by a spoon like an instrument to be placed into the defect site untill filled Fig(7), and condensed gently with a sterile smooth amalgam condenser. suturing is done by 0.3 of non resropable suture Fig(8).

The other side was be subjected only to SRP and depridement of granulation tissue.

The patients will be informed about oral hygiene instructions and motivation. After one week the stitches were be removed Patients were recalled for follow up and rescoring of all indices after 2, 6 and 8 weeks, and a digital panoramic radiographs were be taken again after 12 weeks for radiographic assessment.



Fig (5):- (Protelos 2g) sachet



Fig (6):- strontium ranelate (Protelos 2gm) mixed with 4-6 drops of sterile saline to make putty form.



Fig (7):- the mix of strontium ranelate and sterile saline placed into the defect site untill filled.



Fig (8):- suturing with 0.3 of non resorpable suture.

## Statistical analysis:-

Data management and statistical analysis were performed using Statistical Package for Social Sciences (SPSS) version 21.

Numerical data were summarized using means and standard deviations. Paired t test was done to assess the effect of treatment on different variables. Repeated measure analysis of variance was done to assess changes overtime in each side followed by pairwise comparisons by paired t test. Analysis was repeated by nonparametric methods to ensure robustness of results but presentation was done by parametric method only. All p-values are two-sided. P-values < 0.05 were considered significant.

## **Results:-**

## Effect of treatment on pocket depth:-

Comparing 2 sides :Mean Pocket depth before treatment was  $3.1\pm0.4$  on side A(applied side) and  $3.1\pm0.4$  on side B(control side) (p=0.743). Mean pocket depth level were comparable in both sides before treatment and all over time periods.

Table (1):- Mean and Standard deviation, paired t test for comparing pocket depth in both sides at different time points.

	Side A(n=20	Side A(n=20)		=20)	
Pocket Depth	Mean	SD	Mean	SD	P value
pre	3.1	0.4	3.1	0.4	0.743
2 weeks	2.8	0.3	2.8	0.3	0.936
6 weeks	2.1	0.3	2.2	0.3	0.211
8 weeks	1.5	0.2	2.0	0.3	< 0.001

SD: standard deviation, p<0.05 is considered significant

## Effect of treatment on Bleeding on probing:-

Comparing 2 sides: Mean Bleeding on probing before treatment was  $48.9\% \pm 14.6\%$  on side A and  $48.5\% \pm 15.2\%$  on side B (p=0.866). Mean Bleeding on probing were comparable in both sides before treatment and all over time periods.

Table (2):- Mean and Standard deviation, paired t test for comparing Bleeding on probing in both sides at different time points.

	Side A(n=20)		Side B(n=20)		
Bleeding on probing	Mean	SD	Mean	SD	P value
Pre	48.9%	14.6%	48.5%	15.2%	0.866
2 weeks	31.7%	11.4%	30.3%	11.2%	0.556
6 weeks	17.0%	4.7%	16.9%	4.6%	0.915
8 weeks	13.2%	4.1%	13.5%	4.2%	0.634

SD: standard deviation, p<0.05 is considered significant

## Effect of treatment on Plaque Index:-

Copmaring 2 sides: Mean Plaque Index before treatment was  $48.9\% \pm 21.7\%$  on side A and  $46.8\% \pm 21.1\%$  on side B (p=0.614). Mean Plaque Index were comparable in both sides before treatment and all over time periods.

Table (3):- Mean and Standard deviation, paired t test for comparing Plaque Index in both sides at diffe	erent time
points.	

	Side A(n=20	Side A(n=20)		20)	
Plaque Index	Mean	SD	Mean	SD	P value
Pre	48.9%	21.7%	46.8%	21.1%	0.614
2 weeks	34.1%	15.6%	32.9%	15.1%	0.718
6 weeks	14.8%	3.5%	15.1%	3.9%	0.689
8 weeks	11.6%	1.2%	12.0%	1.5%	0.083

SD: standard deviation, p<0.05 is considered significant

## Effect of treatment on gingival index:-

Comparing 2 sides: Mean Gingival Index before treatment was  $2.1\pm0.2$  on side A and the same value on side B (p=0.577). Mean Gingival Index level were comparable in both sides before treatment and all over time periods.

