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The Clinical Effect of Phenytoin on Oral Wound

Fayhaa AM Al- Mashhadane
BDS, MSc (Lec.)

Department of Dental Basic Science
College of Dentistry, University of Mosul

الخلاصة

الأهداف: لبيان تأثير عقار الفينيتوين المأخوذ عن طريق الفم على شفاء الجروح الفموية في الغشاء المخاطي الخدي عند الأرانب. **المواد و طرائق العمل:** تم إجراء هذا البحث على عشرين أرنبا من الذكور الأصحاء و التي يتراوح وزنها ما بين (١- ٥ ،١) كغم، تم تقسيم الأرانب إلى مجموعتين، المجموعة الأولى تتأل ف من ١٠ أرانب لم تتلقى أي نوع من العلاج وهي مجموعة السيطرة، و المجموعة الثانية تتألف من (١٠) أرانب تم إعطاءها عقار الفينيتوين بجرعة مقدارها (٦٠) ملغم/ كغم من وزن الجسم عن طريق الفم مع (٣) مل من الماء المعقم باستعمال لحقنة الخاصة (cavage needle) لمدة (١٠) أيام، تم إعطاء التخدير العام عن طريق إعطاء مزيج الزايلازين والكيتامين بجرعة 0,5، ٥٠ ملغم/ كغم بالعضلة على التوالي لكل الحيوانات، بعد ذلك تم إجراء جرح بطريقة قياسية ثابتة في النسيج المخاطي الخدي لكل الحيوانات، تمت متابعة حالة الجرح لكل حيوان بشكل يومي و قياس المساحة السطحية للجرح (الطول × العرض) بالسنتيمتر المربع، مع ملاحظة نوع النسيج المخاطي للجرح و الفترة الزمنية اللازمة لشفائه. **النتائج** : استعملت طريقة اختبار t لفحص الفروقات الموجودة في الجروح بين مجموعتي السيطرة و العلاج، و قد وجدت فروقات معنوية بين المجموعتين ($p< 0.001$) فقد وجدت فروقات معنوية بين مجموعة السيطرة والعلاج فيما يتعلق بمساحة الجرح (الطول × العرض) بالسنتيمتر المربع في كل أيام الدراسة،كما وجدت فروقات معنوية بين المجموعتين من حيث نوع النسيج المغطي للجرح في كل أيام الدراسة ماعدا اليومين الثاني والثالث حيث لم تكن هناك فروقات معنوية بين المجموعتين ($p= 0.177, p= 1.000$) على التوالي. **الاستنتاجات**: استعمال عقار الفينيتوين عن طريق الفم يؤخر شفاء الجروح الفموية في منطقة النسيج المخاطي الخدي عند الأرانب.

ABSTRACT

Aims: To study the effect of oral phenytoin on healing of oral wound in buccal mucosa of rabbits.Materials and Methods: This study was carried out on twenty healthy male rabbits weighing between 1.0 – 1.5 Kg, they were divided into 2 groups; first group consisted of 10 untreated rabbits (control) and second group consisted of 10 rabbits treated by phenytoin at dose of 60 mg/Kg orally along with 3 ml/Kg of sterile water using cavage needle for 10 days. All animals were anesthetized with amixture of xylazine hydrochloride and ketamine hydrochloride at 0.5, 50 mg/Kg intramuscular respectively, then a standard wound was made on buccal mucosa of each rabbit, all animals were kept under observation, and their wounds was measured every day with respect to surface area (length x width) in cm^2, type of wound tissue and duration of healing. Results: t – test analysis was performed to test the differences in wound characteristics of both groups, it was found that there was significant differences between control and treatment groups ($p< 0.001$). Conclusions: Systemic use of phenytoin can delay oral wound healing of buccal mucosa.

Key Words: Phenytoin, oral wounds, wound healing , buccal mucosa.

