Vol 4 | Issue 1 | 2014 | 4-7.

e-ISSN 2248 - 9169
Print ISSN 2248 - 9150

International Journal of
Experimental Pharmacology

www.ijepjournal.com

# EFFECT OF PHENYTOIN ON WOUND HEALING IN ALBINO RATS

**Vinod Shivajirao Deshmukh, Vijay Motiram Motghare, Sudhir Laxmanrao Padwal, Rakesh Ramratan Jadhav , Suvarna S Rathod, Asha D Jadhav, Swapnil S Jadhav**

S.R.T.R. Government Medical College, Ambajogai, Maharashtra 431517, India.

**ABSTRACT**

Phenytoin is one of the most commonly used anticonvulsant drug. It is also used for treating cardiac arrhythmias, digitalis intoxication, migraine and trigeminal neuralgia. On long term oral administration it causes dose dependent gingival hyperplasia as side effect and by virtue of this effect Phenytoin may exert the wound healing property and hence present study was planned to see effect of Phenytoin cream on linear incisional wound healing. To study the effect of Phenytoin on wound healing using the acute linear incisional wound model in rats. Wound healing property of topical Phenytoin cream studied in incision wound model of wound healing in albino Wistar rats and it was compared with control and vehicle group. Results were analyzed by one way ANOVA followed by Bonferroni's post hoc test. In present study the wound healing property of topical Phenytoin and of petroleum jelly as a vehicle showed statistically significant activity ($p<0.05$) compared to control and the topical application of Phenytoin showed statistically significant activity ($p<0.05$) compared to petroleum jelly only after 12 day of treatment in acute linear incisional wound model. Phenytoin when applied topically promotes the healing of wound however it did not had significant wound promoting effect in acute linear model of wound healing.

**Keywords:** Epithelialization, Phenytoin, Wound healing, Incisional.

## INTRODUCTION

Wound is disruption or loss of normal anatomical structure and function of living tissue. Healing of wound is dynamic process of restoration of cellular structures and regeneration of dermal and epidermal tissue [1]. For effective management of wound it is essential to know process of wound healing and different stages of healing including inflammatory, proliferative and remodeling. Topical medication should direct specific effect during stages of healing [2].

Phenytoin used as anticonvulsant since 1938 [3]. It was observed that on long term administration, Phenytoin produces gingival hypertrophy and by virtue of this property studies on its effects on wound healing were undertaken, and showed that favorable healing effect in periodontology patient treated with Phenytoin [4]. It is also reported that topical application of Phenytoin promotes the wound healing [5,6]. Wound healing effect of Phenytoin is related to increase in vascularity of granulation tissue, fibroblast proliferation [7-8], increasing collagen content and maturation and decreasing collagenase activity [9].

Since 1950s Phenytoin has been used in the healing of diversity of wounds includes healing of various cutaneous ulcers secondary to variocose vein, diabetic, decubitus and trophic ulcers in leprosy, as well as second degree burns. In spite of all these reports, there are few studies had contradictory reports stating that topical application of Phenytoin has no effect on dermal or epidermal growth suggesting that it does not possess wound healing property (12). So the effect of topical administration of Phenytoin for the promotion of wound healing seems to be a promising approach but requires further evidence.

Therefore, in view of conflicting results, the present study has been planned to evaluate the effect of topical Phenytoin on the rate of wound healing in an acute incisional wound model in rats.

Corresponding Author

**Dr. Vinod S Deshmukh**
Email id: vinod_deshmukh88@yahoo.com

## MATERIALS AND METHODS

The present study was carried out in SRTR Government Medical College, Ambajogai.Dist-Beed, Maharashtra. Study was carried out after prior approval from Institutional Animal Ethics Committee of our institute which is an approved body by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

### Animals

Wister albino rats of either sex weighing between 200-250g were used for the study. Animals were divided into three groups with six animals in each group for Incision wound model.

Animals were acclimatized to laboratory conditions 24 hours prior to study. Animals were housed in separate plastic cages (three animals per cage), with tap water and commercial food *ad libitum.*

### Chemicals

Pure powder form of Phenytoin obtained as gift sample from Sun pharmaceuticals. 1% Phenytoin cream is prepared by mixing one gram of Phenytoin in 99 gram of petroleum jelly as vehicle obtained from commercial resources.

