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Histological and Histomorphometric illustration the endochondral ossification of the mandibular angle defect repair in rats after oral stimulation with bisphosphonate treatment (an in vivo study)

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Abstract

Background: Bio-phosphonates can be used to lower the risk of hip and spine fractures. Additionally, they can be used to treat Paget's disease of the bones in a variety of dosages. In the procedure that replace hyaline cartilage to bone, this procedure i.e. called endochondral ossification. It starts when mesenchymal cells from the mesoderm develop into chondrocytes. Chondrocytes multiply quickly and release an extracellular matrix to create the cartilage that serves as the model for bone.

Objective: To histomorphometric illustration the endochondral ossification of the mandibular angle defect repair in rats after- oral stimulation with bisphosphonate treatment.

Patients and Methods: 20 rats were used in this work and the animals were divided into the following groups: 10 Rats from the control group. The bone defect was healed naturally without medicament and 10 rats were used in the experiment, and taking the biophosphonate medication helped mend the bone defect. Every single group was studied in 7 and 14 day (5 rats for each healing period) and the surgical procedure was performed for histological and Histomorphometrically examination. The data analysis with spss statistic measure & with P vale ($P \leq 0.05$).

Results: Active effect of the bio-phosphate medicament in the endochondral ossification and the cell that responsible for the cartilage formation and accelerated the healing of the mandibular defect with inhibition of the bone resoption and finally decrease the time that need to full healing.

Conclusion: The chemical medicament that represented by bio-phosphonate accelerated the endochondral ossification in a short time and replacement with bone in the site of the defect.

Keywords: Bio-phosphonates, Cartilage, Chondrocytes, endochondral ossification.

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Introduction

One of the two crucial processes during fetal development of the mammalian skeletal system through which bone tissue is formed is endochondral ossification. Callus, is a type of cartilage that frequently develops during fracture repair, Through the process of endochondral ossification, this cartilage eventually transforms into new bone tissue. Recent research has demonstrated that biomimetic bone, such as apatite, suppresses bone formation by hyper-stimulating the extracellular calcium detecting receptors (CaSR) [1]. In this procedure, hyaline cartilage is switched out for bone. Beginning with the differentiation of mesenchymal cells coming from mesoderm into chondrocytes. To create the cartilage that serves as the model for bone, chondrocytes multiply quickly and release an extracellular matrix [2].

Bone has a highly specialized and intricate structure and function [3]. The hard compartment of the skull, which is well known for its pliability, hardness, and capacity to provide protection to the underlying tissues [4], protects and supports the soft compartment of the skull, which is composed of highly active, mineralized, and vascular connective tissue Figure (1) [5].

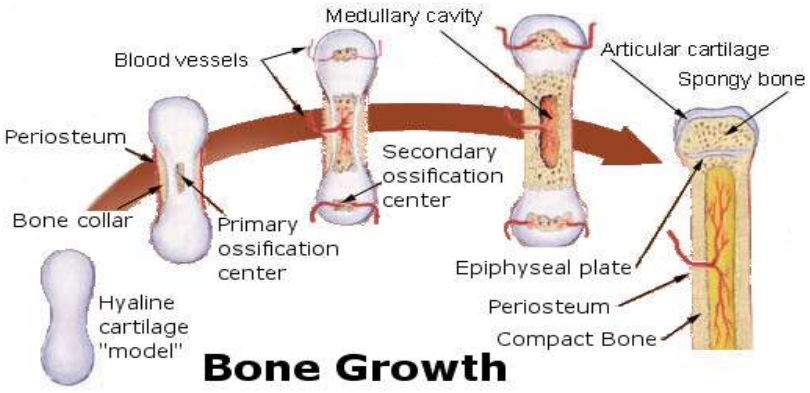

Figure (1): Endochondral ossification [5].

Bone's composite composition gives it special mechanical properties. An organic matrix (mostly Type I collagen) and a mineral matrix (hydroxyapatite crystals embedded in collagen fibers) are the two primary building blocks of bone. The organic matrix is primarily responsible for bone toughness and plastic deformation, despite the fact that the mineral component of bones contributes significantly to bone strength [6]. Multiple anatomical, biomechanical, and biochemical systems work in concert to heal bones. In contrast to many other tissues, skeletal healing may completely restore the biochemical and mechanical characteristics of the wounded tissue[7]. The healing process of bone injuries included the healing of soft and hard tissues. The chemical medicament is widely used in the healing of different wounds topically and systematically [3].

