Original Article

Topical phenytoin for managing various ulcers: A meta-analysis

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Abstract

Objective: The aim of this meta-analysis was to evaluate the efficacy of topical phenytoin in the treatment of ulcers of different origin compared with other standard topical treatment. **Methods:** Randomized controlled trials were identified by searching PubMed, Embase, Medline, and Web of Science. Outcomes were complete wound healing rate and reduction in wound volume or surface area. **Results:** Thirteen studies with 980 patients were included. Topical phenytoin were associated with a statistically significant improvement of complete wound healing rate compared with other line of management in 11 randomized control trial of 815 patients (odds ratio = 3.03, 95% confidence interval 2.23–4.10, Z = 7.14, $P < 0.00001$). No publication bias exists in this meta-analysis. Three studies from India also confirmed that the topical phenytoin was associated with a statistically significant percent reduction in wound volume compared with the other dressing (mean difference 23.56, 95% confidence interval 19.48–27.64, Z = 11.32, $P < 0.00001$). **Conclusion:** The existent evidence shows that topical phenytoin is more effective for ulcer treatment.

Key words: Randomized control trial, topical phenytoin, ulcer, wound healing

INTRODUCTION

Wounds with nonhealing and chronicity are a significant healthcare problem in today's medical practice.[1] Healing of wound is the process of restoration of the physical integrity of internal or external body structures, and it involves a complex interaction between the cells and various factors like the status of the patient, etc.[2] The healing process consists of:[2]

- An inflammatory response
- Regeneration of the epidermis
- Shrinkage of the wound
- Finally, connective tissue formation, and
- Remodeling.

Rational management of wound and caring accelerates the healing process and prevents mixed infection and chronicity of the wound.[3] Different approaches and methods have been used to achieve shorter complete wound healing times.[1] Various agents that have been tried in wound healing are phenytoin, honey, and amlodipine. Phenytoin was earlier introduced in 1937 as an antiseizure drug.[4] A common side effect with phenytoin is the gingival hypertrophy.[5] The stimulatory effect of phenytoin on the connective tissue by inhibiting collagenase enzyme suggested an exciting possibility for its use in wound healing.[3]

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Access this article online	
Quick Response Code:	Website: www.sudanmedicalmonitor.org
	DOI: 10.4103/1858-5000.160951

How to cite this article: Thangaraju P, Tamilselvan T, Venkatesan S, Eswaran T, Singh H, Giri VC, Showkath Ali MK. Topical phenytoin for managing various ulcers: A meta-analysis. Sudan Med Monit 2015;10:63-7.

METHODS

A search of PubMed and Web of Science, from their inception to February 28, 2015, included the terms "topical phenytoin," "ulcer," and "wound healing." The search detail in PubMed was (topical [all fields] and ["phenytoin" [MeSH terms] or "phenytoin" [all fields]]) and (["wound healing" [MeSH terms] or ["wound" [all fields] and "healing" [all fields]] or "wound healing" [all fields]] and ["ulcer" [MeSH terms] or "ulcer" [all fields]]). In the web of Science Citation Database, the authors selected the Science Citation Index Expanded and Conference Proceedings Citation Index Science databases. The authors supplemented the searches by manually reviewing the references of all relevant studies. Language restrictions were applied on these searches and only the English articles were used.

Study selection

The inclusion criteria included the following: Only randomized controlled trials (RCTs) were included, patients had an ulcer of different origin namely leprosy, diabetic, nonmalignant, pressure, burns and venous, topical phenytoin versus other management like Edinburgh University solution of lime, normal saline, silverex, were used in the treatment of ulcers, complete wound healing/appearances of granulation, and reduction in wound volume or surface area was achieved. Case reports, case series, single arm Phase I trials, retrospective case-control studies, and Phase II nonrandomized trials were excluded.

Quality assessment

Jadad scale was used to evaluate the study quality, which offers a score ranging from 1 to 5 based on the following parameters: Randomization (2), double-blinding (2), and withdrawals/dropouts at follow-up (1). A final score of 1–2 is defined as the low quality and 3–5 as high quality.[6] Two reviewers independently assessed the quality of each included study, and disagreements were resolved by discussion.