### Wound healing model used for investigating wound healing property of Phenytoin Incision wound model: [R]

This model use to evaluate the tensile strength of the wound. Adult Wistar rats (200-250gm) of either sex were used in this model. The animals were anesthetized by using ether. After shaving the back of animals, a linear 3cm incision was made over the skin of the back. Eighteen animals will be randomly divided into three groups: control, vehicle and treatment groups. Control group will not receive any drug or vehicle. Animal of vehicle group will receive topical petroleum jelly once a day from beginning of experiments until complete wound closure. Animals of treatment group were treated topically by 1% Phenytoin cream.

### Assessment of wound healing

The animal in each group observed on the alternate day and the healing was assessed by using the parameter wound contraction. The wound contraction is calculated by measuring wound area on every alternate day. The complete wound area photographed by placing the measuring scale to both side of wound using digital camera. The wound area in photograph was measured by using the image J software.

Percentage wound of healing were calculated by using

### Walker formula

Percentage of wound area= Wound area in the day of X / Wound area in the first day *100.

Percentage of wound healing = 100- percentage of wound area.

### Statistical analysis

The results were expressed as mean±SE. The results were analyzed statistically by one way ANOVA followed by post hoc Bonferroni's test. The $P<0.05$ were considered statistically significant.

## RESULTS

The percentage of wound healing is statistically significant in Phenytoin and vehicle group compared to the control group in 2 week duration of treatment. Between Phenytoin and vehicle group Phenytoin has maximum promoting effect on wound healing, however it was statistically significant difference seen after 12 day of treatment. It is concluded that Phenytoin had not significant wound healing effect in acute incisional wound method.

After calculating the percentage of wound healing it was found that topical Phenytoin treated wound showed almost complete healing in two week interval. In vehicle group maximum closure of wound almost in animals occur at the end of second week. The complete healing of wound in control group occurs in 20-22 day after creation.

The percentage of wound healing in control, vehicle and Phenytoin group was tabulated in table no.1 and graph 1.

**Table 1. Shows that percentage of wound healing in Incisional wound method**

| Drug Treatment / Duration of treatment | Control | Vehicle | Phenytoin |
|---|---|---|---|
| **Day 2** | 7.155±2.112 | 4.118±0.8579 | 5.713±1.13 |
| **Day4** | 6.485±1.366 | 5.843±1.582 | 23.12±5.619* |
| **Day6** | 9.933±2.157 | 11.95±2.386* | 37.28±6.378* |
| **Day8** | 9.643±2.138 | 21.27±2.872* | 50.99±6.592* |
| **Day10** | 23.13±4.608 | 28.39±2.976* | 60.17±4.996* |
| **Day12** | 34.55±5.308 | 57.37±2.698* | 82.57±5.874*# |
| **Day14** | 22.01±2.565 | 77.99±2.565* | 90.33±3.098*# |
| **Day16** | 63.76±6.676 | 91.82±1.742* | 95.26±2.048* |

Values are mean ± S.E.M; n= 6 in each group

*$p<0.05$ when compared to control group

# $p<0.05$ when compared to petroleum jelly (Vehicle) group.

**Fig 1. Shows that wound healing in incisional wound model**


## DISCUSSION

In the present study wound healing property of Phenytoin was evaluated in acute linear incision wound model as an experimental study. Phenytoin is primarily used for treating convulsions. It is also used for treating cardiac arrhythmias, digitalis intoxication, migraine and trigeminal neuralgia.

Recently it is also search for use treating wound healing. Topical route application of Phenytoin act directly at the site of wound and promote the healing without entering in the systemic circulation and without the systemic side effects [10]. The side effect associated with topical Phenytoin is only the transient burning sensation when applied to wound and hypertrophic granulation tissue formation [11].

In present study topical application of Phenytoin in incision wound model showed significant healing effect compared to control however not more than that of the vehicle. Our results were in conceseus with study conducted by Morteza Jarrahi *et al*., [12]. The wound healing effect of Phenytoin could be related to increased collagen formations which increase the tensile strength of the wound. Collagen gives the structural support and by increasing synthesis, it accelerates the wound healing [13]. This effect was similar to the study conducted by Moy LS et al suggesting that healing effect of Phenytoin was mainly due to direct stimulation of fibroblast proliferation and increased collagen synthesis [14].

Wound healing potential of Phenytoin might be due to increased gene expression of platelet derived growth factor B chain in macrophase and monocytes [15]. Variety of action could lead to wound promoting property of Phenytoin consist stimulation of fibroblast proliferation, facilitation of collagen deposition, glucocorticoid antagonism and antibacterial activity [16].

