International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

A Comparative Study between Amlodipine Dressings and Phenytoin Dressings in Diabetic Ulcers of Lower Limbs

Varanasi Sathya Narayana Murthy[1], Puducheri Hima bindu[2], Padigala Madhuri[3], Shaik Shahul Hameed[4], Chavali Lakshmi Narayana[5]

Department of general surgery, Sri Venkateswara medical college, Sri Venkateswara ram Narayana ruia government general hospital, Tirupati, Andhra Pradesh, India.

[1]Professor, Department of General Surgery, S.V.Medical College , Tirupati .
[2]Assistant Professor, Department of General Surgery, S.V.Medical College , Tirupati .
[3]Post Graduate, Department of General Surgery, S.V.Medical College , Tirupati
[4]Post Graduate, Department of General Surgery, S.V.Medical College , Tirupati
[5]Post Graduate, Department of General Surgery, S.V.Medical College , Tirupati

Abstract

Background: In India, diabetic ulcers constitute up to 10% of diabetes related hospital admission; and the prevalence of diabetes is 2.4% in rural and 12-17% in urban. The risk of losing limb is 25 times higher in diabetes than other illness. Foot disorders like ulceration, infection, gangrene are the leading causes of hospitalization in patients with diabetes milletus in India.

Methods: This is a prospective study conducted on 100 patients above 18 years of age having diabetic foot ulcers who came to the department of general surgery, S.V.R.R.G.G.H., Tirupati over a period of April 2021 to March 2022.

Results: The data analysis of 100 patients has given the following results. Initially, the presence of granulation tissue of both the groups were nearly similar; and over a time of 4 weeks, the group who received phenytoin dressings were having better visual score when compared to those who received amlodipine dressings. It was observed that the wound healing was better with the group who received amlodipine compared to those who received phenytoin dressings.

Conclusion: As the time progressed in successive weeks, it was observed that the wound healing was better with the group who received amlodipine compared to those who received phenytoin dressings.

Keywords: Diabetic Foot Ulcer, Topical Phenytoin, Topical Amlodipine, Granulation Tissue

INTRODUCTION

In India, diabetic ulcers constitute up to 10 percent of diabetes – related hospital admission and the prevalence of diabetes is 2.4% in rural and 12-17% in urban. Almost 40,000 legs are amputated every year because of infected, neuropathic foot in India. The risk of losing limb is 25 times highest in diabetes than other illness. Non-healing chronic wounds are the most common condition a surgeon will encounter. A

chronic wound can persist despite daily dressings and expensive local treatments. This is especially true for diabetic ulcers, pressure ulcers, and venous ulcers.

Many workers have used phenytoin as a local dressing because of its positive effects on ulcer healing, such as increased fibroblast proliferation and collagen deposition, neovascularization, enhanced granulation tissue formation, decreased collagenase action, and bacterial contamination. In macrophages and monocytes, phenytoin increases gene expression of the platelet derived growth factor chain. Phenytoin's antibacterial activity aided in the removal of Staphylococcus aureus, Escherichia coli, Klebsiella species, and Pseudomonas.

Amlodipine is a Calcium Channel Blocker. It has antioxidant properties and promotes nitric oxide production. NO plays an important role in angiogenesis, wound healing, and the proliferation of epithelial, fibroblasts, and keratinocytes. Tissue collagenases such as matrix metalloproteinases are more prevalent at sites of tissue injury. Their action is dependent on intracellular calcium and inflammatory cytokines.

Additionally, CCBs have been shown to have vasodilatory effects, increasing blood flow to the area and stimulating growth factor formation. Gingival hyperplasia, on the other hand, is a side effect to CCBs. Gingival hyperplasia can occur in both the inflammatory and non-inflammatory channels. The potential up-regulation of certain cytokines (e.g., transforming growth factor-β), in the inflammatory pathway may also benefit healing. Reduced folic acid intake causes collagenase activity to decrease in the non-inflammatory pathway

AIM AND OBJECTIVES OF THE STUDY

AIM:

To study Amlodipine dressings and Phenytoin dressings in diabetic ulcers of lower limbs.

