Original Article

EFFECT OF TETRACYCLINE SOCKED PACK ON ACCELERATION OF HEALING DURING MARSUPIALIZATION AS A PRIMARY TREATMENT FOR LOCALLY INVASIVE LESION SINGLE BLINDED RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Aim of the study: is to evaluate the effect of tetracycline socked pack on acceleration of healing during marsupialization as a primary treatment for locally invasive lesions.

Participants and methods: A single blind randomized control clinical trial on a total of 14 healthy patients of either gender aged from 2040- years who are seeking treatment of a painful intra-body mandibular swelling cystic lesions 3 x 4 cm in size with biopsy conformation that the lesion is a unicystic ameloblastoma. They were treated with either tetracycline socked pack during marsupialization or conventional marsupialization procedure. CBCT radiographic assessment evaluated volumetric changes of the lesion at 3 and 6 months postoperative. **Results:** All cases showed positive healing indications. At 3 months no statistically significant difference between control and test groups was shown. However, at 6 months, a significant difference emerged; indicating that the test group achieved a significantly higher percentage of volume reduction compared to the control group at the 6-month mark. Both groups showed highly significant internal improvements over time ($p<0.001$), but the test group demonstrated a more pronounced reduction percentage

Conclusion: Marsupialization combined with tetracycline socked pack as a primary management for unicystic ameloblastoma has positive effect on lesion shrinkage and may aid in acceleration of healing.

Key Words: Marsupialization, Tetracycline, Locally invasive lesion .

Received: 6 April 2025, **Accepted:** 8 April 2025.

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ISSN: 2090-097X, April 2025, Vol. 16, No. 2

INTRODUCTION

Ameloblastoma is an odontogenic tumor. In spite being a locally invasive benign tumor of high recurrent rate. It represents 18 % of odontogenic tumors [1]. Ameloblastoma; being a silent lesion in behavior; increases in size slowly only becoming symptomatic when it reaches a sizable dimension. [2] The unicyctic ameloblastoma (UA) exhibit 5 % to 15 % of all ameloblastomas, with a recurrence rates of 10 % to 25%. A 90 % of (UA) are in the mandible, predominantly the posterior region [3]. The lesion's clinical and radiographic features are similar to that of an odontogenic cyst however; histologically ameloblastic proliferation grows into the cystic lumen, which either is confined to the cyst lining or invading the cystic wall, therefor it can be subdivided into intraluminar or mural unicyctic ameloblastoma (UA), respectively [4, 5]

Compared to conventional type of ameloblastoma (UA) is less aggressive hence; conservative approaches are widely advocated to treat such lesions, this includes marsupialization as a primary treatment followed by enucleation, or surgical enucleation only or surgical enucleation coupled with application of carnoy's solution. [6, 7] Marsupialization, is simply a procedure by which a pouch is surgically created, where mucoperiosteum over lying the lesion is incised and sutured to the borders of the remaining cyst wall. [8] Once the cyst is decompressed and tension is reduced healing and bone formation begins. [9]

Tetracyclines, was discovered and introduced into the medical field since 1940s, and considered an effective antibiotic against both Gram-positive and Gram-negative bacteria, Chlamydia, rickettsia, mycoplasmas, and protozoan parasites. By blocking of aminoacyl-tRNA form the bacterial ribosome essential protein synthesis in microorganisms is inhibited. [10]

Tetracycline has additional unique properties exceeding the antimicrobial effect, as it is anti-inflammatory in nature. It inhibits matrix metalloproteinases enzyme (MMPs); a group of Zn-dependent enzymes; that not only modulate inflammation but also affects new bone formation. From a histopathological analysis elevation of MMPs causes connective tissue break down and bone resorption. Tetracyclines can inhibit both intracellular

 DOI: 10.21608/omx.2025.321405.1265

and extracellular MMPs. Previous studies have shown that the anti-inflammatory property of tetracyclines is beneficial in the reduction of postoperative complications following extraction. [11] The null hypothesis is that there is no difference between healing rate of marsupialization utilizing tetracycline socked pack and conventional marsupialization.

