The effect of topical application of Strontium Ranelate on induced bone defect's healing in Guinea pigs

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Abstract: This study was done to evaluate histological effect of topical application of Strontium Ranelate on induced bone defect's healing in Guinea pigs. Twelve male guinea pigs were used in this study and randomly divided into three equal groups based on their time of scarification at 2, 4 and 6 weeks post surgically. The animals were subjected to implantation of strontium ranelate (Servier Industries, France) in mandibular surgically induced bony cavity in the right side. Moreover, a second bony cavity of the same size was induced on the left side without application of (SrRan) to serve as control. All the specimens were examined for evaluation of the healing process of the jaw defects. The control histological sections revealed that healing of the bony cavities proceeded in a normal sequence of bone healing starting from 2 weeks to 6 weeks. There was gradual increase in the formation of bone trabeculae and decrease in the amount of granulation tissue. In the study groups, there was slower formation of bone than in the control group. It was proved that healing was slower or delay with SrRan.
[Mena Tamer Nassief Elsaieed, Hamdy Abdel-Megid Marzook, Wael Mohammed Said Ahmed Mohamed Abd Elrahman Mohamed. **The effect of topical application of Strontium Ranelate on induced bone defect's healing in Guinea pigs.** *J Am Sci* 2017;13(8):17-23]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org. 3. doi:10.7537/marsjas130817.03.

Keywords: effect; topical application; Strontium; Ranelate; bone; Guinea pigs

1. Introduction

Filling of bone defect with normal bone is representing a challenge in dentistry. Local loss of bone tissue can be derived from several causes such as dental extraction, fractures, infection and bone metastasis. Several factor can affect the filling of bone defect with bone which include presence of concomitant diseases, the individual age, nutrition and status of hormone.(1)

Bone defect healing is multiphase process start with phase of bleeding and inflammation then to the second phase which is the formation of the woven bone which undergo remodeling by ostoclast followed by the replacing it by the lamellar bon by osteoblast.(2)

Bone Grafting is highly recommended in case of extensive bone loss especially in individual with systemic bone disease as osteoporosis to insure well being and life quality, traditional approaches, such as bone graft and the insertion of scaffolds of osteoinductive biomaterials might have an advantageous alternatives which is the local or systemic administration of anabolic or anticatabolic drugs, growth factors and mesenchymal stem cells.(3-6)

Promoting of bone defect healing in osteoporotic patient by the anabolic or anticatabolic drugs administration commonly used to increase bone formation and inhibit bone resorption, Strontium ranelate (SrRan), has the double benefits so it attract the interest in investigation looking for improvement of bone defect healing In several study on animal model has been reported the dual effect of SR, where it has been approved that SR prevent bone loss by increase bone formation and inhibit bone resorption.(7-11)

SrRan has been shown to have dual effect on the bone by reducing bone resorption by inhibition of osteoclasts and increasing bone formation by stimulation of osteoblasts,(12-14)SrRan stimulates the proliferation and differentiation of osteoplastic cells and inhibits the activity and differentiation of osteoclasts, thereby enhancing matrix deposition and ultimately new bone formation.(15-22)

Strontium ranelate is shown a distinct advantage compared to bisphosphonates as its treatment not associated with osteonecrosis of the jaw (ONJ).(23)

Recent studies on healthy animals have reported that systemic oral administration of SrRan improves the bone volume and strength.(24, 25) however the systemic treatment with SrRan might show the occurrence of some side effects such as headache, nausea, diarrhea and in rare cases, cutaneous hypersensitivity.(26)

Developing of systems for local administration and topical application of strontium to overcome the

adverse systemic effects and achieve acceleration and increasing of bone healing by The positive effects of SrRan on bone homeostasis may be an important indicator of success in relation to decreasing the healing periods associated with bone defect.[27]

2. Materials and methods

Twelve adult guinea pigs with an average weight of 350-500 gm. were used in this study. All animals were kept under the same nutritional and environmental conditions. Each animal was subjected to implantation of strontium ranelate (SrRan) granules (Servier Industries, France) in surgically induced bony cavity in the right side of the submental area of the mandible. Moreover, a second bony cavity of the same size was induced on the left side without application of (SrRan) granules to serve as control.