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INTRODUCTION

Delayed healing or chronic wounds are a significant health care problem today; the quest for better wound – healing agent is one of the oldest challenges for medical and dental practice. One agent that has been tried in wound healing is phenytoin[1]. Oral phenytoin (diphenyl hydantoin) is used widely for the treatment of convulsive disorders. It served as an effective anticonvulsant against tonic – clonic and partial seizures. Although the mechanism of action responsible for this effect of phenytoin is not established, prolonging Na^+ channel inactivation is the most compelling explanation for its anticonvulsant effect.[2] A common side effect with phenytoin treatment of epilepsy is the development of fibrous overgrowth of gingiva, apparent stimulatory effect of phenytoin on connective tissue suggested an exciting possibility for its use in wound healing.[3]

Researchers suggested that phenytoin has a powerful effect in skin wounds healing and it may be useful in clinical practice.[4-6] The aim of this study was to evaluate the effectiveness of oral phenytoin in oral wound healing in rabbits.

MATERIALS AND METHODS

The study was carried out on twenty healthy male rabbits weighing between 1.0 – 1.5 Kg. The animals were kept in standard animal housing condition with the room temperature of 25±2°C. All rabbits were anesthetized by intramuscular administration of xylazine hydrochloride (Holland, Castenray, interchemra) and ketamine hydrochloride (Aleppo – Syria, El-Saad) at dose of 0.5 , 50 mg/Kg respectivly. A standard surgical incision was applied to the buccal oral mucosa of the upper jaw of all rabbits (about 1 cm length) horizontally using surgical blade (no. 12). The procedure was carried out at the pharmacology Lab. / College of Dentistry / University of Mosul. After oral mucosal incision, rabbits were divided into 2 groups as follows: first group consist of 10 untreated rabbits (control), second group consist of 10 rabbits treated with phenytoin sodium (Germany, Gödecke AG), each rabbit was given phenytoin at dose of 60 mg/Kg orally diluted with 3 ml/Kg of sterile water using cavage needle. The dose of drug were calculated based on body weight of rabbits in comparison to human dose.[2] Phenytoin treatment was given 2 days before surgical incision application to all rabbits in the treatment group and continue for 8 days later. [7-9] After doing the surgical incisions there was an every day observation and measurement of wounds size, they are categorized with respect to surface area that is calculated by measuring the greatest length and the greatest width (side to side) using a centimeter ruler then multiply these two measurements (length × width) to obtain an estimate of surface area in cm^2 ,the subscores of wound surface area were as follow:

0 = 0, 1=<0.3, 2=0.3-0.6, 3=0.7-1.0, 4=1.1-2.0, 5=2.1-3.0, 6=3.1-4.0, 7=4.1-8.0, 8 =8.1-12.0, 9 =12.1-24.0, 10 = >24.0

The type of wound tissue that is present in wound bed was determined by clinical observation and the subscores were as follows:

4 - Necrotic Tissue (Eschar): black, brown, or tan tissue that adheres firmly to the wound bed

3 - Slough: yellow or white tissue that adheres to the wound bed

2 - Granulation Tissue: pink or beefy red tissue with a shiny, moist, granular appearance.

1 - Epithelial Tissue: for superficial ulcers, new pink or shiny tissue that grows in from the edges or as islands on the wound surface.

0 - Closed/Resurfaced: the wound is completely covered with epithelium. Then these parameters were added to obtain total score. Acomparison of total scores measured over time and the duration of healing in days provide an indication of the improvement or deterioration in wound healing.[10] The wounds were measured by the same clinician with the animals in the same position at regular intervals (every day), digital camera was also used to had an image of wounds for both groups of rabbits. [11 -15]

RESULTS

Descriptive statistics showed that the complete healing of oral wound in rabbits was seen after 7 days in control group, while in treatment group it was achieved after 10 days (Table 1).

T – test analysis was performed to test the differences in parameter of wound characteristics including surface area (length × width in cm^2), tissue type and total scores for both control and treatment groups in all study days (Table 2).

Table (1): L Mean ± SD of wound characteristics for both control and treatment groups in all study days.