PARTICIPANTS AND METHODS

Ethical consideration:

The study protocol receive clearance from Review and Ethics Committee, Faculty of Dentistry, Minia University under code number (110974/). Then it was registered to (www.clinicaltrials.gov) registry ID. (NCT06759610) and complied to principles of the Declaration of Helsinki. The study followed a prospective single blinded randomized clinical trial with a parallel armed design of a ratio (1: 1). All patients were informed thoroughly of the study details and signed consent forms before participating. The radiologist assessing CBCT images all through the study was blinded to the treatment groups.

Sample size calculation

A power analysis; performed using G*Power version 3.1.9; was applied the null hypothesis that there is no difference would be found between the control and test group according to previous study. (12) Sample size calculation was and determined to be 14 patients (7 patients for each group).

Selection of participants and Recruitment strategy:

The patients were enrolled from the outpatient clinic-Minia University and Ministry of Health- Minia governorate, according to the predetermined Inclusion criteria; healthy patients (class I category according to ASA) over 20 years and under 40 years of age, of either gender who are seeking treatment of a painful intra-body mandibular swelling lesions in the range of 3 x 4 cm in size with biopsy conformation that the lesion is a unicystic ameloblastoma. Subjects were excluded from the study if they had: systemic disease that interferes with bone healing, significant medical condition, uncontrolled periodontal disease, or patients on drugs that affect the bone healing, patients who reported pregnancy, lactation. Recording of clinical and dental history was established for each patient followed by a through clinic examination and preoperative panoramic radiographic was performed. Once the patient was enrolled a preoperative CBCT was done and the lesion measurement was established. A histopathological examination confirmed the lesion to be a Uni-cystic ameloblastoma. The participants were randomly divided into two equal groups: test group (n=7) subjected to marsupialization procedure with a tetracycline socked pack during marsupialization while, control group (n=7), subjected to conventional marsupialization procedure.

Procedural Intervention:

Marsupialization procedure for all cases were performed under local anesthesia with vasoconstrictor. Mucosal incision using a #15 scalpel was done followed by a window created through the bone to give access to the walls of the lesion. Once the lining of the lesion was exposed, a part of cyst wall was removed and transported in 10 % buffered formalin serving as incisional biopsy for histopathological assessment, the edge of the cystic lesion was sutured to the oral mucosa. The cystic cavity was copiously irrigated with normal sterile saline.

For the test group a gauze pack was impregnated with 1ml of tetracycline gel (Terramycin, Pfizer, USA) and used to pack the cystic cavity while for the control group a plan gauze drain was used. The gauze pack was allowed to stand for 2 days after which an alginate impression was established for fabrication of an acrylic obturator. On insertion of the acrylic obturator a space was made for the accommodation of tetracycline socked pack in test group while in the control group the obturator was left unchanged. Augmentin 1 gm (Smith-line/ Beecham Pharmaceutical Co., Bentford, England) every 12 hours for 5 days post-operatively and diclofenac potassium 50 mg (Cataflam 50mg tablets, Novartis Pharma AG, Basle, Switzerland) three times daily for one week and chlorhexidine gluconate mouth wash (Hexitol, Arab Drug Co, Egypt) three times daily for two weeks was prescribed for all patients. Every two days, for the first week, the surgical site was examined for any signs of infection, swelling and suture loss. A full Explanation was given to all the patients how to remove the acrylic obturator and perform irrigation at home using sterile saline. As the lesion shrinks the obturator is readjusted.

Outcome Assessment:

Radiographic assessment CBCT (Planmeca Promax 3DMid machine, Helsinki Finland) scan was obtained at 3 and 6 months postoperatively, and the volumetric assessment of the lesion was determined at each period interval then the reduction percentage of lesion at each period was calculated. The radiologist assessing CBCT images, all through the study, was blinded to the treatment groups.

Statistical analysis:

Collected data were tabulated and entered electronically. Participant files and records were stored securely. Statistical analysis was performed using a commercially available software program (SPSS Chicago, IL, USA). The results were recorded as the mean and standard deviation values (mean ± SD). P-values was set at 0.05 or less were considered statistically significant

Declaration of interests: The study is self-funded and there is no conflict of interest to declare.