After operation the animals were transferred to their cages for daily observation till complete recovery.

At 2, 4, and 6 weeks, the animals of all groups were sacrificed and divided equally among groups A, B, and C respectively.

After sacrificing the animals, their mandibles were separated for preparation of paraffin blocks and histological evaluation.

3. Histological results

The control group (left Cavity):

The histological sections revealed that healing of the bony cavities proceeded in a normal sequence of bone healing starting from 2 weeks and completed at 6 weeks.

At 2 weeks postsurgically the bony cavities were found to be filled with granulation tissue and newly formed bony trabeculae**.** From 2 to 6 weeks there was gradual increase in number and size of the newly formed bony trabeculae with widening of narrow spaces, and appearance of resting lines in between bone lamellae. The amount of granulation tissue gradually decreased.

The study group (rightcavity):

The results of the present study at 2 weeks showed a cavity wound with an empty space and a condensation of granulation tissue at the cavity opening. At 4 weeks the experimental sections informed that bridge of bone at wound opening, granulation tissue seen at cavity center. At 6 weeks the experimental sections showed appearance of heavy condensation of granulation tissue with thin bone trabecule could be seen.

4. Discussion

Bone tissue regeneration and bone defect healing still represent a significant challenge in the dentistry especially with large cavity that exceeds the critical size which cannot heal normally by regeneration. Recent studies tried to enhance the bone formation and overcome the limitation of bone graft material by using anabolic agent that accelerate bone healing.[28]

Strontium (SR) in human biology and pathology has less attention than calcium and magnesium, and for many years it did not have clinical interest. Although this is still true, there is an growing knowledge of the biological effect of SR after the releasing of the drug strontium ranelate, which has recently been reported to decrease risk of fractures in osteoporotic patients.[19]

At the last decade, several studies have revealed that strontium as a stable element shows positive effects on bone formation and resorption and enhances trabecular bone mass when administrated in animals, without inducing deleterious effect on bone mineralization.[29, 30]

There are growing evidences that strontium controls bone remodeling by affecting both bone formation and bone resorption. In vitro, strontium reduces bone resorption,[8] and induces bone formation,[31] In vivo, low concentration strontium administration decreases bone resorption,[32] and increases bone formation, as evaluated by bone histomorphometry in[33, 34] osteoporotic patients.[18]

