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TO ASSESS THE WOUND HEALING PROPERTY OF TOPIRAMATE – EXCISION MODEL IN IMMUNOSUPRESSED ALBINO RATS

Dr. Dwajani S.*[1], Abhijit B.R.[2] and Dr. Sahajananda[3]

[1]Senior Research Associate, Central Research Laboratory, Rajarajeswari Medical College and Hospital, Kambipura, Mysore Road Bangalore.

[2]Phase IV MBBS Student, Rajarajeswari Medical College and Hospital, Kambipura, Mysore road Bangalore.

[3]Professor and Head/ Co-Ordinator, Anaesthesiology/ Central Research Lab, Rajarajeswari Medical College and Hospital, Kambipura, Mysore Road Bangalore.

***Corresponding Author: Dr. Dwajani S.**

Senior Research Associate, Central Research Laboratory, Rajarajeswari Medical College and Hospital, Kambipura, Mysore road Bangalore.

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ABSTRACT

Aim: To evaluate the wound healing activity of Topiramate [TPM] in excision model and to study its effects on Dexamethasone suppressed wound healing. **Methods:** For assessment of wound healing activity excision model was used. Group I received distilled water, orally, Group II, Group III and Group IV received increasing doses of TPM, p.o, Group V received Dexamethasone intramuscularly (i.m) and Group VI, Group VII, Group VIII received Dexamethasone i.m and TPM, p.o. Parameters observed were epithelization and wound contraction of excision model. **Results**: The TPM exhibited significant wound healing activity as compared to control in excision wound model. No statistical significant results were shown in any of the groups treated with dexamethasone. **Discussion**: Since TPM to certain extent enhances wound contraction it would have either enhanced contractile property of myofibroblasts or increased the number of myofibroblasts recruited into the wound area. Hence, it is concluded that TPM may be capable of promoting wound healing activity.

KEYWORDS: Wound Healing, TPM, Dexamethasone, Excision.

INTRODUCTION

Wounds are result of injuries to skin that disrupts other soft tissue. Healing of wound is a complex and protracted process of tissue repair and remodeling in response to injury. A wound can be described as a defect or a break in the skin, resulting from physical or thermal damage or as a result of the presence of an underlying medical or physiological condition.[1] Wound healing involves a complex interaction between epidermal and dermal cells and this dynamic process is classically divided into three overlapping phases Inflammation, Proliferation and Remodeling.[2] The state of art products in wound-healing include silver in microbial prophylaxis and treatment, including issues involving resistance and side effects, the use of negative pressure wound devices, advanced dressings and skin substitutes, biologic wound products including growth factor applications and hyperbaric oxygen as an adjunct in wound healing.[3]

It has been well documented that TPM has anticonvulsant property, while various attempts have been made to underline and emphasize the hypothesis that TPM can aid in wound healing in humans.[4]

Animal models are important biological tools to understand basic processes of tissue repair, to develop and validate strategies for clinical treatment. Human wound healing has many unique aspects that relate to the physiology, age and environment of the species.[5] Since this is a preliminary study and as rats are easy to handle, easy to subject for testing and their nutrition resembles that of man, they are used for the present study. Hence it was designed to determine the wound healing activity of TPM in excision and incision models and in immunocompromised albino rats.

MATERIALS AND METHODS

Institutional Ethical clearance was obtained before conducting the study. Twelve-week old healthy albino rats weighing 200-250gm of either sex was selected for the study. They were housed under controlled conditions of temperature (23±20°C), humidity (50±5%) and 10-14 hours of light and dark cycles. The animals were housed individually in polypropylene cages containing sterile paddy husk bedding and free access to food and water *ad libitum*. Animals were grouped into 8 of six animals each (n=48 for each model. Therefore, for 2 different models n = 96).

Study Group

Animals were randomly allocated into four groups of

six[6] animals each.
Group I : Control, received 2ml Distilled water.
Group II : Received / 0.5mg, p.o[6].
Group III : Received TPM 1mg[6], p.o
Group IV : Received TPM 2mg[6], p.o
Group V : Received Dexamethasone 0.17mg/kg[7], intramuscularly.
Group VI : Received Dexamethasone, intramuscularly + TPM 0.5mg, p.o
Group VII : Received Dexamethasone, intramuscularly + TPM 1mg, p.o
Group VIII : Received Dexamethasone, intramuscularly + TPM 2mg, p.o

Dosing Schedule
TPM was administered orally, once daily from day 0 to 15th post-operative day. In the wound healing model. Dexamethasone was given i.m on alternative days from day 0 to 15th postoperative day. For the assessment of wound healing activity – excision wound model was used. All wounding procedures was carried out under ketamine anaesthesia i.m 100mg/kg.

