Comparison between Simvastatin and Allantoin in Bone Formation after Surgical Extraction of Mandibular Third Molars

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Abstract:

Objective: To compare the efficacy of two materials on bone formation after surgical removal of mandibular third molars. **Materials and Methods:** A prospective study was done on thirty patients requiring all mandibular molar extractions in Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Mansoura University, Egypt. Patients were selected based on inclusion and exclusion criteria. The procedure was performed under local anesthesia (lignocaine 2% with epinephrine 1:100,000. Mandibular molars were extracted carefully, with minimal soft tissue reflection and without causing any damage to the underlying alveolar bone. The socket was then gently irrigated with normal saline and hemostasis was achieved. Immediately after the extraction, a gelfoam mixed with simvastatin (20 mg simvistatin mixed with normal saline) was placed in the extraction sockets of simvistatin group, a gelfoam mixed with allantoin (20 mg melatonin mixed with normal saline) will be placed in extraction sockets of allantoin group. Afterwards, the sockets were closed with 3-0 vicryl to prevent the carrier from getting displaced and immediate post-operative IOPA was taken for extraction sites. **Results:** Highest values of bone density were related to simvastatin followed by allantoin. Pain was normal in both simvastatin and allantoin groups but, severe pain was recorded in some cases of control group. Soft tissue healing was better with allantoin and simvastatin than in control group. **Conclusion:** The two materials are capable of enhancing bone regeneration in the site of extraction.

Introduction

The most widely performed dental procedure is tooth extraction. After the extraction, a remodeling process starts and dimensional changes happen for the bone vertically and horizontally as well as soft tissue volume. Studies in canine model 1 have demonstrated presence of dimensional changes in the bone at extraction site in the first 2–3 months after extraction.[1]

There are a lot of types of biomaterials that can be used for bone regeneration techniques including: autografts with osteogenic capacity; allografts and xenografts, deproteinized mineral materials; alloplastic grafts, natural and synthetic polymers that are osteoconductive.[2]

Fresh bone creation is a process including making of new bone matrix by osteoblasts and its following mineralization. In the procedure of bone formation, plentiful osteo inductive factors like bone morphogenetic proteins (BMPs) show significant role in the growth and diversity of osteoblasts. BMP-2 differentiates multipotent stem cell line into osteoblast-like cells.[3]

Statins work by reversibly inhibiting HMG-CoA reductase through side chains that bind to the enzyme's active site and block the substrate–product transition state of the enzyme. Over the past decade, animal studies have shown their anabolic effect on bone. Simvastatin stimulates BMP-2 and nitric oxide formation and regional bone formation in rat mandible models. Simvastatin increases mRNA expression for BMP-2, vascular endothelial growth factor (VEGF), alkaline phosphatase, type 1 collagen, bone sialoprotien and osteocalcin in MC3T3-E1 cells.[4]

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Actions, amid them: wound healing, anti-irritating, hydrating, improving the cell mitosis; as well as promoter of epithelial creation, analgesic action, and keratolytic activity. So, the allantoin has been applied in cosmetic and pharmaceutical preparations for more than 66 years with dissimilar therapeutic purposes and particularly as a wound healing supporter. Nevertheless, there are no data that support these pharmaco-dynamic actions and the allantoin mechanism of action is still mysterious.[5]

In this study we compared the effect of two material, simvastatin and allantoin in bone formation after extraction of mandibuilar third molars.

Materials and Methods:

A prospective study was done on thirty patients requiring all mandibular molar extractions in Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Mansoura University, Egypt. Patients were selected based on inclusion and exclusion criteria.

The procedure will be performed under local anesthesia (lignocaine 2% with epinephrine 1:100,000. Mandibular molars were be extracted carefully, with minimal soft tissue reflection and without causing any damage to the underlying alveolar bone. The socket was then gently irrigated with normal saline and hemostasis will be achieved.

The patients were randomly divided into three groups, each comprised 10 patients:

1. Group I (negative group): After extraction, no material was packed in the socket.
2. Group II (simvistatin group): After extraction, the extraction socket was packed with collagen cone soacked with simvistatin.
3. Group III (allantoin group): After extraction, the socket was packed with collagen cone soaked with allantoin.