A group of medications known as bisphosphonates is used to treat osteoporosis and related conditions because they end the loss of bone density. They are the medications for osteoporosis that are most

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frequently administered [8]. Because they contain two phosphonate (PO(OH)2) groups, they are known as bisphosphonates. Diphosphonates (bis- or di- + phosphonate) is another name for them. According to the evidence, they lower the risk of fracture in post-menopausal women who have osteoporosis [9],[10],[11]. Bone resorption can be effectively inhibited by bisphosphonates. Alendronate, Etidronate, Pamidronate, Ibandronate, Risedronate, Clodronate, Tiludronate, and Zoledronate are among the medications in this family that can be used either as free acids or as sodium salts. In addition to treating hypercalcemia of malignancy and Paget's disease of the bones, they are widely employed in the treatment and prevention of bone loss caused by glucocorticoid medication, post-menopausal estrogen loss, or malignant illness. The medications are pyrophosphate analogs, which have been demonstrated to limit calcium phosphate dissolution in vitro but not in vivo over a long period of time Fleisch (2002)[12].

For a long time, the molecular basis of how bisphosphonates work was poorly known (Figure 2) [13]. Etidronate and clodronate, the first researched bisphosphonate compounds, were later shown to produce lethal non-hydrolyzable analogs of adenosine triphosphate (ATP) that interfere with ATP-dependent intracellular functions. These substances may have interfered with mitochondrial ATP translocases, which is why osteoclast cells died following therapy. [14].The more powerful compounds, which are nitrogen-containing bisphosphonates, are not converted to ATP analogs. Instead, they work to impede the mevalonate/cholesterol biosynthesis pathway enzyme farnesyl pyrophosphate synthase (FPPS). Farnesyl diphosphate and geranyl geranyl diphosphate, in particular, are not biosynthesized when FPPS is inhibited[16],[15].

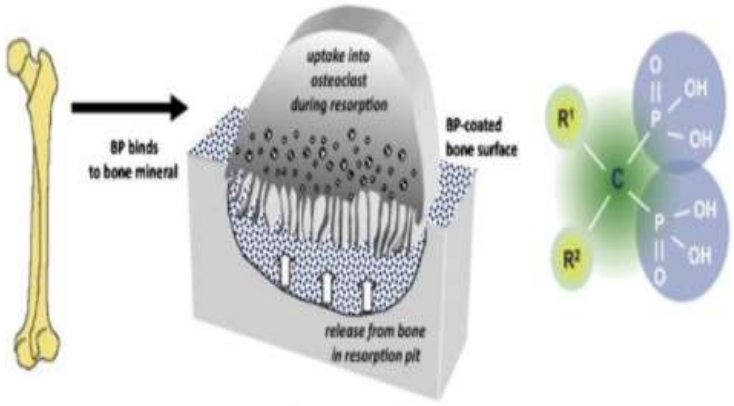

Figure (2): Work of bisphosphonate[13].

Osteoblasts build bone, and osteoclasts break it down, keeping bone tissue constantly remodeling and in balance (homeostasis). By inducing osteoclasts to go through apoptosis, or cell death, bisphosphonates slow down bone loss by preventing the digestion of bone. The uses of bisphosphonates include the prevention and treatment of osteoporosis, Paget's disease of bone, bone metastasis (with or without hypercalcemia), multiple myeloma, primary hyperparathyroidism, osteogenesis imperfecta, fibrous dysplasia,

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and other conditions that exhibit bone fragility [17].

The mandible is a complicated structure in terms of its makeup, place in developmental history, and purpose. The ramus, the coronoid, the condylar and angular processes, and the alveolar components—where the teeth erupt—are among the anatomical units that make up this structure[18].

The presence of bony trabeculae wrapped in a cartilaginous cap can be used to assess the angle of the mandible, which histologically contains the protein osteocalcin (OC). Histologically, OC should be distinguished from osteoma, which is made up of hard, dense, and compact lamellar bone, benign osteoblastoma, which is made up of well-vascularized connective tissue stroma and widely dilated capillaries and actively produces osteoid and woven bone, chondroma, which is made up of lobules of hyaline cartilage with chondrocytes within well-formed lacunae[19][20].