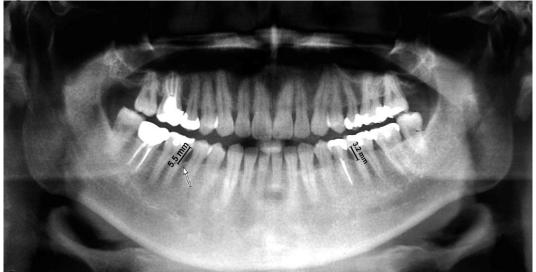
Table (10):- Mean and Standard deviation, paired t test for comparing Gingival Index in both sides at different time points.

	Side A(n=20)		Side B(n=20)		
Gingival Index	Mean	SD	Mean	SD	P value
Pre	2.1	0.2	2.1	0.2	0.577
2 weeks	1.28	0.18	1.26	0.17	0.772

6 weeks	1.1	0.2	1.1	0.2	0.577
8 weeks	1.06	0.11	1.04	0.09	0.285

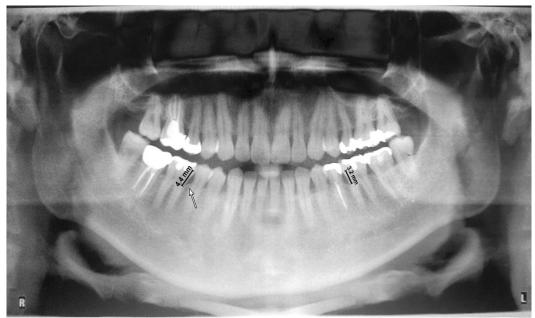
SD: standard deviation, p<0.05 is considered significant

#### **Radioghraphic results:-**



Fig(13): digital Panoramic x-ray has taken to the patient no:1 at the baseline showed; bone resorption in the both sides between the lower five and the lower six due to periodontal disease.
Pre-operative bone defect mesurement (at baseline):

Right side (applied side) : 5.5mm. Left side (control side) : 3.2mm.



**Fig(14):** digital panoramic x-ray for the patient no:1 after 12 weeks showed; increase in the height of the bone level 1.1 mm between the lower right five and the lower right six ( applied side ), while on the other side (control side)

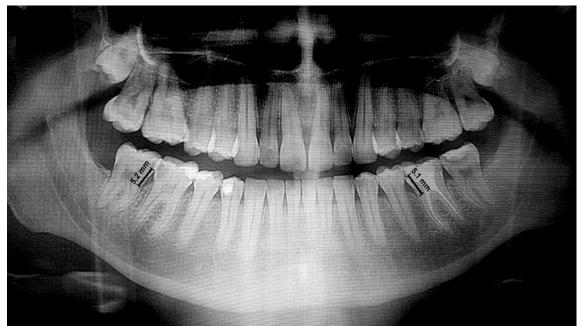
there was no increase in the bone level between the lower left five and the lower left six.

Postoperative bone fill mesurement (after 3 months):

Right side (applied side): 1.1mm

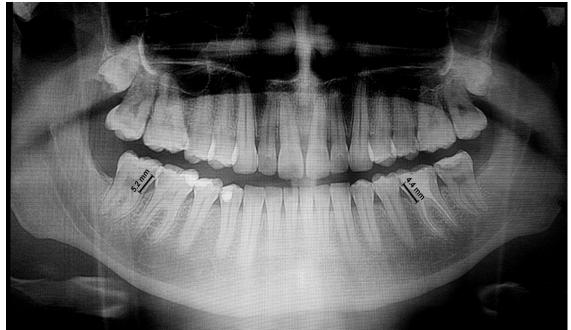
Left side (control side): 0.0 mm

all measurements on the digital panoramic x-rays were calculated by image analysis programme.



Fig(15): digital Panoramic x-ray has taken to the patient no:2 at the baseline showed; bone resorption between the lower right six and lower right seven and between the lower left five and the lower left six due to periodontal disease.

Pre-operative bone defect mesurement (at baseline): Right side (control side) : 5.2mm. Left side (applied side) : 5.1mm.



**Fig**(16): digital panoramic x-ray for the patient no:2 after 12 weeks showed; increase in the height of the bone level 0.7 mm between the lower left five and the lower left six ( applied side ), while on the other side (control side) there was no increase in the bone level between the lower right six and the lower right seven.

Postoperative bone fill mesurement (after 3 months):

Right side (control side): 0.0 mm

Left side (applied side): 0.7 mm

all measurements on the digital panoramic x-rays were calculated by image analysis programme.