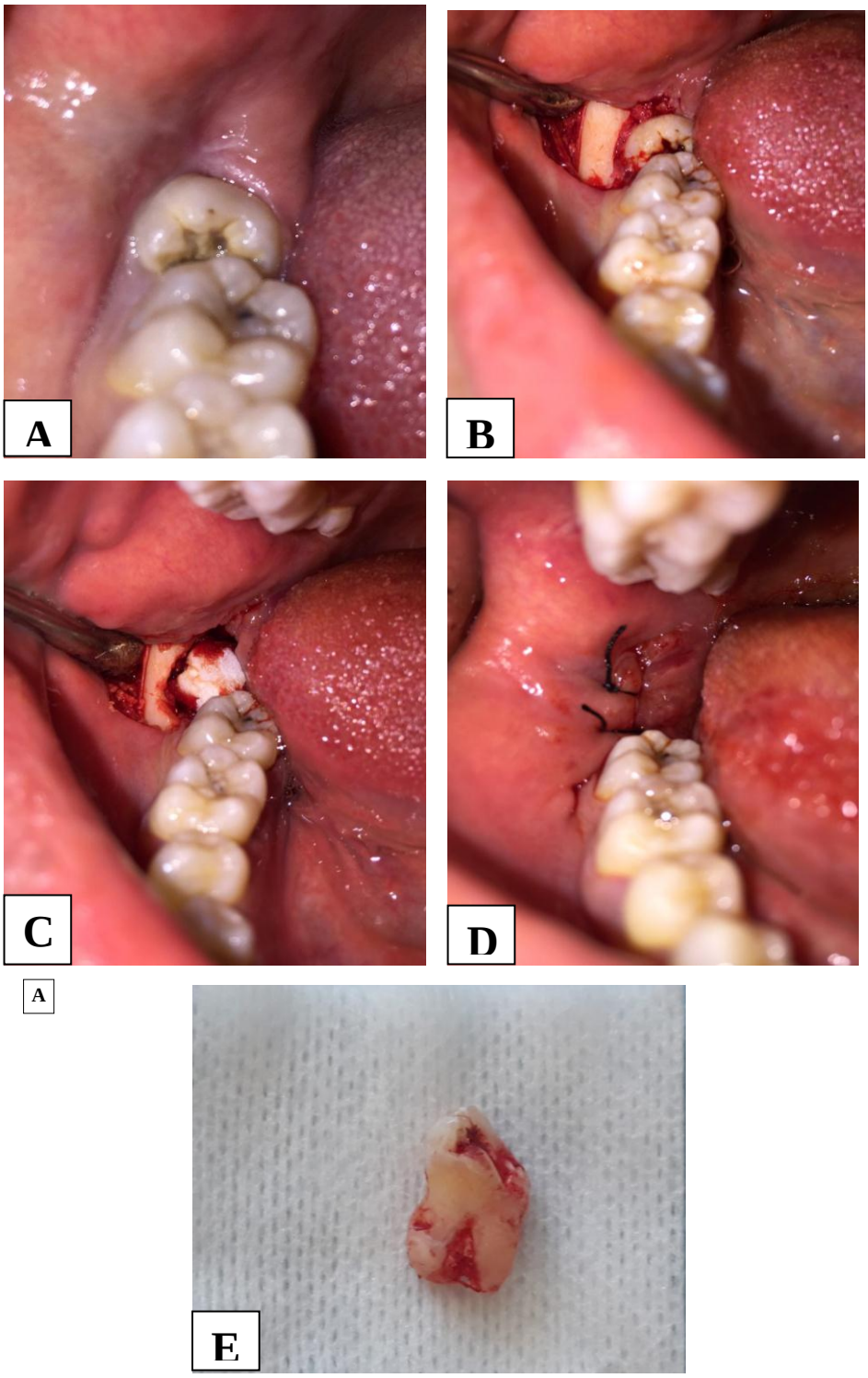

Figure 1: Preoperative photo showing mesioangular impaction of mandibular third molar (A), Full thickness mucoperiosteal flap raised (B), Tooth is removed and the socket is packed with gel foam (C), Socket soft tissue margins are sutured (D), Extracted wisdom tooth (E).

Preparation of simvistatin and allantoin: Simvistatin and allantoin powder was prepared in mash premiere for pharmaceutical industry and weighed as 20 mg for each application filled in capsules.

