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RESEARCH ARTICLE

THE EFFECT OF PHENYTOIN ON WOUND HEALING IN EXPERIMENTAL MODEL

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ABSTRACT

Background: Unhealed and chronic wounds create significant health care problem and enhance financial burden of society. This study was conducted in experimental rat model to judge the effect of phenytoin on wound healing.

Material and methods: Wistar rats were divided into two groups, (n=6 each group) and a wound was created which was treated with petroleum jelly in group A and Phenytoin Cream in group B. The wound healing and epithelisation of wound was evaluated at day 4,8,12,16 and 20.

Results: Group A showed an average wound size of 348±13.0 on day 4, 278±10.5 on day 8, 119±9.8 on day 12, 86±9.2 on day 16 and 100% wound healing was observed day 20 onwards. Group B showed an average wound size of 265±10.0 on day 4, 180±8.0 on day 8, 78± 5.5 on day 12 and complete wound healing was observed day 16 onwards in the test group.

Conclusion: Topical application of phenytoin on excisional wound accelerated the wound healing.

INTRODUCTION

Wound healing is a complex process which results in to the restoration of physical integrity and continuity of external or internal body tissues. Wound healing undergoes through stages like hemostasis, inflammatory phase followed by proliferation and maturation phase.[1,2] Wound creates anatomical discontinuity and disturbed functions locally. If not treated properly leads to chronicity and its pathological and functional complications. Unhealed and chronic wounds create significant health care problem and enhance financial burden of society.[3,4]Despite the numerous measures available to treat wound, its treatment remains still unsatisfactory.[1,3] Phenytoin was one drug which had been tried topically to treat wound, hoping to promote its healing. Phenytoin was introduced in year 1937 to treat convulsive disorders.[5] Gingival hypertrophy or its fibrous hyper growth was commonly observed adverse effect of this drug .[6] This possible stimulatory effect of phenytoin on connective tissue encouraged researchers to study the effect of this drug on wound healing. As per some studies phenytoin was proved to possess wound healing potential [1, 7-10] but certain studies failed to observe this positive effect on wound.[11,12] Hence this study was conducted in experimental rat model to judge the effect of phenytoin on wound healing.

MATERIAL AND METHODS

This study was conducted in the department of pharmacology and in the central animal house of Bharati vidyapeeth deemed university medical college and hospital Sangli, after getting approval for this project from the institutional ethical committee [IAEC].

The 12 male wistar rats were selected randomly from the animal stock weighing between 200-300gms. These were randomly allotted for control [group A] and topical phenytoin cream group [group B] having 6 rats in each group. Each animal was housed separately in an individual cage. Light and dark cycle was maintained. They had free access for standard pellet diet and water ad libitum except 12 hours prior to the wound creation and until the rats regained full consciousness after the creation of the wound. Experiments were carried out between 9.00 to 16.00 hours. Back of the rats were shaved. On the next day surgical intervention was carried out under general anaesthesia with the thiopental sodium in the dose of 25mgs/kg body wt. 500mm^2 full thickness circular skin was excised with the scalpel blade over the nape of the neck of each animal.

For the preparation of phenytoin cream 1 gram of phenytoin was added to 99gram of petroleum jelly and was applied locally over the wound surface in group B. Animal wounds in group A recieved local application of petroleum jelly only. The application of petroleum jelly and phenytoin cream was done daily from the next day over the wounds till the complete healing of wound took place. To measure the size of the wound a transparent plastic paper was placed on the wound and the shape of wound was drawn on the paper with the help

of marker. This was then matched with the graph paper to find out the area of wound to be expressed in mm^2. Wound size was measured on day 4,8,12,16 and then as per need till the complete healing of wound took place. Statistical analysis was carried out by independent t test to compare the wound healing i.e average wound measurements and average time of epithelisation between the control and test group. Probability of $p<0.05$ was considered to be significant. All the analysis was conducted using SPSS ver 13.0