Study days	Mean ± SD for total score of wound characteristics in control group	Mean ± SD for total score of wound characteristics in treatment group
1st day	6.30 ± 0.483	7.00 ± 0.471
2nd day	5.70 ± 0.823	7.30 ± 0.675
3rd day	5.10 ± 1.101	7.00 ± 0.471
4th day	4.00 ± 0.943	6.90 ± 0.568
5th day	3.10 ± 0.876	5.60 ± 1.430
6th day	1.50 ± 0.527	5.50 ± 0.707
7th day	0.00 ± 0.000	4.80 ± 0.789
8th day	0.00 ± 0.000	3.90 ± 0.568
9th day	0.00 ± 0.000	2.00 ± 0.943
10th day	0.00 ± 0.000	0.00 ± 0.000

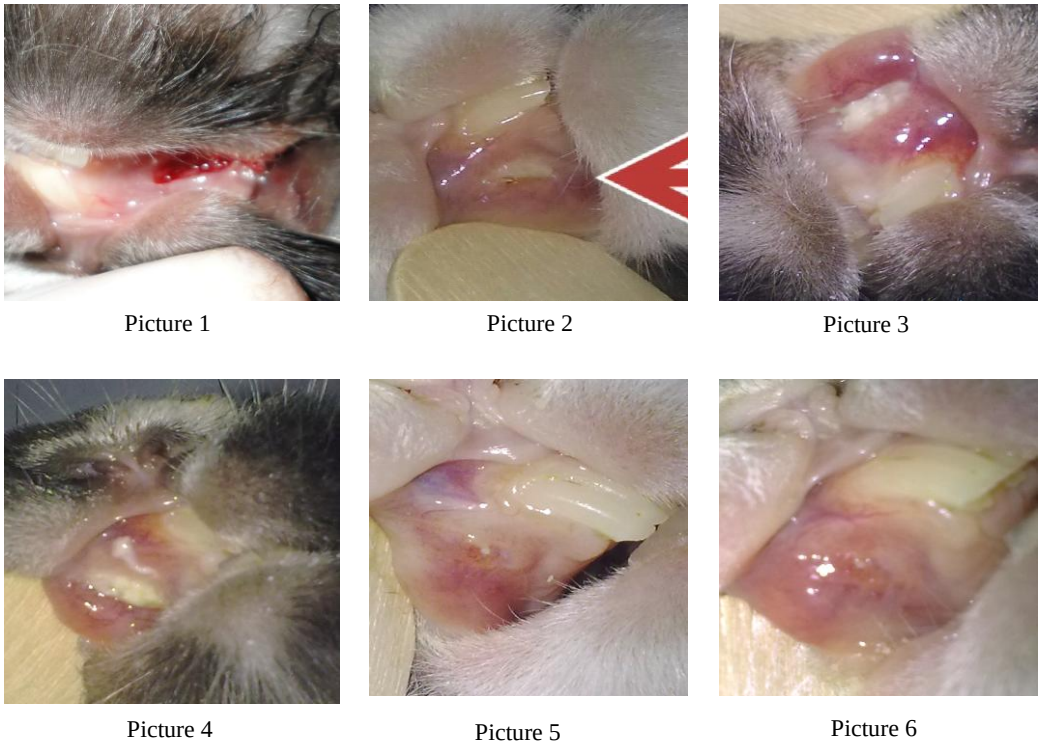
* SD : Standard deviation for 10 rabbits\ group.

Table (2): t- test for equality of means for wound characteristics in all study days.

Study days	Wound characteristics	t - test	P - value
1st day	W × L in cm^2	**6.573	0.000
	Tissue type	2.611	0.018
	Total	3.280	0.004
2nd day	W × L in cm^2	**6.788	0.000
	Tissue type	0.000	1.000
	Total	**4.753	0.000
3rd day	W × L in cm^2	**4.951	0.000
	Tissue type	1.406	0.177
	Total	**5.019	0.000
4th day	W × L in cm^2	**6.971	0.000
	Tissue type	**4.919	0.000
	Total	**8.333	0.000
5th day	W × L in cm^2	3.280	0.004
	Tissue type	**6.788	0.000
	Total	**4.715	0.000
6th day	W × L in cm^2	**5.267	0.000
	Tissue type	**13.056	0.000
	Total	**14.343	0.000
7th day	W × L in cm^2	**16.500	0.000
	Tissue type	**15.922	0.000
	Total	**19.243	0.000

