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A COMPARATIVE STUDY OF THE TOPICAL USE OF PHENYTOIN AND SUCRALFATE IN CHRONIC ULCERS AT A TERTIARY CARE HOSPITAL

Shreya Jaiwant Gudigar[1], Dr. Mohammed Arif[2], Dhananjay Kumar B R[3], Manas V Karlekar[4]

[1]Student/ Intern, Shimoga Institute of Medical Sciences, Shivamogga, Karnataka
[2]Associate Professor,Department of General Surgery, Shimoga Institute of Medical Sciences, Shivamogga
[3]Assistant Professor, Department of General Surgery, Shimoga Institute of Medical Sciences, Shivamogga
[4]Student/ Intern, Shimoga Institute of Medical Sciences, Shivamogga, Karnataka, India
Corresponding Author: Dhananjay Kumar B R

Abstract

Introduction: Wound healing is the process of restoration of the physical integrity of internal and external body structures and involves complex interactions between the cells and several other factors. Phenytoin(diphenylhydantoin)acts by blocking neuronal excitation by binding to sodium channels at rest, preventing them from becoming functional and generating excitatory action potentials. This apparent stimulatory effect of phenytoin on connective tissue suggested an exciting possibility for its use in wound healing.On the other hand, Sucralfate (aluminum hydroxide salt of the disaccharide sucrose octasulfate), was first used as an anti-gastro-duodenal ulcer drug. Studies have also proven that topical sucralfate promotes healing of decubitus ulcers, venous stasis ulcers, traumatic wounds, burns, trophic ulcers and was seen to be superior management of diabetic ulcers.

Materials and Methods: This prospective study was conducted among patients with long standing chronic ulcers in the Tertiary care hospital. This study was carried out on 60 patients, out of which 30 patients underwent phenytoin dressing, and the other 30 patients underwent sucralfate dressing. Patients who have long standing non-healing ulcers like diabetic ulcers, venous ulcers, pressure ulcers(slough, contamination, edema and foul smell) of age groups between 20-80 years were included in the study. Acute wounds (like burns, abrasions, lacerations), ischemic limb, clean and granulated ulcers, were excluded from the study.

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Results: This study included 60 patients, out of which 30 patients underwent phenytoin dressing, and the other 30 patients underwent sucralfate dressing. 51.66% were traumatic in origin, trauma being the triggering factor secondary to neuropathy. 48.33% of the ulcers were spontaneous in origin secondary to blister formation or unnoticed trivial trauma. Rate of granulation tissue formation is greater with Phenytoin (Mean=58.65) when compared with sucralfate(Mean=52.76). On applying independent t value, we got $p < 0.05$ which suggests that the results are statistically significant. Sucralfate has better wound reduction rate when compared to Phenytoin whose interquartile range are 65 and 30.643 respectively. On applying independent t-test, we got $p > 0.05$ which suggests that the results are not statistically significant.

Conclusion: In this study, it is concluded that, the phenytoin has a better rate of granulation tissue formation in comparison to sucralfate. It is also seen that both phenytoin and sucralfate have similar area of wound reduction rate. Thus, topical phenytoin is better compared to sucralfate in the treatment of chronic ulcers.

Keywords: Phenytoin,Sucralfate, Chronic Ulcers

INTRODUCTION

In this millennium, the issue of management of non-healing and chronic wounds continue to be an enigmatic challenge. From time immemorial, doctors are trying different methods to treat this kind of ulcers. The notion that ulcers should be kept dry, although still held by a considerable number of clinicians, is steadily losing ground. We now know that ulcers re-epithelialize or develop granulation tissue faster when treated with dressings which allow moist wound healing [1].

Wound healing is the process of restoration of the physical integrity of internal and external body structures and involves complex interactions between the cells and several other factors [2]. Chronic wounds are those that have not proceeded through orderly and timely reparation to produce anatomic and functional integrity after 3 months [3]. Sharma and John opined that "chronicity may be considered when there is no complete healing after 6 weeks or if there is poor response to a treatment change" [4].

An ulcer care revolution is currently in the making. Many techniques have been tried over the centuries to heal chronic ulcers. Although wound dressings have been used for at least two millennia, there exists no ideal dressing. Surgical dressing of wounds depends on tradition, training and the surgeon's own philosophy. During the last 2 ½ decades, a wide range of innovative dressings have been introduced. People

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have tried various nonconventional topical therapies in wound healing, such as Aloe Vera, Benzoyl peroxide, collagen, gentian violet, 2 impregnated gauze, mercurochrome, oxygen therapy, sugar and vinegar.