RESULTS:

Twenty-one patients were considered for the study; 6 patients did not meet inclusion criteria and 1 patients refused to participate in the study following the CONSORT guideline for clinical trials Fig. (1).

the control group having 3 males (42.9%) and 4 females (57.1%), with a p-value of 1.0 suggesting no significant gender imbalance. These results suggest the two groups were well-matched for baseline characteristics. Tab. (1)

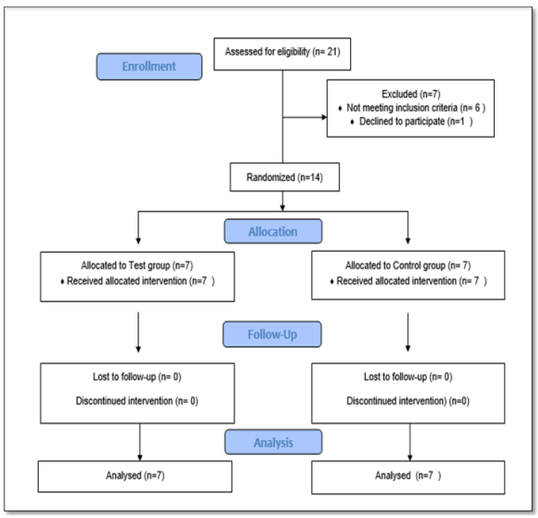

Figure (1): Flow chart sample selection, treatment and analysis following CONSORT

Table 1: Comparison of demographic data between the test and control groups

		Test	Control	P value
		N=7	N=7	
Age	Range	(20-39)	(21-37)	0.658
	Mean ± SD	30.6±7.7	28.7±7.5	
Gender	Male	4(57.1%)	3(2.9%)	1
	Female	3(42.9%)	4(57.1%)	

- Independent Samples T test for quantitative data between the two groups
- Fisher's exact test for qualitative data between the two groups
- Significant level at P value < 0.05

The lesion volumes at T0, T3, and T6 time points show no statistically significant differences between test and control groups at individual time points (p-values 0.812, 0.844, and 0.475 respectively). However, within each group, there are highly significant changes in lesion volume over time (p<0.001), with both groups demonstrating consistent and significant volume reductions between T0, T3, and T6. The post-hoc comparisons between consecutive time points (T0 vs T3, T0 vs T6, T3 vs T6) were all statistically significant (p<0.001 or p=0.002), indicating a progressive and consistent reduction in lesion volume. Tab. (2), Fig. (2)

Table 2: Comparison of lesion volume at different times between the two groups

		Test	Control	P value
		N=7	N=7	
T0	Range	(26860-37518)	(20007-39986)	0.812
	Mean ± SD	32399.1±4009.2	31532±8537.6	
T3	Range	(22293-29468)	(17123-34098)	0.844
	Mean ± SD	26072.7±2872.5	26627.3±6728.1	
T6	Range	(18722-24940)	(14088-29987)	0.475
	Mean ± SD	21025.7±2225.7	22809.3±5992.4	
P value between times		<0.001*	<0.001*	
T0 vs T3		<0.001*	0.002*	
T0 vs T6		<0.001*	0.001*	
T3 vs T6		<0.001*	<0.001*	

- Independent Samples T test for quantitative data between the two groups
- Repeated measure ANOVA test for quantitative data between different times within each group, followed by post hoc LSD test between each two times
- *: Significant level at P value < 0.05

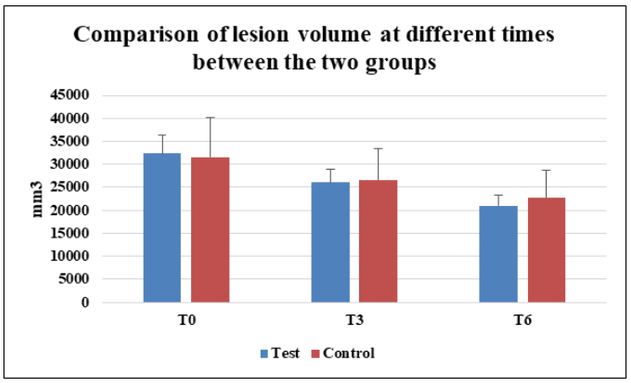

Figure (2): Bar chart showing lesion volume at different times between the two groups