Data extraction

An initial form was used to extract data on first author, year of publication, country and number of patients, average duration of treatment, complete wound healing/granulation rate, and volume/surface area reduction in wound in two groups, respectively.

Statistical analysis

Statistical heterogeneity was explored by inconsistency (I^2) statistics. The values of 0–30% represented minimal heterogeneity, 31–50% moderate heterogeneity, and >50% substantial heterogeneity.[7] If there was minimal heterogeneity, a fixed effects model was used for meta-analysis, otherwise, a random effect model based on the DerSimonian and Laird estimator was used.[8] Summary odds ratio (OR) was calculated by taking a weighted average of individual study results. Two-sided $P < 0.050$ was considered statistically significant. Potential publication bias was tested by funnel graph. Analyses were all performed with RevMan 5.2.

RESULTS

Eligible studies and quality

Thirteen RCT studies[9-21] that met the inclusion criteria for meta-analysis were identified. Figure 1 shows the stages in identifying studies for inclusion in this analysis. Characteristics of the studies from the 13 articles included in the meta-analysis are shown in Table 1. Eight studies were conducted in India while Pakistan, Tanzania, Egypt, and UK contributed rest studies. Of the 13 studies, the sample sizes ranged from 28 to 104, the patients' age ranged from 15 to 80 years and in one study <5 years contributed 69%, the duration of treatment ranged from 2 weeks to 16 weeks. The Jadad scale of 10 included studies scored more than three, which indicated high quality. Eleven studies reported data on hospital care; the other two studies reported data on combined hospital and home care.

Complete wound healing rate in topical phenytoin versus other line of management

A total of 11 studies[9,11-19,21] provided sufficient data to analyze complete wound healing, which included 815 patients. The summary OR of the complete wound healing rate in patients treated with topical phenytoin compared with patients treated with other dressings was 3.03, 95% confidence interval 2.23–4.10, Z = 7.14, $P < 0.00001$ [Table 2]. Among those, six studies were done in India.[14-18,21] Funnel plot showed the symmetrical