Wound Model
An excision wound was made by cutting away a circular area of full thickness of skin measuring 500mm^2 on the depilated back of the rat, in the dorsal interscapular region, 5cm away from the ears. Period of epithelization was noted as the number of days after wound healing required for the eschar to fall off leaving no raw wound behind. Wound contraction rate was monitored by planimetric measurement of wound area on alternate days. This was done by tracing the wound area on a graph paper. Reduction in the wound size was expressed as percentage of original wound size.[7]

% Wound contraction =Healed area/total area *100

STATISTICAL ANALYSIS
The results will be analysed by One Way Analysis of Variance (ANOVA) followed by using SPSS computer package version 19.

RESULTS
The results of excision wound model are shown in the below table. The TPM exhibited significant wound healing activity as compared to control in excision wound model. It is observed that the wound contracting ability of group III and IV ie, 1mg and 2mg of TPM respectively, treated groups showed faster healing process when compared to group I and group II. But a statistically significant wound healing was observed in group III i.e., in animals treated with 1mg of TPM. The wound closure time was faster, as well as the percentage of wound contraction was more with the 1mg of TPM treated group. The epithelization of wound with 1mg TPM treated group was found to be earlier as compared to control and group I. In the animals treated with 1mg and 2mg TPM, the wounds were completely healed (epithelization period) in 16 ± 2 days whereas in the control animals it took more than 20± 2 days. In animals treated with dexamethasone, group VII and VIII i.e., 1mg and 2mg TPM showed better results in healing process and in epithelization period when compared to group V and group VI. No statistical significant results were shown in any of the groups treated with dexamethasone.

TABLE 1: Drugs, Dose, Route of administration and Period of wound contraction

Drugs, Dose and route	Period of wound contraction (Days) mean ± SEM			
	4	8	12	16
Distilled water 2ml p.o	482.7±28.08	350.2±24.5	189.5±26.5	53.5±18.4
TPM 0.5mg p.o	471.0±20.2	339.1±16.0	158.0±10.8	42.6±8.9
TPM 1mg p.o	443.5±6.45*	286.0±5.01**	130.25±5.5**	00**
TPM 2mg p.o	460.8±18.0	323.9±12	141.9±10.6	20.7±6.9
Dexamethasone 0.17mg/kg, im	515.5±18.7	390±15.68	286±13.03	180.90±9.80
Dexamethasone 0.17mg/kg, im + TPM 0.5mg p.o	512.0±16.48	350.86±13.09	249.8±9.01	165.00±8.94
Dexamethasone 0.17mg/kg, im + TPM 1mg p.o	485.5±13.7	301.40±11.8	176.67±8.9	89.89±6.6
Dexamethasone 0.17mg/kg, im + TPM 2mg p.o	510.91±14.46	325,45±13.11	200.00±9.09	122.0±7.9

Each value is the mean ± S.E.M. of five rats.; *P < 0.05, **p<0.01 vs. control.

DISCUSSION
Successful wound care involves optimizing patient local and systemic conditions in conjunction with an ideal wound healing environment. Newer products are currently being used to replace or augment various substrates in the wound healing cascade.[8]

Wound contraction is the process of mobilizing healthy skin surrounding the wound to cover the denuded area. This centripetal movement of wound margin is believed to be due to the activity of myofibroblasts.[9]

Since TPM to certain extent enhances wound contraction it would have either enhanced contractile property of myofibroblasts or increased the number of myofibroblasts recruited into the wound area.

Dexamethasone inhibits wound contraction, granulation tissue and collagen formation.[10] This is the cause of suppressed wound healing in the Dexamethasone treated group in all wound models. There was no statistically significant reversal of Dexamethasone suppressed wound healing by TPM. Though, TPM being an AED, it has been used as an off label drug for many conditions. It can be of great advantage that TPM can be used alone or in combination in the treatment of wound and can thereby reduce the adverse effects of the established standard drugs.

Our data demonstrates that TPM may be capable of promoting wound healing activity. However, it needs further evaluation in clinical settings before consideration for the treatment of wounds.

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