The percentage of volume reduction shows interesting trends. At 3 months the percentage of volume reduction for test group: 19.4±2.5% and control group: 15±5.4%, p=0.073) demonstrating no statistically significant difference between groups. However, at 6 months, a significant difference emerged (test: 34.8±5.2%, control: 27.2±7%, p=0.040*),

indicating that the test group achieved a significantly higher percentage of volume reduction in comparison to the control group at the 6-month mark. Both groups showed highly significant internal improvements over time at p value < (0.001), none the less test group demonstrated a more pronounced reduction percentage.

Table 3: Comparison of percentage of volume reduction at different times between the two groups

Percentage of volume reduction%		Test	Control	P value
		N=7	N=7	
At 3 months	Range	(16-23.2)	(9.3-22)	0.073
	Mean ± SD	19.4±2.5	15±5.4	
At 6 months	Range	(28-43.1)	(16.5-34.7)	0.040*
	Mean ± SD	34.8±5.2	27.2±7	
P value		<0.001*	<0.001*	

-Independent Samples T test for quantitative data between the two groups
- Paired Samples T-test for quantitative data between two times within each group

- *: Significant level at P value < 0.05

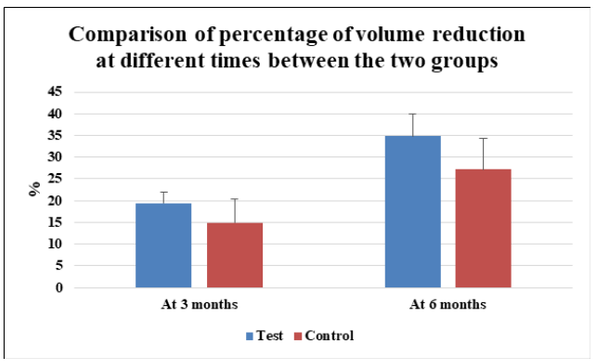

Figure (3): Bar chart showing comparison of percentage of volume reduction at different times between the two groups

DISCUSSION:

Ameloblastoma inspire being a benign slowly growing tumor, they are locally invasive epithelial odontogenic tumor. Unicystic ameloblastoma (UA) is a lesion which clinically and radiographically show features similar to that of an odontogenic cyst however; histologically ameloblastic proliferation grows into the cystic lumen and 90 % of (UA) occur in the mandible, predominantly the posterior region. [3, 13]

In concordance with previous studies, the present study showed no sex predilection. Regarding age range test group showed a mean of 30 years and control group showed mean of 28 years. However, Kessler et al [14] and Philpsen et al [15] documented that the average age range was 22 years.

Up till now, regarding management of ameloblastoma, treatment of such lesions is still controversial. Treatment ranges from radical to conservative. Although radical management would yield lower recurrent rate, it unfortunately leads to serious morbidity and more complications. Hence, conservative approaches are more favorable; specially that unicystic type, grows slowly, is only locally invasive, and very rarely metastasizing. [16, 17, 18]

The CBCT volumetric analysis showed reduction in lesion size. Both groups showed highly significant internal improvements over time with p value < (0.001) indicating that marsupialization was an effective management for such cases to reduce the size of the lesions as a primary stage of treatment. This comes in accordance with Briki etal [19] who described a series of clinical cases with different lesions that were treated by marsupialization and showed significant improvement in reducing the lesion size.

Further; the present results are in agreement with Moujoud etal [20] who have demonstrated that marsupialization, as a sole treatment or combined with other treatments, is an effective and conservative management for (UA) which is appropriate for all ages, especially young patients with sizable lesions. They also stated that this minimally invasive approach; marsupialization; is much favored as it offers many advantages including slow and steady volume reduction of the cystic cavity, preservation of oral tissues and dental structure, decreased risk of vital anatomical structures damage, decrease mandibular fracture risk, enhanced bone regeneration, and a reduce risk of recurrence.