Clinical evaluation:

Pain: Pain was measured with visual analogue scale (VAS). Patients were asked to fill the record after seven days.

Soft tissue healing: The healing index of Landry et al 6 was used after one week to assess soft tissue healing after one week.

Radiographic evaluation: To assess bone formation capability in three groups using digital software program "Adobe Photoshop version 7.0" that widens the standard intra-oral periapical radiograph with better firmness. A specific area is designated on the intra-oral periapical film

which included the deficiency. The mean value of that particular area is noted and compared Figures (1-3).

Results:

The following factors were evaluated for all patients included in this study:

Pain: The pain level in allantoin group and simvastatin group was normal and regularly decreased postoperatively to the seventh day without severe pain in any case but, in control group severe pain was noticed in 8 cases and it was statistically significant (P<0.001), Table 1.

Soft tissue healing: Regarding the soft tissue healing, no statistical significance was found between simvastatin group and allantoin group, with normal healing at the seventh day, although poor soft tissue healing was observed at seventh day in control group with high statistical significant difference (P<0.001), Table 2.

Table 1: Comparison between the three groups according to pain

Postoperative pain	Control (n = 10)		Allantoin (n = 10)		Simvistatin (n = 10)		χ^2	MC_p
	No.	%	No.	%	No.	%		
Slight pain	1^a	10.0	0^a	0.0	0^a	0.0		
Mild pain	4^a	40.0	4^a	40.0	6^a	60.0		
Moderate pain	1^a	10.0	6^b	60.0	4^b	40.0	24.141*	<0.001*
Severe pain	4^a	40.0	0^b	0.0	0^b	0.0		

Table 1: Comparison between the three groups according to soft tissue healing

Soft tissue healing index and healing	Control (n = 10)		Allantoin (n = 10)		Simvistatin (n = 10)		χ^2	MC_p
	No.	%	No.	%	No.	%		
Poor	3^a	30.0	0^b	0.0	0^b	0.0		
Good	4^a	40.0	5^a	50.0	1^b	10.0		
Very good	2^a	20.0	5^b	50.0	7^b	70.0	24.354*	<0.001*
Excellent	1^{ab}	10.0	0^b	0.0	2^a	20.0		

Bone Formation: The mean values of gray level histogram at post-operative day 1 was 65.5 with a minimum and maximum of 46.3 and 84.5, respectively in control group, whereas, 65.8 was the mean value with minimum and maximum of 49.1 and 82.5 in the allantoin group. No Significant differences were observed between the control and allantoin groups, 71.5 was the mean value with minimum and maximum of 55 and 87 in simvastatin group. Significant differences were observed between control group and simvastatin group

After one month, the mean values of gray level histogram were 71.3 with a minimum and maximum of 61.3 and 91.5, respectively in control group, whereas, 83.3 was the mean value with minimum and maximum of 68.0 and 98.5 in the allantoin group. Significant difference was observed between control group and allantoin group. 89.3 was the mean value with minimum and maximum of 74.3 and 104.2 in simvastatin group. Significant differences were observed between the control and simvistatin group, when analysed by paired‘t’ test, with‘t’ value of 2.06 and probability of 0.047.

After three months, the mean value of gray level histogram at post-operative stage was 104.7 with a minimum and maximum of 92.3 and 117.1, respectively in the control group. The mean value was 110 with minimum and maximum of 95.2 and 124.8 in allantoin group. Significant difference was found between control group and allantoin group whereas the mean value was 130 with minimum and maximum of 105.6 and 154.4 respectively. Highly significant differences were observed between the control and the simvistatin groups.