Phenytoin is anticonvulsant associated wound healing activity. Phenytoin has no antibacterial activity however it changes PH of wound, helps for reduction of discharge of wound [17]. Smith et.al reported that Phenytoin possess the analgesic property by virtue of inhibition of repetitive neuronal activity and synaptic transmission [18] Shapiro *et al.*, reported that topical Phenytoin gel promotes the wound healing due to rapid organization of blood clots and early formation of connective tissue elements [19].

Absence of systemic side effects, easy availability, inexpensive for topical application Phenytoin could be useful wound healing agent for a long term effect in future. In our study Phenytoin does not show conclusive effect in acute model of wound healing. The predominant mechanism responsible for the wound healing property of phenytoin amongst the various proposed hypothesis needs to be identified. Hence further studies are required for establishing the clinical application of Phenytoin as a wound healing promoting agent.

## CONCLUSION

Phenytoin when applied topically promotes the healing of wound however it did not showed significant wound promoting effect in acute linear model of wound healing.

## REFERENCES

1. Mercandetti M, Cohen AJ. Wound healing, healing and repair. Updated March 27, 2008. http://emedicine.medscape.com/article/1298129-overview**.**
2. Lozier SM. Topical wound therapy. In: Harari J, editor. Surgical complications and wound healing in small animal practice. Saunders, Philadelphia, 1993, 63-88.
3. Rall TW, Schleifer LS. Drugs effective in the therapy of the epilepsies. In: Goodman Gilman A, Goodman LS, Rall TW, Murad F, eds. Goodman & Gilman's the pharmacological basis of therapeutics. New York: Macmillan Publishing Company, 7th ed, 1985, 446-72.

4. Shapiro M. Acceleration of gingival wound healing in nonepileptic patients recieving diphenylhydantoin sodium (dilantin, epanutin). *Exp Med Surg*, 16(1), 1958, 41-53.
5. Smith BH, Bogock S and Dreyfus J. The Broad Range of Clinical Use of Phenytoin. Dreyfus Health Foundation. New York. 1988; 89-120.
6. Pendse AK and Sodan A. Topical phenytoin in wound healing. *Int. J. dermatol*, 32(3), 1993, 214-216.
7. Matsuo A and Yajima T. Cell proliferation and collagen fibrogenesis of cultured fibroblasts. *Jpn. J Oral Biol*., 27, 1985, 53-63.
8. Bazin, S. and Delaunay A. Effect of phenytoin in the maturation of collagen in normal skin and granulomatous tissue. *CR Acad Sci*., 1972; 275:509-511.
9. Talas G, Brown RA, McGrouther DA. Role of Phenytoin in wound healing: a wound pharmacology perspective. *Biochem Pharmacol*, 10, 1999, 1085-94.
10. Muthukumarasamy MG, Sivkumar G, Manoharan G. Topical Phenytoin in diabetic foot ulcers. *Diab Care*, 14, 1991, 909-11.
11. Morteza J, Abbas Ali V. Effect of topical Phenytoin cream on linear incisional wound healing in albino rats. *DARU*, 12(4), 2004.
12. Kiran K & Asad M. Wound healing activity of sesamum indicum linn seed and oil in rats. *Indian J Exp Biol*, 46, 2008, 777.
13. Moy LS, Tan E, Holness R, uitto J. Phenytoin modulates connective tissue metabolism and cell proliferation in human skin fibroblast culture. *Arch Dermatol*, 121, 1985, 79-83.
14. Dill RE, Miller EK, Weil T, Lesley S, Farmer GR, lacopino AM. Phenytoin increases gene expression for platelet-derived growth factor B chain in macrophages and monocytes. *J Periodontol*, 64, 1993, 169-73.
15. Anstead GM, Hart LM, Sunahara JF, Liter ME. Phenytoin in wound healing. *Ann pharmcother*, 30, 1996, 768-75.
16. Mukherjee PK, Verpoortr R and Suresh B. Evaluation of *in vivo* wound healing of hypericum patulum leaf extract on different wound models in rats. *J. ethanopharmacol*, 70, 2000, 315-321.
17. El-Zayat S. Preliminary experience with topical Phenytoin in wound healing in war zone. *Milit. Med*, 154, 1989, 178-180.
18. Smith BH, Bogock S and Dreyfus J. The Broad range of clinical use of Phenytoin. Dreyfus Health Foundation. New York. 1988, 89-120.
19. Da Costa ML, Regan MC, al Sader M, Leader M, Bouchier Hayes D. Diphenylhydantion sodium promotes early and marked angiogenesis and results in increased collagen deposition and tensile strength in healing wounds. *Surgery*, 123, 1998, 287-290.