*W: width of wound , L: length of wound , ** significant at $p<0.001$

It was found that there were significant differences between control and treatment groups ($p < 0.001$) in relation to wound size (length × width in cm^2) during all study days, while for tissue type there were significant differences between control and treatment groups during study days except in second and 3rd days of study that there was a non significant differences between two groups ($p = 1.000$, $p = 0.177$) respectively.Pictures of control and treatment groups were showed in (Figures 1, 2) respectively.



Picture 1 Picture 2 Picture 3

Picture 4 Picture 5 Picture 6

Figure (2): Oral wounds during study days in treatment group of rabbits.

DISCUSSION

The wound healing process involves many complex factors. These may be classified as local factors, systemic factors and organ and species variability in response to injury.[7] Chronic wounds are a significant health care problem. Phenytoin (diphenyl hydantoin) which was introduced into therapy in 1937 for the effective control of convulsive disorders has been tried in wound healing,[1] a common side effect with chronic phenytoin treatment is the development of fibrous over growth of gingiva. This apparent stimulatory effect of phenytoin on connective tissue suggested an exciting possibility for its use in wound healing.[16] Both topical and oral uses of phenytoin for wound healing are within the guidelines set forth by the FDA.[17] In this study oral phenytoin has been tried in healing of wounds in buccal mucosa of rabbit mouth, mean time to complete healing was 7 days in the control group of rabbits compared with 10 days in the phenytoin group. Significant differences can be seen between control and phenytoin treatment groups. According to the relation to wound size and tissue type, they were found in the results of this study and provide evidence that phenytoin can cause delayed healing in the wounds of buccal mucosa and this was in agreement. Some studies indicated that phenytoin can increase the risk of oral infections and the intensity of bleeding and exudates of wounds which contribute to delay in wound healing.[4,18] While in other studies, topical phenytoin on skin may have the potential to alter the dynamics of wound healing, and to promote it mainly by increasing granulation tissue formation.[19,20] Favorable therapeutic responses has been reported with oral phenytoin in patients with epidermolysis bullosa, however, oral administration of this drug is not widely accepted as effective.[1] Also topical use of phenytoin as mouth wash has been found to accelerate wound healing and resolution of mucositis.[5] This overview provided the evidence that phenytoin can accelerate wound healing mainly when used topically, while oral administration of this drug is not so effective, this can be due to the differences between the pharmacokinetics of topical phenytoin compared to oral one.[18] Studies indicated that topical phenytoin accelerated wound healing by increasing the number of wound macrophages and improving the macrophage function, also this topical agent act locally and do not undergo classic systemic metabolism modifications which can not be achieved when

phenytoin was used orally.[21,22] Another hand phenytoin mainly accelerate wound healing on skin which differ from oral wounds in relation to healing capacities glucose transporter protein–1 (GLUT–1) which is membrane protein act as carrier for glucose uptake into cell thus its expression can be a parameter of cell proliferation activity and wound healing. In the skin, glucose transporter protein–1 (GLUT –1) observed in the epidermal basal cell layer while the buccal mucosa showed no GLUT–1 protein expression in its basal cell layer, and this can affect the healing rate of wounds in skin and oral buccal mucosa.[23] So, different formulations are required for oral mucosal wound healing.

CONCLUSIONS

An interesting proposal is to use phenytoin (topical and\or systemic) to enhance wound healing, considerable evidence exists that this procedure holds promise. There is an interest in applying modern knowledge of growth factor to aid in the healing of oral wounds because phenytoin is widely available and relatively inexpensive, it might be helpful in some cases, research in this area is clearly needed.