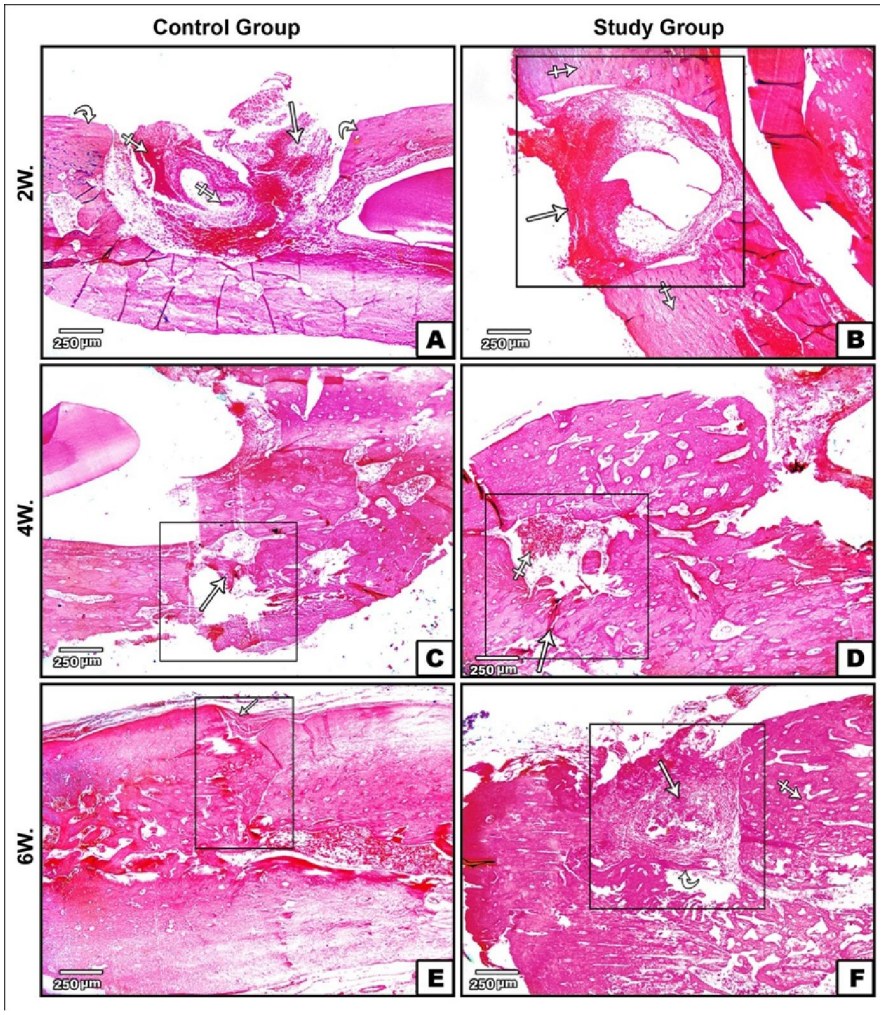
The great effect of SrRan on bone fracture healing according to several studies made by **Aslam et al,**[35], **Neves et al,**[36] and **Tan et al,**[37] who has approved the benifacial effect of SrRan in promoting the bone healing. Not only promoting effect but SrRan has a dual effect on bone inducing bone formation and reducing of bone resorption.[38, 39]

Although, the previously mentioned marvelous effect of SrRan on bone healing but there are rapidly growing evidence about the side effect of systemic administration of the SrRan which include:[40, 41]venous thromboembolism:[42] gastrointestinal disturbance,[43] DRESS[44, 45] and Rarely memory loss.[46]

To overcome the systemic side effect several studies has been demonstrated to use local delivary system in order to achieve maximum benefit of SrRan without its systemic side effect,[47]**Tian et al,** studied the effect of titanium implant coated with SR on osseointegration which reported that SR enhances the osseointegration between bone and implant interface.[48, 49] also **Baier et al,** conclude that strontium based calcium phosphate cement accelerate the implant osseointegration in osteoprotic patient,[50] In present study in order to overcame systemic drawbacks and to make topical application is more easier and simple we used SrRan granules which may be more control in application.

In dentistry, the study of pharmaceutical drugs that flavor bone healing and regeneration is a vital

importance,[51] in the present study the dual effect of strontium ranelate on bone healing was evaluated on bone defect in normal guinea pigs mandible.



A: The wound cavity filled with granulation tissue (arrow) interspersed with small fragment of new bone pieces (crossedarrows) border of old bone (curvedarrows). **B**: cavity wound with an empty space and a condensation of granulation tissue at cavity opening (arrow) old mature bone (crossedarrow) **C**: Partial closure of the cavity with bone trabecule (arrow). **D**: Bridge of bone at wound opening (arrow) granulation tissue seen at cavity center (crossed arrow). **E**: complete obliteration of the wound cavity arrow refers to opening of the wound. **F**: heavy condensation of granulation tissue (arrow) with thin bone tarbecule (curved arrow).