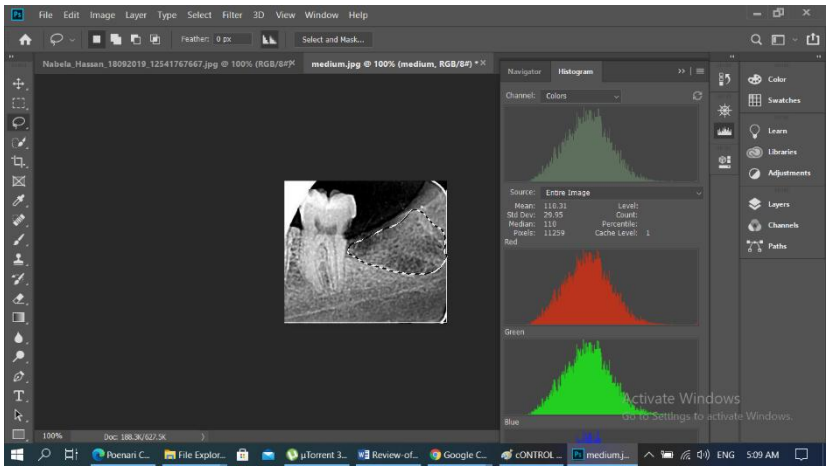

Figure (1): Analysis of Bone density immediately after extraction

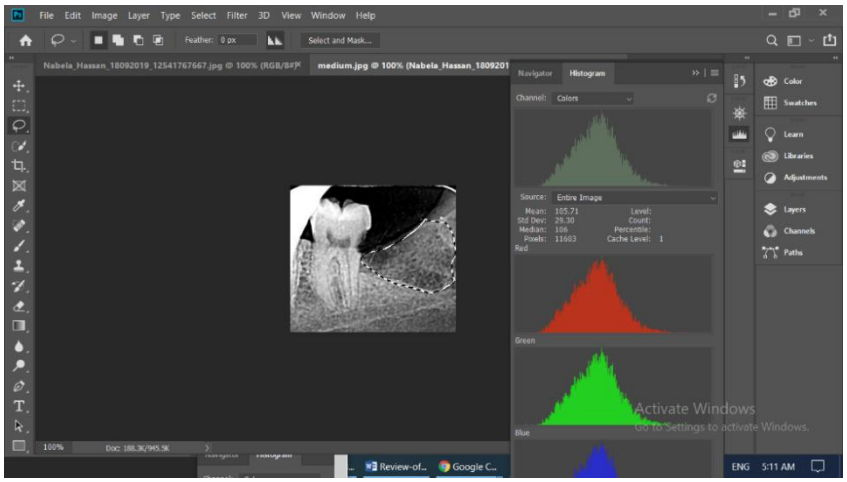

Figure (2): Bone density one month after surgery

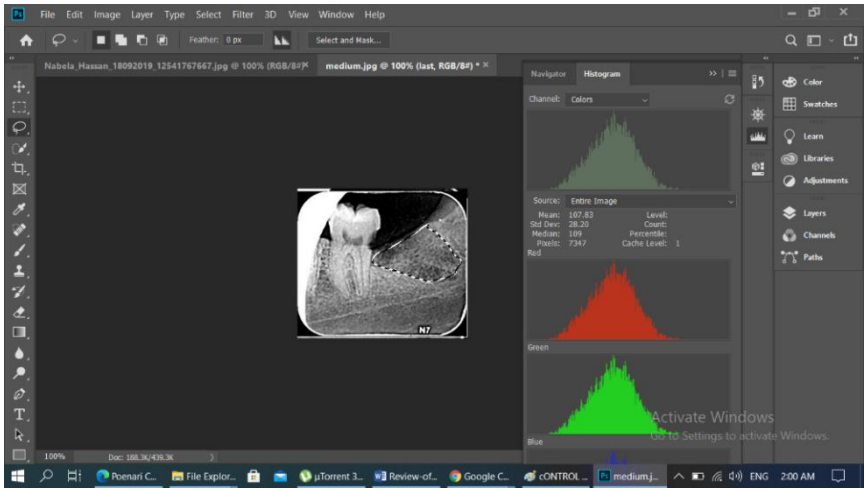

Figure (3): Bone density three months after surgery

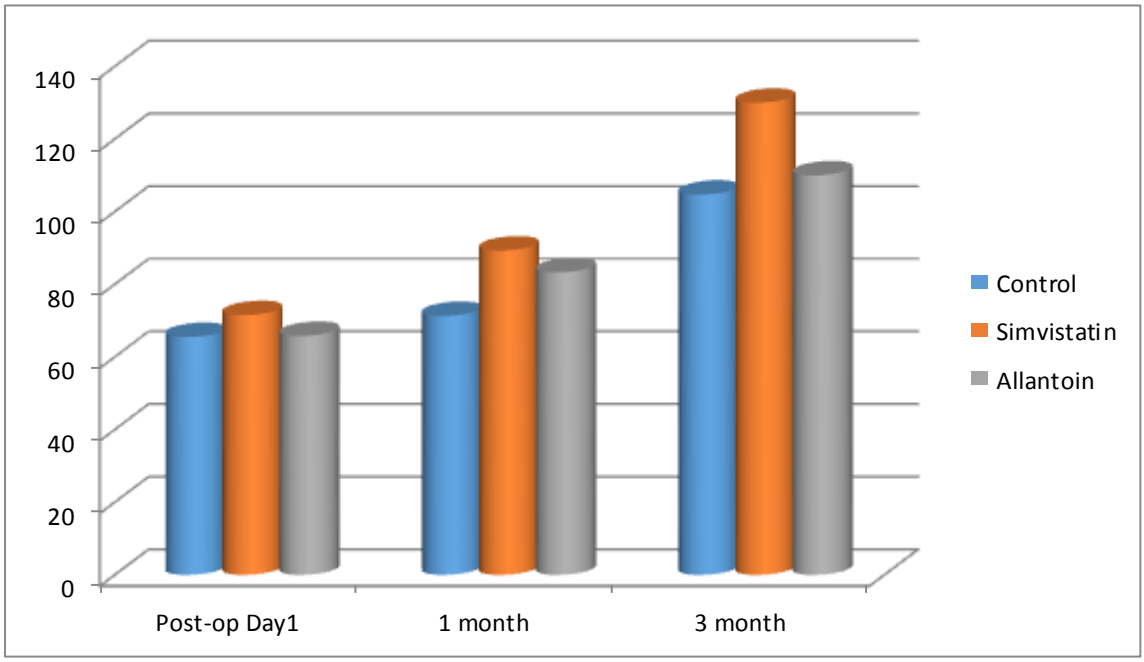

Figure (4): Comparison between the three groups according to bone formation

Discussion:

Various materials are used in modern dental and maxillofacial surgery for bone tissue substitution and reconstruction. All osteoplastic materials can be divided into four groups by origin: autogenic (the donor is the patient), allogenic (the donor is another person), xenogenic (the donor is an animal) and synthetic (based on calcium salts). Success achieved in the development of xenogenic and synthetic biomaterials which possess osteoconductive and osteoinductive properties, allow a decrease in the use of auto- and allo-transplantation methods that have certain disadvantages.[7] The demand for an ideal nonautogenous bone grafting material is increasing due to its unlimited supply, easy storage, and sterility.[8]

Synthetic bone replacements (alloplasts) are osteoconductive - that is, they provide a scaffold for bone deposition—as opposed to osteoinductive materials such as autografts, which may include growth factors necessary for osteogenesis. Commercially available synthetic bone replacements have been made of hydroxyapatite, tricalcium phosphate, calcium sulfate, and combinations of these minerals, and fabrication techniques, crystal configurations, pore dimensions, mechanical properties, and resorption rates vary.[9]

There are a variety of bone augmentation techniques using one or more of the following bone fillers: bioactive glass with calcium sulfate (BG/CS), freeze dried bone allograft (FDBA), magnesium-enriched hydroxyapatite, organic cancellous porcine bone xenograft (CPB), and calcium sulfate (CS).

Our findings are supported by Maciel-Oliveira et al.[10] and Griffiths and Cartmell.[11] In their study, they suggest that simvastatin stimulates bone regeneration when it is locally administered into defects created in the rat alveolar process. As the ultrastructural and immunocytochemical observations have shown, bone formation started earlier in the simvastatin-treated rats than in the controls. Additionally, the laid down matrix presented a lamellar appearance.

Our study also is in accordance with Ayukawa et al.[12]. In their study they demonstrated the effect of the local administration of simvastatin on the healing of artificially created bone defects. In the histologic and histomorphometric study, local application of simvastatin successfully increased the bone regeneration.

We decided to study the effect of another promoting drug in terms of bone formation –allantoin- which was prepared as powder and carried on a gel foam carrier. Our findings were less markable increase in bone formation than simvastatin.

Conclusion:

Simvstatin has the best effect in bone formation after surgical extraction of mandibular third molars followed by allantoin.

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