REFERENCES

1. Ashima Bhatia M, Bhatia M, Surys D. Topical pnenytoin for wound healing. *Dermatology Online J*. 2004; 10(1): 5.
2. Vahn A. Anticonvulsants. In pharmacology and therapeutics for dentistry. 5th ed. ELSEVIER MOSBY. 2004; 225- 226.
3. Alaa K, Mohammed M, Ashraf B. High – performance liquid chromatographic method for determination of phenytoin in rabbits receiving Sildenafil. *Analytical Chemistry In sights*. 2008; 3: 61-67.
4. Pereira C, Alchorne O. Assessment of the effect of phenytoin on cutaneous healing from excision of melanocytic nevi on the face and on the back. *MC Dermatol*. 2010; 24(10): 7.
5. Baharvand M, Sarrafi M, Alavi K, Jalali Moghaddam E. Efficiency of topical phenytoin on chemotherapy – induced oral mucositis: a pilot study. *DARU*. 2010; 18(1): 46- 50.
6. Shaw J, Hughes C, Lagan K, Bell P. The clinical effect of topical phenytoin on wound healing: a systemic review. *Br J Dermatol*. 2007; 157(5): 997-1004.
7. Yesari E, Ibrahi, C, Sibel S. Comparison of healing effects of propolis to silver sulfadiazine on full thickness skin wounds in rabbits. *ARASTIRMA*. 2008; 22(1): 17-20.
8. Coskun S, Karatas Fm Acarturk F, et al. The effect of L – NAME administration after oral mucosal incision on wound NO level in rabbit. *Molecular and Cellular Biochemistry*. 2005; 278 (1-2): 65-69.
9. Gary S, Islam A, Kumar N, et al. Effect of Mentat on the pharmacokinetics of single and multiple doses of phenytoin in rabbits. Neurol India. 1999; 47: 104.
10. Npua P. Pressure ulcer scale for healing (PUSH). *Advances in wound care.* 1997; 10(5): 11F.
11. Feinstein A. An additional basic science for clinical medicine: IV. The development of clinimetrics. Ann Int Med.; 1983; 99(6): 843 – 848.
12. Majesk C. Reliability of wound surface area measurements. *Phys Ther*. 1992; 72(2): 138-141.
13. Robson M, Hill D, Woodske E, Steed D. Wound healing trajectories as predictors of effectiveness of therapeutic agents. *Arch Surg*. 2000; 135: 773-777.
14. Jos A, John T, Phillip T. Depressive symptoms predict mucosal wound healing. *Psychosomatic Medicine*. 2007; 69: 597-605.
15. Rhodes R, Heyneman C, Culbertson V, et al. Topical phenytoin treatment of stage II decubitus ulcers in the elderly. *Ann pharmacother*. 2001; 35(6): 675-681.
16. Frieda A, Geza T. Anticonvulsant drugs. In: Basic principles of pharmacology with dental hygiene applications. 1st ed. Wolters Kluwer. 2009: 244-248.
17. Anstead G, Hart L, Sunahara J, Liter M. Phenytoin in wound healing. *Ann Pharmacol*. 1996; 30: 768-775.
18. American Academy of Periodontology. Drug – associated gingival enlargement. *J Periodontol*. 2004; 75: 1424-1431.

19. Talas G, Brown R, McGrouther D. Role of phenytoin in wound healing – a wound pharmacology perspective. *Biochem Pharmacol*. 1999; 10: 57.
20. Nidal Y, Abla A, Darwish B, Salwan O. Wound bed preparation with 10 percent phenytoin ointment increases the take of split – thickness skin graft in large diabetic ulcers. *Dermatology Online J*. 2006; 12(6): 5.
21. Song S, Cheng T. The effect of systemic and local irradiation on wound macrophages and the repair promoting action of phenytoin sodium. *Zhonghua Yi Xue Za Zhi*. 1997; 77(1): 54-57.
22. Shinsuke K, Satoshi Y, Hiroto T, et al. Epithelialization in oral mucous wound healing in terms of energy metabolism. *Kobe J Med Sci*. 2009; 55(2): E5-E15.
23. Yadav J, Singhvi A, Kumar N, Garg S. Topical phenytoin in the treatment of split – thickness skin autograft donor sites: a comparative study with polyurethane membrane drape and conventional dressing. Burns. 1993; 19(4): 306- 310.