Patients and Methods

All experimental methods were completed in conformity with the moral guidelines for using animals in research, and all work and data will be collected according to ethical approval from diyala university, college of medicine with ID(2023MAH758) . Twenty albino rats, weighing between 300 and 400 grams and being between 6 and 8 months old, were used in this experiment. The medial side of the mandible's angle was operated on surgically on the animals. The animals were divided into following groups:

1-10 rats from the control group. The bone defect was allowed to naturally mend on its own then divided in to two healing periods:

a-5 rats are taken after one week(7 days)

b-5 rats are taken after two week(14 days)

2-10 rats were used in the experiment, and taking the bisphosphonate medication helped the bone defect which mend then divided in to two healing periods:

a-5 rats are taken after one week(7 days)

b-5 rats are taken after two week(14 days)

All surgical tools have been sterilized in the oven at 150 °C for 1 hour to ensure maximum sterilization. The instruments were then wrapped in aluminum foil and sterilized in the autoclave at 150 °C and 15 bar/cm2 for 1 hour [21] Figure (3).

Figure (3): Surgical tools.

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The procedure was performed using a skillful surgical technique and under very sterile settings. After shaving the animal's skin, it was cleansed and disinfected using a piece of cotton dipped in 96 % alcohol and iodine. A skin incision was made with a sharp blade (no.10), and the skin and fascia flap were reflected.

The rotational speed used for bone penetration was 1500 rpm. A bone defect hole of 1.8mm was performed with a small round bur[20]. After the hole was prepared, the drilling site was cleaned using a saline solution to get rid of any drilling debris. On the mandibular angle bone, a defect was formed Figure (4).

Figure (4): The rotational speed used for bone penetration.

After the operation, wash the area with normal saline. The muscle was sutured with a 3/0 absorbable (catgut) suture, and skin was sutured with 3/0 silk suture. The period was carried with 2.5 mg/day dose (one time take in the day) of oral bisphosphonate medicament supported the healing process[21]. Using overdose anesthesia, after the animals were scarified at intervals of the surgical location, skin, fascia, and muscles were removed. After that, bone specimens were produced by removing around 5 mm of bone from the area surrounding the surgery site, irrigating the area continuously with saline to prevent bone injury, and dissecting the fragment and fixing it in 10% buffered formalin. Tissue Processing and Staining for histological examination were done and stained with H&E stain for slide were preparation and histological examination and examined under 10 X magnification to determined the effect of the medicament histologically and Histomorphometrically.

Statistical analysis

Statistically according to Table (1) showed the cells in difference of the study group in the count of cells in each every healing periods (7 & 14 days), the table showed higher significant difference of both chondroblast & chondrocytes cell between the experimental and control group at 7 days of healing period.

Results

After producing a H&E slide and examined under a light microscope with10 X magnification power. The microarchitectures

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were measured by counting the chondroblasts. Chondrocyte, Osteoblast ,Osteocyte and Osteoclast cell number / mm^2 in 7 and 14 days healing periods.

At 7 days duration: the histological slide of rats that were treated with bisphosphonate medicament Figure (5) showed new cartilage cells (chondroblast) at the region of active ossification and filled the area of the defect with the presence of iso-group number of chondrocytes embedded in the perichondrium , little inflammatory cell, fat cells and blood vessel adjacent to progenitor cells. In addition to the cartilage we showed bright red spongy bone fragments are encircled by a long row of osteoblasts the number of the bone building cell less than the cartilage building cell.Osteocytes, which are the osteoblasts that were previously imprisoned in their own matrix deposits, are found in lacunae within the spicule this cell showed in little account in contrast with bone building cell and showed lesser number of osteoclast cell in contrast with other cells at 7 day healing periods. In contrast with the control group Figure (6) that showed low number of chondroblast that form the cartilage matrix with high number of inflammatory cells, while the bone building cells showed low account number with absences of the chondrocyte and osteocyte and osteoclast Figure (7).