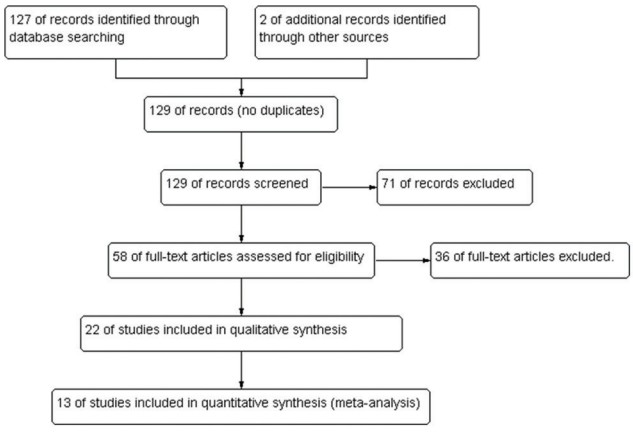


Figure 1: Flow diagram of the study

Table 1: Characteristics of included studies

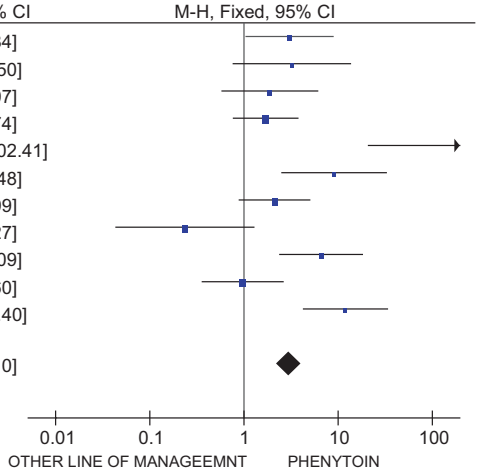
Study ID	Country	Setting	Patients	Age (years)	Dressings	Duration of treatment	Jadad
ARIS DU 2014	PAKISTAN	Hospital care	30 (30)	53.83+-6.66	Vaseline	8 weeks	5
BANSAL LU 1993	INDIA	Hospital care	50 (50)	20-60	Saline	4 weeks	1
CARNEIRO BW 2002	TANZANIA	Hospital care	32 (32)	<5 (69%)	Silverex	2 weeks	3
CARNERIO NMCU 2003	TANZANIA	Hospital care	50 (52)	15-56	EUSOL	4 weeks	5
HOKKAM CVU 2011	EGYPT	Hospital and home	54 (50)	47.3+-6.4	Saline	8 weeks	4
LODHA ABS 1991	INDIA	Hospital	20 (20)	NR	EUSOL	4 weeks 2 days	3
MALHOTRA LU 1991	INDIA	Hospital	50 (22)	30-50 (60%)	ZINC OXIDE	12 weeks	2
MUTHU DU 1991	INDIA	Hospital care	50 (50)	40-80	Saline	5 weeks	4
PAI M DU 2001	INDIA	Hospital	36 (34)	35-70	TALC + SILICONDIOXIDE	6 weeks	5
PENDESE CSU1993	INDIA	Hospital care	40 (75)	35.3	Saline	4 weeks	2
SHAW DU 2011	UK	Hospital and home	31 (34)	61.7+-13.4	Saline	16 weeks	5
SUBBANA 2007	INDIA	Hospital	14 (14)	10-55	Saline	2 weeks 1 day	5
VIJAYA DU 2013	INDIA	Hospital care	50 (50)	22-75	Saline	5 weeks	4

Table 2: Complete healing of wound analysis

	PHENYTOIN		OTHER LINE OF MANAGEMENT			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
ARIS DU 2014	21	30	13	30	8.1%	3.05 [1.05, 8.84]
CARNEIRO BW 2002	29	32	24	32	4.7%	3.22 [0.77, 13.50]
CARNERIO NMCU 2003	45	50	43	52	8.7%	1.88 [0.58, 6.07]
HOKKAM CVU 2011	35	54	26	50	19.7%	1.70 [0.77, 3.74]
LODHA ABS 1991	19	20	1	20	0.1%	361.00 [21.01, 6202.41]
MALHOTRA LU 1991	34	43	5	17	3.1%	9.07 [2.53, 32.48]
MUTHU DU 1991	20	50	12	50	14.9%	2.11 [0.89, 4.99]
PAI M DU 2001	2	20	8	25	13.3%	0.24 [0.04, 1.27]
PENDESE CSU1993	29	40	10	35	6.1%	6.59 [2.40, 18.09]
SHAW DU 2011	18	31	20	34	16.6%	0.97 [0.36, 2.60]
VIJAYA DU 2013	31	50	6	50	4.7%	11.96 [4.29, 33.40]
Total (95% CI)		420		395	100.0%	3.03 [2.23, 4.10]
Total events	283		168			

Heterogeneity: Chi² = 40.15, df = 10 (P < 0.0001); I² = 75%

Test for overall effect: Z = 7.14 (P < 0.00001)



distribution of the studies in this meta-analysis with two studies outlier [Figure 2].

Wound volume reduction in topical phenytoin group

Three studies[10,14,20] dealt with the percentage reduction of ulcer volume in response to topical phenytoin. Mean difference between the two groups in the three studies was 23.56 with 95% confidence interval of 19.48–27.64, Z = 11.32 with a value of $P < 0.00001$ [Table 3]. All the three studies were from India.

DISCUSSION

The aim of the meta-analysis was to determine the current evidence to support the use of topical phenytoin in wound healing by assessing the quality of RCTs in India and the rest of world. A systematic review[22] was done in 2007 for the period up to 2005.This meta-analysis includes studies up to 2015, to know any spectral change in the response of topical phenytoin after 2007, in increased sample sizes. The various category of wounds in our study includes diabetic (395), leprosy (172), burns (64), nonmalignant (102), chronic venous (104), abscess (40), chronic skin ulcer (75), and paraplegic ulcer (28) [Figure 3].