This was asserted by our results of lesion volume reduction percentage at 3 months, as no significant difference was shown between test and control groups (test: 19.4±2.5%, control: 15±5.4%, p=0.073); while within each group a significant reduction was shown compared to preoperative lesion volume. Once the marsupialization procedure has been performed decompression of the lesion takes place which leads to reduced osmotic pressure produced by cystic fluid on the surrounding bone structure. New bone deposition, and mineralization takes place, subsequently. Moreover, as the pressure decreases favorable biological behavior of cells regarding proliferation, migration and apoptosis starts to proceed. [21] However, at 6 months, a significant intergroup difference emerged (test: 34.8±5.2%, control: 27.2±7%, p=0.040*), indicating that the test group achieved a significantly higher percentage of volume reduction compared to the control group at the 6-month mark. Both groups showed highly significant internal improvements over time (p<0.001), but the test group demonstrated a more pronounced bone healing and regeneration. This comes in accordance with Philippart et al [22]

who in their study evaluated bone regeneration quality by mixing autologous ground bone with platelet-rich plasma (PRP) and tetracycline in augmentation of maxillary sinus floor; reported a 90.3% success rate of grafting and demonstrated an increase in bone height at 6 months postoperative.
Park et al [23] who treated a case of implant periapical lesion due to a retained root tip with removal of the cause and application of demineralized freeze-dried bone allograft (DFDBA) impregnated with tetracycline. Bone density was reported to increase radiographically at 5-months postoperatively.

Moreover, in agreement with Parker [24] who in a case report combined tetracycline with deproteinised bovine bone for treatment of peri-implantitis. The treatment produced improved clinical results and periapical radiograph demonstrated increased radiopacity around the implant.
Shrivastava et al [25] reviewed the potential benefits bone grafts impregnated with tetracycline on bone regeneration around dental implants and for the management of periimplantitis through local antimicrobial action and concluded that tetracycline did have positive effect on bone height and density indicating the favorable effect on bone healing and regeneration.

The significantly more lesion volume reduction percent in the test group can be explained by the diffusion of the tetracycline through the mucosa from the tetracycline impregnated pack into the underlining bone which not only is effective in preventing infection to develop but also in modulating bone deposition favorably.
Moreover, tetracycline has the unique ability of binding to bone and retention in the bone matrix for a long period of time, this adds to our study that even though the tetracycline was applied for 4 weeks only of the study the prolonged effect was beneficial. 26
Many studies have demonstrated enhanced osteoblastic differentiation and proliferation when tetracyclines was administrated which has been observed in diabetic rats resulting in new bone formation and improvements to osteopenia [27, 28]

Osteoblasts are essential for new bone formation. Recent studies evaluating the effect of tetracyclines on osteoblastic activity indicates that these cells can respond even to low levels of tetracycline, such as those attained in plasma and crevicular fluid, inducing cell proliferation and to increase in human bone mesenchymal stem cells (BMSCs) [29]
Meticulous histopathological and molecular studies explained that tetracyclines affects osteoclast function, which in turn inhibits bone resorption through many pathways as: altering calcium concentration and interaction with calcium receptor, reducing the ruffled border and acid production, decreasing secretion of lysosomal proteinase, and inducing programmed cell death (apoptosis) of osteoclasts [30,31]

Moreover; Tetracyclines are effective inhibitors of mammalian matrix metalloproteinase enzyme (MMPs). The elevation of MMPs results in connective tissue degradation and bone resorption during various inflammatory conditions. Tetracyclines has the ability to inhibit MMPs directly preventing tissue break down. [11] Due to the positive effect of using tetracycline socked packs with marsupialization on reduction of the unicyctic ameloblastic lesion at the end of the study period compared to the plane marsupialization the null hypothesis was rejected.

CONCLUSION:

Marsupialization combined with tetracycline socked pack as a primary management for unicystic ameloblastoma has positive effect on lesion shrinkage and may aid in acceleration of healing.

CONFLICT OF INTEREST

This clinical study was self-funded by the authors, with no conflict of interest.

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