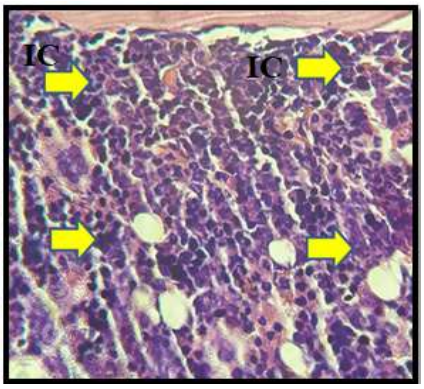

Figure (6): control group at 7 days that showed high count number of inflammatory cell (IC) at defect area.

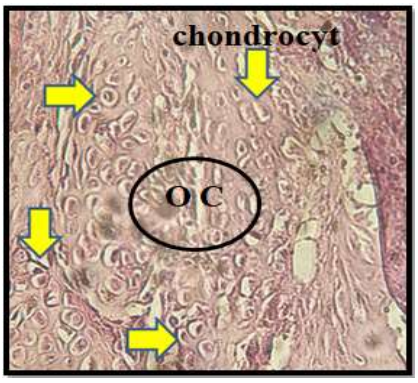

Figure (5): experimental group at 7 days showed high number of cartilage cell (both chondrocyte and chondroblast) that related to endochondral in ossification center (OC) ossifications.

In Figure (7) represented mean number of cell at 7 days healing period showed high count number of chondrocytes and condroblasts number of experimantal group when we compaired with control group showed large differences in count number of same cell but in control group, and shoewd higher count of bone building cells rather than control group. The control group in 7 days healing period showed lower number of osteoclast and osteocytes cell than the count of same cells but in experimantal group and other different cells in the feiled.

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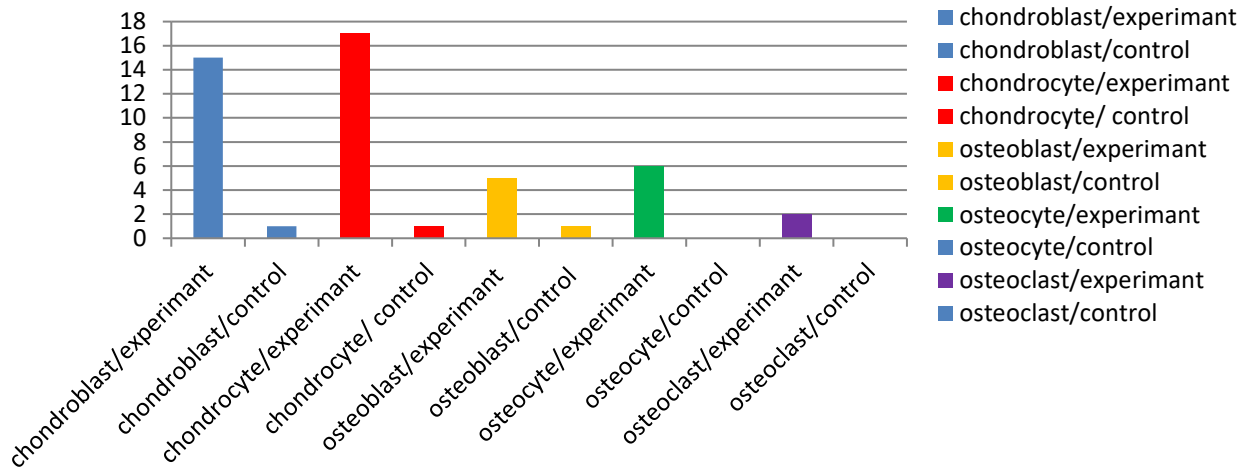

Figure (7): Mean of cells at 7 days healing period

At 14 days healing periods, the experimantal group showed rappid bone lying down with a high number of osteocyte cell in its laqunae incontrast with cartilage cells (chondrocyte and condroblast) showing lower count in the slides and precence of the bone building cells (osteoblast) with alow count of osteoclast and large area of bone matrix in contrast with bone marrow Figure (8). In the control group at 14 days healing periods showed specules of bone trabecule with large area of bone marrow among the trabecule in contrast with experimantal group that showed more bone area to bone marrow area with presence of same osteocytes in the center of the bone trabecule and osteoblast cells on the perifery of bone the trabecule Figure (9).