One such agent that has been tried in wound healing is Phenytoin(diphenylhydantoin), which was introduced into therapy in 1937 for the effective control of convulsive disorders [5]. It acts by blocking neuronal excitation by binding to sodium channels at rest, preventing them from becoming functional and generating excitatory action potentials [6]. The possibility of its use as a healing agent began to be investigated by primary experimental studies in the field of dentistry, when, in 1939, hyper granulation of gingival tissue was recognized as its adverse effect, which suggested possible use of this drug as a healing agent in wounds[7-8].This apparent stimulatory effect of phenytoin on connective tissue suggested an exciting possibility for its use in wound healing. Used topically, phenytoin appears to enhance healing without side effects.

The exact mechanism through which phenytoin induces tissue healing is unclear, and the ways to apply it for this purpose are not standardized[9] but its wound-related pharmacology has been investigated[10]. Phenytoin is a low-cost drug, and the study of its healing capacity for clinical practice is important. However, there is a need for research that can elucidate the subject and encourage its discussion in our context. Therefore, this research chose as the subject of investigative interest the scientific production on the therapeutic potential of phenytoin in the wound healing process in humans.

On the other hand, Sucralfate (aluminum hydroxide salt of the disaccharide sucrose octasulfate), was first used as an anti-gastro-duodenal ulcer drug [11]. Studies have also proven that topical sucralfate promotes healing of decubitus ulcers, venous stasis ulcers, traumatic wounds, burns, trophic ulcers and was seen to be superior management of diabetic ulcers [12].

Sucralfate is a cytoprotective agent. It is a safe and well tolerated drug as demonstrated by the complete lack of side effects, and for this reason it is widely employed in clinical practice to prevent or treat several gastrointestinal diseases such as gastroesophageal reflux, gastritis, peptic ulcer, stress ulcer, and dyspepsia, and in the treatment of recurrent aphthous stomatitis[13-15]. Furthermore, the stimulating effects of sucralfate on vascular factors, including angiogenesis, which play important roles in tissue repair, have been demonstrated [16-19].

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AIM: To determine wound healing rates after phenytoin and sucralfate dressings on long standing chronic ulcers.

Materials and Methods

This prospective study was conducted among patients with long standing chronic ulcers in the Tertiary care hospital. This study was carried out on 60 patients, out of which 30 patients underwent phenytoin dressing, and the other 30 patients underwent sucralfate dressing.

Inclusion criteria: Patients who have long standing non-healing ulcers like diabetic ulcers, venous ulcers, pressure ulcers(slough, contamination, edema and foul smell) of age groups between 20-80 years were included in the study.

Exclusion criteria: Acute wounds (like burns, abrasions, lacerations), ischemic limb, clean and granulated ulcers, were excluded from the study.

Methodology: After obtaining approval and clearance from the institutional ethics committee, and informed consent in patient's own language, the patients fulfilling inclusion criteria were enrolled for the study. A group of 60 patients were included in this study, out of which 30 patients underwent phenytoin dressing, and the other 30 patients underwent sucralfate dressing. Selection of patients was done by purposive sampling method. All patients underwent detailed clinical examination along with relevant investigations and the wounds were thoroughly debrided. The ulcer dimensions and the surface area were assessed using Vernier calipers, during each phenytoin and sucralfate dressing. The patients were followed up on a daily basis for 10 days.

Application of Dress:

For Topical Phenytoin Dressing:

The ulcer was cleaned with Normal Saline. A 2ml single phenytoin sodium vial mixed with 4ml of sterile normal saline to form a miscible. Sterile gauze was soaked in the miscible and placed over the wound. Here, every time a new phenytoin vial was used.

For topical sucralfate dressing:

The ulcer was cleaned with Normal Saline. A single one-gram sucralfate tablet was crushed, powdered and placed in 5ml of sterile normal saline to form a suspension. Sterile gauze was soaked in the suspension and placed over the woun.d

At the end of 10 days, the wounds in both the groups were inspected and the wounds were compared based on the following parameters.

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- Rate of granulation tissue formation
- Percentage of the ulcer surface
- Present dimensions and surface area of the ulcer

RESULTS

This study included 60 patients, out of which 30 patients underwent phenytoin dressing, and the other 30 patients underwent sucralfate dressing.

Table 1: AGE DISTRIBUTION

Age in years	Phenytoin	Sucralfate	TOTAL
21-30	0	0	0
31-40	8	8	16 (26.66%)
41-50	4	12	16 (26.66%)
51-60	4	2	6 (10%)
61-70	2	0	2 (3.33%)
71-80	12	8	20 (33.3%)

The age of the patients varied from 21 to 80. In phenytoin group, maximum no of cases belonged to age group 71-80(40%) followed by age group 31-40(26.6%). In sucralfate group, maximum no of cases belonged to age group 41-50(40%) followed by age group 31-40 and 71-80(26.66%).