## **Discussion:-**

There is growing evidence that strontium influences bone remodeling by affecting both bone resorption and bone formation. In vitro, strontium inhibits bone resorption<sup>8</sup>, and stimulates bone formation<sup>10</sup>.

In vivo, the administration of strontium at low concentrations inhibits bone resorption<sup>11,12</sup>, and stimulates bone formation, as evaluated by bone histomorphometry in osteoporotic patients<sup>13</sup>.

Studies on healthy animals confirm that strontium ranelate improves bone microarchitecture at both trabecular and cortical levels and preserves the structure of bone matrix crystals without affecting the mineralization process. These changes can possibly be attributed to the improvement in the biomechanical properties of bone<sup>17</sup>.

Therefore, the present study was designed to evaluate and asses the clinical efficacy of strontium ranelate (Protoles) when used as adjunct to scaling and root planning (SRP) in patients with bone loss due to periodontal disease. Also, comparing these results with conventional mechanical debridement alone in the same patients but on the other side of mouth (split mouth techneque)having also bone defect.

Subjects with an age range of 25 to 45 years were recruited in the study. Subjects had no periodontal treatment for at least three months before starting the study.

Subjects were excluded : subjects with a history of local and/or systemic antibiotic therapy within the last six months before baseline examination , Have systemic disease that may influence the severity or progression of periodontitis such as HIV infection or diabetes mellitus type 1 &2.

Receiving medications that may adversely influence the periodontium (e.g., phenytoin, nifedipine, or non-steroidal anti-inflammatory drugs).

In this study, subjects were evaluated clinically at the baseline, 2,6 and 8 weeks after treatment using different clinical parameters as ;

plaque index, gingival index, bleeding index, probing pocket depth .Furthermore the operative sites were also evaluated radiographicaly at the baseline and after 12 weeks .

The clinical results of the current study showed greater improvement in all clinical parameters especially those of the applied side comparing to control side.

Clinical results of probing depth revealed that; there was more improvement in the scores in the applied side than the control side and it was statistically significant.

Clinical results of plaque index (PI) of both groups revealed that; there was no statistically significant difference between mean change percent of applied and control sides.

Clinical results of gingival index (GI) revealed that; there was no statistically significant difference between mean change percent of applied and control sides.

Both the plaque and gingival indices remained satisfactory during the entire studying period, suggesting patients complied with oral hygiene instructions. The reduction in plaque and gingival scores could be due to SRP and proper oral hygiene maintains.

Clinical results of bleeding index revealed that ;there was no statistically significant difference between mean change percent of applied and control sides.

Study carried by J. BUEHLER,1 P. CHAPPUIS,2 J. L. SAFFAR,3 Y. TSOUDEROS,4 and A. VIGNERY, 2001<sup>18</sup>, showed that 6 months treatment with strontiumranelate (administerated orally by gavage) significantly reduces the indices of bone resorptionwhile maintaining those of bone formation in alveolar bone in normal adult monkeys.

The same study has revealed that strontiumranelate could decrease the number of osteoclasts ,suggesting that bone resorption was reduced. Other results obtained in vitro suggest that the inhibitory effect of strontium ranelate on bone resorptionis related to a direct effection osteoclast activity<sup>19</sup>.

Another study carried by **Pierre J. Marie and Monique Hott, et al**,1985<sup>20</sup>, showed that oral Stroniumranelate supplementation at the dose of 0.27% was shown to be effective in stimulating bone formation and bone density when administered for nine weeks in rats.

Low doses of Sr supplementation in drinking water were previously shown to increase parameters of bone formation in rats, and this effect resulted in a 10% increase in the trabecular calcified bone volume<sup>21</sup>. It also revealed that short-term treatment with oral Srtransiently reduces the osteoclasticactivity and that longer term Sr supplementation induces asignificant stimulation of bone formation and a positive trabecular bone balance<sup>21</sup>.

According to sudy carried by Marie PJ, Chabot G, Glorieux FH et al ,1985<sup>22</sup>, Stimulation of bone formation has also recently been documented in humans treated for six months with Sr at low dosage level."

In their study both static and dynamic parameters of bone formation wereincreased, but the relative short period of treatment did not allow a significant increase in the trabecular bone volume.

## **Conclusion:-**

In the present study the clinical and radiographic results obviously showed statistically significant and provides evidence that strontium ranelate can be succesfully used for management of alveolar bone loss assiociated with periodontal diseases.

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