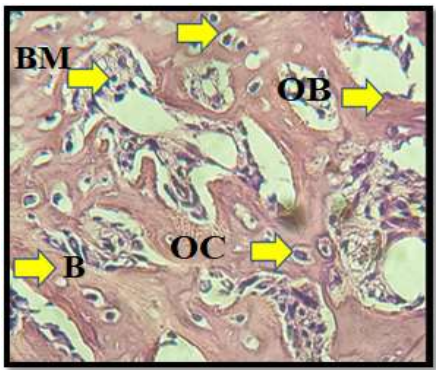

Figure (9): control group at 14 days that showed little number of osteocyte (OC) in little bone area and high bone marrow area (BM).

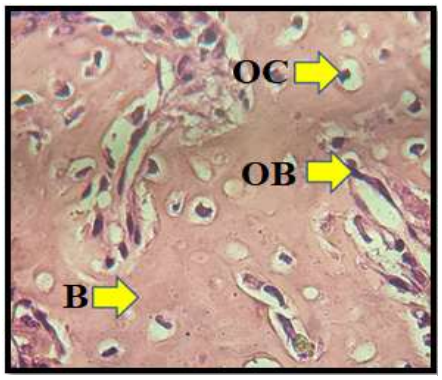

Figure (8): Experimental group at 14 days showed high number osteocytes (OC) and large area of bone (B) rather than bone marrow area.

In Figure (10) represented mean number of cell at 14 days healing period showed high count number of osteocytes cell number of experimantal group when we compaired with control group showed large differences in count number of same cell but in control group, and shoewd higher count of bone building cells rather than control group and showed lower count of cartilage cells.

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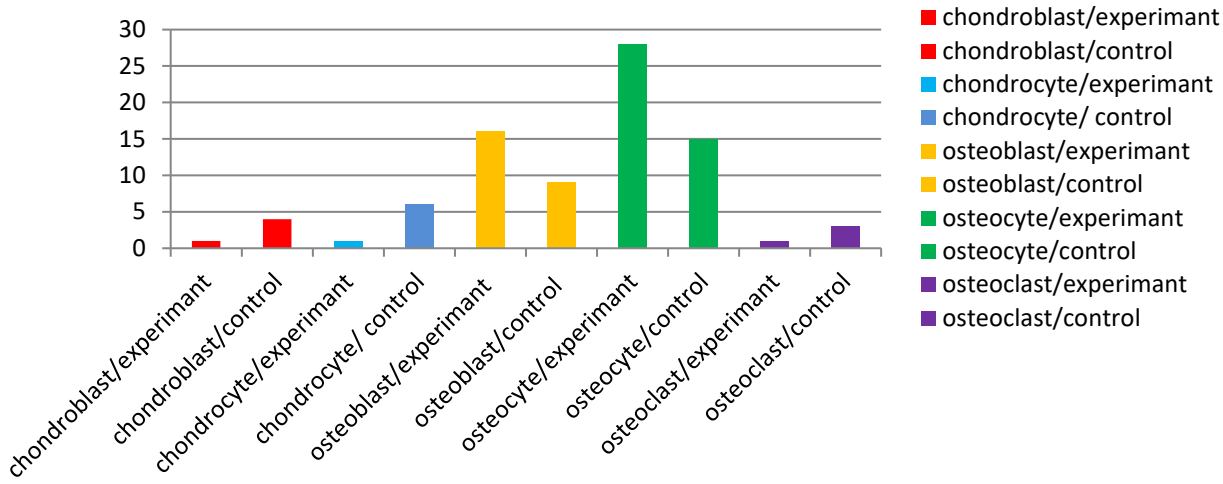

Figure (10): Mean of cells at 14 days healing period.

While these cells at 14 days showing non-significant difference between the study groups. The bone building cells (osteoblast shoed at7 days significant difference while showed a non-significant difference at 14 days healing period. In both 7& 14 day showed a significant difference between the groups in the osteocyte cells count and showed non-significant difference in the count of osteoclast in all study groups.

Table (1): Descriptive statistics of the cells count (H&E) and groups' difference in each duration (ANOVA test).