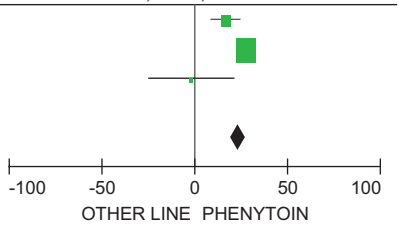
In any study, the sample size is crucial for the study to be sufficiently powered for detecting a true treatment effect.[23] In the 13 studies reviewed, sample size ranged from 28 to 104. An independent randomization process and adequate blinding are the important determinants that contribute to the overall strength of the study. The randomization process was adequately described in many studies, with subjects being randomized truly by an independent process.[9,11-14,16,17,19-21] To minimize study bias, the concept of double-blinding has long been regarded as essential. In general in our meta-analysis, proper double-blinding was

Table 3: Analysis of percentage reduction of ulcer volume

Study or Subgroup	PHENYTOIN Mean	SD	Total	OTHER LINE OF MANAGEMENT Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
BANSAL LU 1993	72.1	19.9	55	55.5	21.6	55	27.6%	16.60 [8.84, 24.36]
LODHA ABS 1991	99.7	1.4	20	72.2	11.1	20	69.2%	27.50 [22.60, 32.40]
SUBBANA 2007	53.94	31.2	12	55.76	27.75	14	3.2%	-1.82 [-24.69, 21.05]
Total (95% CI)			87			89	100.0%	23.56 [19.48, 27.64]

Heterogeneity: Chi² = 10.30, df = 2 (P = 0.006); I² = 81%

Test for overall effect: Z = 11.32 (P < 0.00001)



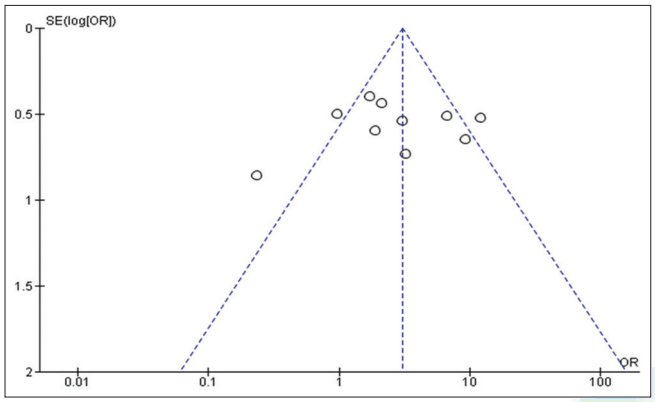


Figure 2: Funnel graph of the studies

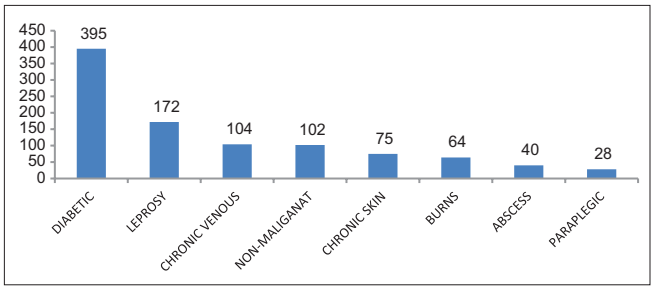


Figure 3: Distribution of various ulcers

reported in 10 studies reported as above, in randomization.

Within the group of 13 studies, there was a similarity in the length of the study treatment period of <5 weeks in eight studies followed by 6, 8, 12, and 16 weeks in other studies. Majority of the studies considered an outcome measure involving complete healing and few studies focused on percentage reduction in wound volume over time. Five[8,14,15,18,21] of the 11 studies reported a statistically significant complete healing rate in the phenytoin-treated group when compared with the control groups in various wound types. Where possible, the calculation of a percentage reduction in ulcer volume in treatment effect also showed that the phenytoin-treated groups had a positive outcome in three studies.[10,14,20]

Two randomized controlled studies[24,25] not included in this meta-analysis also showed some results in two extremes. One of the studies by Bhatia *et al.*,[25] from India showed statistically significant improvement in complete healing and wound volume reduction in 2% and 4% topical phenytoin group which included 30 inpatients. A study[24] showed a negative response toward topical phenytoin when compared with hydrocolloids.

From this meta-analysis, it is seen that topical phenytoin have the property of wound healing in various category of ulcers. Hence, with this meta-analysis, strong evidence is generated in favor of topical phenytoin in different time period and with different population groups.

CONCLUSION

The existing evidence shows that topical phenytoin is more effective than other dressings for various ulcer treatments. Cost-wise also it has its own benefits.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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