In total, maximum number of cases belonged to age group between 71-80 (33.33%) showing that as age increases, incidence of ulcer also increases.

Table 2: SEX-WISE DISTRIBUTION

	Phenytoin	Sucralfate	TOTAL
Male	18	22	40 (66.66%)
Female	12	8	20 (33.34%)

In both phenytoin and sucralfate group, chronic ulcers are more common in males when compared to females. Among them, 66.66% were male and 33.34% were females.

Table 3: ONSET OF ULCER FORMATION

Onset	Phenytoin	Sucralfate	TOTAL
Trauma	17	14	31 (51.66%)
Spontaneous	13	16	29 (48.33%)

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51.66% were traumatic in origin, trauma being the triggering factor secondary to neuropathy. 48.33% of the ulcers were spontaneous in origin secondary to blister formation or unnoticed trivial trauma

Table 4: RATE OF GRANULATION TISSUE FORMATION:

	MEAN	STANDARD DEVIATION	P VALUE (by student t test)
Phenytoin	58.63	17.38	P <0.05
Sucralfate	52.76	17.27	

Rate of granulation tissue formation is greater with Phenytoin (Mean=58.65) when compared with sucralfate(Mean=52.76). On applying independent t value, we got p <0.05 which suggests that the results are statistically significant.

Table 5: AREA OF REDUCTION

	MEDIAN	INTERQUARTILE RANGE	P VALUE (by student t test)
Phenytoin	53.84	30.643	P>0.05
Sucralfate	50	65	

Sucralfate has better wound reduction rate when compared to Phenytoin whose interquartile range are 65 and 30.643 respectively. On applying indepentent t test, we got p>0.05 which suggests that the results are not statistically significant.

DISCUSSION

Wound dressings have evolved from the status of providing physical protection to the raw surface, absorbing exudates and controlling local infections by local medications to the level of providing adequate environment promoting wound healing. This has been achieved by modern wound dressing equines promoting granulation tissue formation. The concept of moist wound dressings which came into vogue in 1960 revolutionized wound care.[21,22]This led to further research in this direction leading to influx of many products.People have tried various non-conventional topical agents in wound healing such as Aloe Vera, antacids, benzoyl per-oxide, collagen, gentian violet, impregnated gauze, insulin, mercurochrome oxygen therapy, sugar and vinegar. Each claiming a better wound healing rate than the others. As the concept of outcome-based medicine evolved, the need for better wound dressing modality became more acute. Now wound dressing systems were compared not only on the basis of the rate of

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granulation tissue formed or the rate of wound healing but also on the cost and duration of hospital stay of the patient which was considered as a measure of the morbidity of the patient[23].

The study is similar to the study conducted by Dr. Naveen H Mahadev. The difference between the present study and the one done by Dr. Naveen is that he used phenytoin capsule over the wound, and he compared it with conventional saline dressing. In this study, we used phenytoin vial over the wound and compared it with sucralfate capsule dressing.

The study samples were sixty, thirty in each group. Maximum number of cases belonged to age group between 71-80 (33.33%). In study by Dr. Naveen H Mahadev et al[23] ,study's sample size was 100, 50 in each group, Maximum number of cases(57%) belong to the age group of 45 to 65years.

In our study, 66.66% were males and 33.34% were females. This showed that the chronic ulcers are more in males when compared to females. Similar inference was seen in the study by Dr.Aurif F et al[12], where incidence of chronic lower limb ulcers were more in males (76.00%) as compared to females (24.00%).

In this study, 51% were traumatic in origin, trauma being the triggering factor secondary to neuropathy. 49% of the ulcers were spontaneous in origin secondary to blister formation or unnoticed trivial trauma.Similar results were seen in the study by Dr.Mohammad Shafi et al[20] ,where traumatic onset(66%) is more compared to spontaneous onset(34%)

In phenytoin group, the mean of rate of granulation tissue formation was 58.63. In sucralfate group, the mean of rate of granulation tissue formation was 52.76. On applying independent t value test, we found $p<0.05$, which is statistically significant. Therefore, we can say that phenytoin has better rate of granulation tissue formation.
Sucralfate has better wound reduction rate when compared to Phenytoin whose interquartile range are 65 and 30.643 respectively.

Rate of reduction of wound after 10 days = $\frac{\text{(Initial area- Final area)} \times 100}{\text{Initial area}}$

On applying independent t value test, we found $p>0.05$, which suggests that the results obtained are not statistically significant i.e. both phenytoin and sucralfate have similar rate of wound reduction rate.