In the present study we use the guinea pigs to serve as animal models duo to the similarity in the histological and hematological reaction in evaluation of bone formation according to **Skoloudik's** study who chosen guinea pigs to evaluate effect of transplanted mesenchymal stromal cells in the treatment of postoperative temporal bone defect,[52] also **Jang et al,** used guinea pigs to assess the role of bioactive glass as a bone graft materials.[53]

Duo to the clinical importance of critical size defect in testing of biomaterials, Standardized 5mm bone defects were created bilateral to the midline at submental area in this study to see the difference in the bone defect repair between the groups received the strontium ranelate and control groups.[54, 55]

According the study done by **Passeri et al,** which reported that bone healing includes fibrous connective tissue and the immature bone and so it was easily to evaluate the effect of stratiumranelate on healing process so we made histological evaluation after 2, 4 and 6 weeks as the best tissue quality could be evaluated within the shortest time period assuming that the bone will be remodeled throughout animal life.[56]

In this study, the histological findings on control group A, normal bone healing sequence was observed.

Starting with condensed granulation tissue filling the cavity with discrete areas of new bone formation in the osseous defect. These results are in accordance with the study done by **Tawfik and El–Hawary** in the detection of effect of OSTEON II in healing of induced bony cavity in guinea pigs, they noticed formation of wide area of granulation tissue in their control group after 2 weeks.(57)

On the other hand, the study group A showed a cavity wound with an empty space and a condensation of granulation tissue at the cavity opening. These results correlate with previous study made by **Basu et al,** who reported that this was no significance difference between SrRan treated and non SrRan treated groups when he evaluate the formation of bone tubercular bone inside the cavity after 2 week.(58)

In contradict with the **Lourenço et al**, who studied the effect of different injectable hybrid system for strontium local delivery in enhancement of bone repair in rat critical size defect, his study reported that there are major significance difference between the histological evaluation as seen higher cell invasion was observed at the sr-hybrid group than the other groups at 15 days.(59)

After 4 week, the histological findings of control group B reported partial closure of the cavity wound with bone trabecule. This agrees with **Louis's et al,** study while he was studying the effect of non-selective and selective cyclooxygenase-2 non-steroidal anti-inflammatory drugs, he reported that bone healing is highly significant in control group in comparison to study group.(60)

According to **Tian et al,** who study the effect of porous strontium-doped calcium polyphosphate scaffolds as a bone substitute, they noticed that after 4 weeks there was highly signeficent difference with strontium group duo to active bone formation, which was evident by large number of osteoblasts and osteocytes.(61)

Also the results of the study made by **li et al,** which reported that filling of the fracture gaps and endochondral ossification lead to bone regeneration showed greater and denser newly forming trabeculae than the nontreated OVX animals.(62) in contradict to this result the histological outcome of study group B informed that bone bridge formation at wound opening and granulation tissue seen at cavity center, this result is agreed with **Cebesoy et al,** who studied effect of strontium ranelate on fracture healing in rat tibia that reported no significant differences in callus formation or bone union could be demonstrated between the strontium group and the control group radiologically while in histopathology it was seen the fractures healed normally in both group with no significant difference during the first 4 weeks after the fracture.(63)

After 6 week, the histological finding on control group C showed complete obliteration of the wound cavity with mature bone trabecule. However, the histological results of study subgroup C showed showing heavy condensation of granulation tissue this resut is agreed with study made by **Mohamed et al**, who found that the treatment with strontium ranelate may interfere with the mineralization process as through the tasted blood parameter showed no significant difference in serum level of calcium and phosphate at 1,3,6 weeks while there were high statistical significance difference of serum alkaline phosphatase and osteocalcin between treated group with strontium and control group with droping lower of serum ALP so he conclude that strontium ranelate has slow action onest on the bone marker and also that strontium ranelate might delay bone formation during the early stage of fracture healing with bone gab.(54)

In contrast to our study result, **Thormann et al,** studided the effect the strontium modified calcium phosphate bone cement on bone formation, he reported that there was higher significance difference in bone formation between experimental and control group.(64)

Conclusion

Healing of the induced jaw osseus defects in guinea pigswas delayed with topical application of Stranotium Ranelate

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8/1/2017