The cell	duration	group	Descriptive statistics	Group difference	
			S D	P value	Description of p value
Chondroblast	7 days	Experimental	1.386	0.000	HS
		control	0.587		
	14 days	Experimental	0.432	0.666	NS
		control	0.654		
Chondrocytes	7 days	Experimental	1.337	0.004	HS
		control	0.778		
	14 days	Experimental	0.32	0.123	NS
		control	0.54		
Osteoblast	7 days	Experimental	1.5	0.014	S
		control	1.04		
	14 days	Experimental	0.430	0.632	NS
		control	0.431		
Osteocytes	7 days	Experimental	0.802	0.012	S
		control	0.1274		
	14 days	Experimental	0.816	0.045	S
		control	1.164		
Osteoclast	7 days	Experimental	0.230	0.453	NS
		control	0.301		
	14 days	Experimental	0.345	0.332	NS
		control	0.321		

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Statistically according to Table (2) showed the difference of duration in cells in all the study group (experimental and control group) the table represented high significant difference of both chondroblast & chondrocytes cell in 7 days healing time in expeimantal group, while this cell showed non-significant difference in 14 days healing periods in the control group. The osteoblast cells showed significant difference in the experimental group but showed non-significant difference in control group in both healing periods. The statistic result represented high significant difference in the osteocytes cell in experimental group between the 7&14 days healing periods, while showed non-significant difference in control group. The osteoclast cell showed non-significant difference in each healing periods and the study group.

Table (2): Descriptive statistics of the cells count (H&E) and durations' difference in each group.

The cell	group	duration	Descriptive statistics	Group difference	
			S D	P value	Description of p value
Chondroblast	Experimental	7 days	0.611	0.000	HS
		14 days	0.951		
	control	7 days	0.200	0.088	NS
		14 days	0.202		
Chondrocytes	Experimental	7 days	0.306	0.002	HS
		14 days	0.445		
	control	7 days	0.520	0.451	NS
		14 days	0.550		
Osteoblast	Experimental	7 days	1.8	0.18	S
		14 days	0.976		
	control	7 days	0.801	0.306	NS
		14 days	1.060		
Osteocytes	Experimental	7 days	0.654	0.001	HS
		14 days	0.307		
	control	7 days	0.501	0.33	S
		14 days	0.432		
Osteoclast	Experimental	7 days	0.34	0.270	NS
		14 days	0.3		
	control	7 days	0.234	0.231	NS
		14 days	0.254		

Discussion

The pharmaceutical industry now views traditional medicine as a source for identifying bioactive molecules that may be employed in the creation of synthetic medications. Chemical medicines (bisphosphonate medicament) have always been a significant part of the healthcare system [22]. The inorganic pyrophosphate is a naturally occurring polyphosphate present

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in sera and urine [23]. In our study used bisphosphonates as an initiator for endochondral ossification due to their strong affinity for the hydroxyapatite on the surface of bones in areas of bone production or bone remodeling agree with [24] when included the bisphosphonate to retained bone trabeculae with osteoid development among the malignant cells. Due to bisphosphonates used to accelerate the healing by inactivation of clastic cells' (resorptive activity), and calcified cartilage fragments remained embedded inside the produced bone trabeculae at the mandible of young rats agree with [25] when used the alendronate-administrated as a treated to formed trabeculae during the endochondral ossification of the mandibular condyle.

Complex interactions among cells of the cartilage lineage and the mesenchymal bone cell and inflammatory cell lineage play a major role in the pathophysiology of bone healing. The current study depicts an inflammatory response and formation of the cartilage and replacement with bone in experimental groups and at various stages (7, 14 days) of the bone healing process [7]. The progression of bone healing as indicated by matrix deposition by activation the ossification center to synthesized cartilage cells and synthesis of osteoblasts during the first week (7 days) and bone trabeculae formation within newly formed bone as shown in histological sections that increased in number and width throughout the 14 days intervals. The presence of resorptive cell represented by osteoclast that retain in residing Howship lacunae indicates remodeling process during the healing periods, with high significant activation and increase in count of the cartilage cells and replacement the cartilage matrix with bone matrix and precipitation the inorganic substance to enhance the time that required to heal the defect area after used the bisphosphonate as an initiator this histological changes was detected by histomorphometry analysis. These findings of experimental group is agreed with [26] stated that osteoporosis female Wistar rats was fed their food daily with L. sativum seeds.