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CONCLUSION

In this study, it is concluded that, the phenytoin has a better rate of granulation tissue formation in comparison to sucralfate. It is also seen that both phenytoin and sucralfate have similar area of wound reduction rate. Thus, topical phenytoin is better compared to sucralfate in the treatment of chronic ulcers.

REFERENCES

1. G Nagalakshmi, A John Amalan, Heber Anandan, Clinical Study of Comparison Between Efficacy of Topical Sucralfate and Conventional Dressing in the Management of Diabetic Ulcer,10.17354/ijss/2017/302
2. Siddharth P. Dubhashi and Rajat D. Sindwaani, A Comparative Study of Honey and Phenytoin Dressings for Chronic Wounds, 10.1007/s12262-015-1251-6
3. Werdin F, Tenenhaus M, Rennekampff HO. Chronic wound care. Lancet. 2008;372:1860–1862. doi: 10.1016/S0140-6736(08)61793-6.
4. Sharma RK, John JR. Role of stem cells in the management of chronic wounds. Indian J Plast Surg. 2012;45:237–253. doi: 10.4103/0970-0358.101286.
5. Bhatia A, Prakash S. Topical phenytoin for wound healing. Dermatol Online J. 2004; 10:5.
6. Hasamnis AA, Mohanty BK, Patil S. Evaluation of wound healing effect of topical phenytoin on excisional wound in albino rats. J Young Pharm. 2010;2(1):59-62.
7. Arya R, Gulati S. Phenytoin-induced gingival overgrowth. Acta Neurol Scand. 2012;125(3):149-55.
8. Shaw J, Hughes CM, Lagan KM, Bell PM. The clinical effect of topical phenytoin on wound healing: a systematic review. Br J Dermatol. 2007;157(5):997-1004.
9. Firmino F. Potencial terapêutico da fenitoína na cicatrização de radiodermites. Esc Anna Nery Rev Enferm. 2007;11(1):143-9.
10. G. Talas, R.A. Brown, D.A. McGrouther. Role of phenytoin in wound healing: a wound pharmacology perspective Biochem Pharmacol, 57 (10) (1999), pp. 1085-1094.
11. Masuelli L, Tumino G, Turriziani M, Modesti A, Bei R. Topical use of sucralfate in epithelial wound healing: clinical evidence and molecular mechanisms of action. Recent patents on inflammation & allergy drug discovery. 2010 Jan 1;4(1):25-36.
12. Aurif F. A prospective study of comparision between efficacy of topical sucralfate and conventional dressings in the management of chronic lower limb ulcers (Doctoral dissertation).

ISSN:0975-3583,0976-2833 VOL13,ISSUE04,2022

13. Marques Da Costa R, Jesus FM, Aniceto C and Mendes M: Double blind randomized dose-ranging of granulocytemacrophage colony-stimulating factor in patients with chronic venous leg ulcers. Wound Rep Reg 7: 17-25, 1999. 13.
14. McCarthy DM. Sucralfate. New England Journal of Medicine. 1991 Oct 3;325(14):1017-25.
15. Sweetman SC, Sucralfate. In: Martindale: The Complete Drug Reference. 33rd edition, The Pharmaceutical Press, London, pp1250-1251, 2002.
16. Rattan J, Schneider M, Arber N, Gorsky M, Dayan D. Sucralfate suspension as a treatment of recurrent aphthous stomatitis. Journal of internal medicine. 1994 Sep;236(3):341-3.
17. Folkman J, Szabo S, Stovroff M, Mcneil P, Li W, Shing Y. Duodenal ulcer. Discovery of a new mechanism and development of angiogenic therapy that accelerates healing. Annals of surgery. 1991 Oct;214(4):414.
18. Szabo S, Vattay P, Scarbrough E, Folkman J. Role of vascular factors, including angiogenesis, in the mechanisms of action of sucralfate. The American journal of medicine. 1991 Aug 8;91(2):S158-60.
19. Koshariya M, Shitole A, Agarwal V, Dave S. Role of topical Sucralfate in healing of burn wounds. International Surgery Journal. 2018 Aug 25;5(9):2995-3001.
20. Shafi M. To compare the efficacy of recombinant Human Platelet derived growth factor dressing versus conventional wound dressing in wound reduction in patients with chronic diabetic foot ulcer A randomized controlled trial (Doctoral dissertation, RGUHS).
21. Mulder GD, Haberer PA, Jeter KF, editors. Clinicians' Pocket Guide to Chronic Wound Repair. Springhouse Publishing Company; 1999.
22. Madden JW. Textbook of Surgery, The Biological Basis of Modern Surgical Science
23. MAHADEV NH. A study of efficacy of topical phenytoin in the management of diabetic ulcers (Doctoral dissertation, SRI DEVARAJ URS MEDICAL COLLEGE).