RESULTS

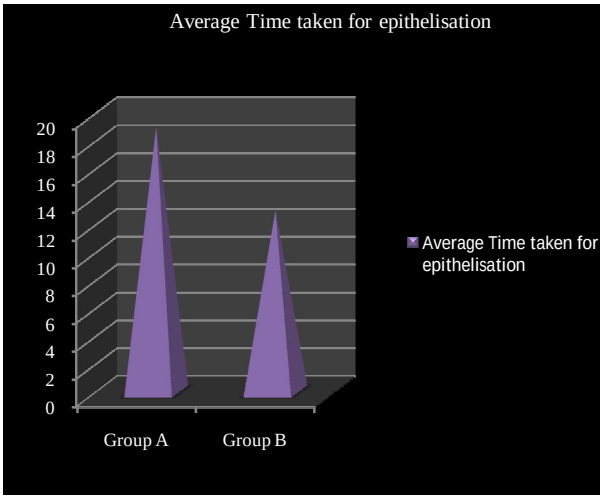
Group A showed an average wound size of 348±13.0 on day 4, 278±10.5 on day 8, 119±9.8 on day 12, 86±9.2 on day 16 and 100% wound healing was observed day 20 onwards. Group B showed an average wound size of 265±10.0 on day 4, 180±8.0 on day 8, 78± 5.5 on day 12 and complete wound healing was observed day 16 onwards in the test group. Independent t test results showed a statistically significant difference in the average wound measurements between both the groups at day 4, 8, 12, 16. (table 1)

Table 1 Comparison of average wound measurement between the control and test group

Groups	Wound area mm^2			
	Day 4	Day 8	Day 12	Day 16
Group A (control group)	348±13.0	278±10.5	119±9.8	86±9.2
Group B (test group)	265±10.0	180±8.0	78± 5.5	Complete wound healing (0.0±0.0)
P value	< 0.002	<0.001	<0.001	< 003

* p value <0.05 is considered significant
Independent t test

The average time taken for epithelisation of the wound was found to be on average of 19 ± 1.0 for group A and 13± 1.0 for group B. Independent t test shows a significant difference between the average time taken for epithelisation of the wound between group A and Group B.(p =<0.002) (Graph 1)



Graph 1 Average time taken for epithelisation of wound

DISCUSSION

In our study it was observed that group B which received topical phenytoin cream on excisional wound has shown accelerated wound healing in terms of time duration and extent of healing as compared to control group. Phenytoin was introduced in year 1937 for the treatment of convulsive disorders.[5]. In due course with long term use of phenytoin, gum hypertrophy was observed as an adverse effect of this drug by Kimball in 1939.[6] This adverse drug reaction prompted researchers to take up the studies to conclude whether phenytoin has any wound healing potential. As per few studies phenytoin was found to possess wound healing activity.[1,7-9] But some studies did not find this property of wound healing potential of this drug. [11,12] First clinical trial was conducted by Shapiro *et al* in 1958 on periodontal surgical wounds and found that patients pretreated with phenytoin had less inflammation and pain and had better wound healing as compared to controls.[7] Similarly healing of dental extraction socket was observed to be promoted with phenytoin.[11] Shafer *et al* concluded that phenytoin increases the tensile strength of skin wounds.[12] Chan F C *et al* observed significant increase in wound breaking tensile strength and hydroxyproline levels at the site of wound due to topical phenytoin application and also enhanced wound healing in diabetic rats as compared to control.[13] Between year 1989 to 1993 many researchers have found the usefulness of topical phenytoin on trophic ulcers in leprosy[14-16], in decubitus ulcers, missile wound injuries[17] and in gluteal abscesses secondary to intramuscular injections.[18] Hasamnis *et al* found that topical phenytoin accelerated wound healing in excisional wound model in rats as compared to control group who received local application of cream base only. Phenytoin was found to reduce the load of bacteria in wounds. Topical phenytoin application for 7-9days has reduced or eradicated infections due to Staphylococcus aureus, E.coli, Klebsiella and Pseudomonas species from the wound. This effect seems to be more prominent on gram negative organisms than gram positive .This antibacterial effect of phenytoin whether is due to its intrinsic antibacterial activity or due to its effect on inflammatory cells or as result of neovascularisation is not very clear.[19] Studies done by Deshmukh *et al*[11] and Jarrahi *et al*[12] did not find wound healing by local phenytoin application as compared to control group either with cream or petroleum jelly.

The mechanism by which phenytoin stimulates the process of wound healing is not very clear. The possible mechanisms are stimulation of fibroblast proliferation, decrease is collagenase enzyme activity resulting in to increased synthesis of collagen tissue and its deposition. The formation of granulation tissue and deposition of other connective tissue contributes to the process of wound healing. Decreased bacterial contamination, neovascularisation, collagenisation, reduced exudation and infiltration of polymorphonuclear cells and eosinophils helps in wound healing. [13,20, 21] Relief of pain locally in the area of application of phenytoin was attributed to its membrane stabilizing action and was noted in some studies.[13,22]Local application of phenytoin provides direct access to target site of wound and prevents the risk of systemic effects which are commonly observed with long term oral therapy .In our study it has been seen that topical application of phenytoin on excisional wound accelerated the wound healing. This effect of phenytoin can be tried extensively by undertaking clinical studies to gather the authentic information about its wound healing activity which will encourage its use in clinical conditions more and more.

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