Regarding results of histomorphometrical analysis have shown that the nonequivalence of count difference of examined cartilage parameters and recorded microarchitecture between control and experimental groups, clarified a high avalue in experimental groups than those of control groups in different intervals time especially in 7 days healing period due to active endochondral ossification at site of bone defect, with show bone trabeculae filled a proximately the whole defect in comparison to histologic views for control group after 14 days healing period. this agree with [7] that used herbal material that represented by Symphytum officinale oil when applied locally on generated bone defect healing in rat tibia and shown it was very effective in healing the bone defect.

Conclusions

The endochondral ossification of the mandibular angle defect was considerably changed in young rats treated with bisphosphonates. However, they remained dormant and could remodel the calcified cartilage/primary bone trabeculae into the spongy bone at the mandibular angle. It did not prevent the recruitment and fusion of

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cartilage cells and bone cells during the ossification of the defect area with deposited matrix, which were abundant at the ossification areas. The current findings highlight the risk of impairing maxillofacial growth in young patients who receive bisphosphonate therapy, which is recommended for the treatment of bone disorders in childhood such as osteogenesis imperfecta, juvenile Paget's disease, and secondary osteoporosis related to anorexia nervosa, cerebral palsy, and post-renal transplants.

Recommendations

One of the most important medicaments that has been scientifically proven (laboratory and histologically) to be one of the effective medicaments in treating osteoporosis and bone fractures and repairing them in a good standard period in order to increase the efficiency of bone-building cells and cells that maintain the skeleton of the bone.

Source of funding: The current study was funded by our charges with no any other funding sources elsewhere.

Ethical clearance: This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2023MAH798).

Conflict of interest: Nil

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رسم توضيحي نسيجي ونسيجي للتعظم الغضروفي لإصلاح عيب زاوية الفك السفلي في الجرذان بعد التحفيز الفموي باستخدام علاج البايفوسفونيت (دراسة في الجسم الحي)

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الملخص

خلفية الدراسة: يمكن استخدام الفوسفونات الحيوية لتقليل خطر الإصابة بكسور الورك والعمود الفقري. بالإضافة إلى ذلك، يمكن استخدامها لعلاج مرض باجيت الذي يصيب العظام بجرعات متنوعة. في الإجراء الذي يتم فيه استبدال الغضروف الزجاجي بالعظام، يسمى هذا الإجراء التعظم الغضروفي. يبدأ عندما تتطور الخلايا الوسيطة من الأديم المتوسط إلى خلايا غضروفية. تتكاثر الخلايا الغضروفية بسرعة وتطلق مصفوفة خارج الخلية لتكوين الغضروف الذي يعمل كنموذج للعظام.

اهداف الدراسة: لتوضيح نسيجي وهستومورفومتري لعملية التعظم الغضروفي لإصلاح عيب الزاوية السفلية في الفئران بعد التحفيز الفموي باستخدام علاج البيسفوسفونات.

المرضى والطرائق: تم استخدام ٢٠ فأراً في هذا العمل وتم تقسيم الحيوانات إلى المجموعات التالية: ١٠ فئران من المجموعة الضابطة. وتم شفاء العيب العظمي بشكل طبيعي دون دواء وتم استخدام ١٠ فئران في التجربة، كما ساعد تناول دواء البيوفوسفونات في إصلاح العيب العظمي. تمت دراسة كل مجموعة خلال ٧ و ١٤ يوم (٥ فئران لكل فترة شفاء) وتم إجراء العملية الجراحية للفحص النسيجي والنسيجي. تم تحليل البيانات باستخدام المقياس الإحصائي spss وبقيمة ($P \geq 0.05$) P.

النتائج: تأثير فعال لدواء الفوسفات الحيوي في التعظم الغضروفي والخلية المسؤولة عن تكوين الغضروف وتسريع شفاء عيب الفك السفلي مع تثبيط إعادة العظام وأخيرًا تقليل الوقت اللازم للشفاء الكامل.

الاستنتاجات: الدواء الكيميائي المتمثل بالبيوفوسفونات يسرع عملية التعظّم الغضروفي في وقت قصير واستبداله بالعظم في مكان الخلل.

الكلمات المفتاحية: الفوسفونات الحيوية, الغضروف، الخلايا الغضروفية، التعظم الغضروفي

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