Objectives:

1. To study Amlodipine and phenytoin dressings in patients with diabetic ulcers of lower limbs.
2. To compare the rate of wound healing in patients with diabetic ulcers of lower limbs with Amlodipine dressings and Phenytoin dressings.
3. To compare the rate of skin graft, take up in patients with diabetic ulcers of lower limbs with Amlodipine dressings and Phenytoin dressings.

MATERIALS AND METHODS

This is a prospective study conducted among 100 patients presenting with diabetic foot ulcers above 18 years of age who came to the department of general surgery , S.V.R.R.G.G.H ,Tirupati , over a period of one year after obtaining approval from ethical and scientific committee.

Inclusion criteria:

1. Patients with diabetic ulcers of lower limbs.
2. Patients with age more than 18 years.
3. Ulcer less than 50 sq.cm. after debridement.
4.

Exclusion criteria:

1. Patients with x-ray showing osteomyelitis.
2. Doppler showing venous abnormalities like varicosities.
3. Patients receiving corticosteroids, immunosuppressive agents radiation, or chemotherapy prior to entry into the study.

MATERIALS AND METHODS

METHODS OF COLLECTION OF DATA

- A detailed history was taken including history of mode of onset, duration, progression of ulcer.
- Clinical examination.
- Routine laboratory investigations.
- Relevant special investigations.
- Follow up.

INVESTIGATIONS REQUIRED FOR THIS STUDY

- Blood - Hb%, TC, DC, ESR, RBS, Blood Urea, Serum Creatinine, Fasting and Post Prandial Blood Sugar
- Urine -Albumin, Sugar, Microscopy, Ketone bodies.
- Radiological study - Plain x-ray of affected limb, Chest x-ray.
- Specific investigations - Doppler of lower limbs (both arterial and venous), Swab Culture and sensitivity test.

Study method:

Data was collected in standardized proforma from all the patients presenting to department of General Surgery, S.V.R.R.G.G.H./Sri Venkateswara Medical College, Tirupati.

Patients fulfilling the inclusion and exclusion criteria are selected. Informed written consent would be taken from patients included in the study. Patients were divided into two groups by single blind method. Group A treated with Amlodipine dressings. Group P treated with Phenytoin dressings with bedside surgical debridement done whenever indicated. Patients will be followed every week up to 4 weeks (at 1, 2, 3, 4 weeks) and ulcer status was noted at each visit.

RESULTS

Table 1: Age distribution

	Amlodipine		Phenytoin		Total	
	N	%	N	%	N	%
21 – 30	1	2%	2	4%	3	3%
31 – 40	4	8%	4	8%	8	8%
41 – 50	17	34%	17	34%	34	34%
51 – 60	12	24%	11	22%	23	23%
61 – 70	14	28%	13	26%	27	27%
71 – 80	2	4%	3	6%	5	5%
Total	50	100%	50	100%	100	100%
Chi square test = 0.61, p= 0.98, Not statistically significant						

In the present study, 3% of the subjects were aged 21-30 years, 8% were aged 31-40 years, 34% were aged 41-50 years, 23% were aged 51-60 years, 27% were aged 61-70 years, 5% were aged 71-80 years.

Table 2: Diabetes mellitus status

	Amlodipine		Phenytoin		Total	
	N	%	N	%	N	%
Present	31	62%	30	60%	61	61%
Newly detected	19	38%	20	40%	39	39%
Total	50	100%	50	100%	100	100%
Chi square test = 0.04, p= 0.84, Not statistically significant						

In the present study, 61% of the subjects were diabetics, 39% were newly detected diabetics.

There was statistically significant difference across the groups in terms of diabetes, thus both the groups stand comparable in terms of diabetes.

Table 3: Size of Ulcers in cm

	Amlodipine		Phenytoin		Total	
	N	%	N	%	N	%
< 5	2	4%	3	6%	5	5%
6 – 10	26	52%	25	50%	51	51%
11 – 20	21	42%	20	40%	41	41%
>20	1	2%	2	4%	3	3%
Total	50	100%	50	100%	100	100%
Chi square test = 0.57, p= 0.90, Not statistically significant						

In the present study, it was observed that the ulcer was <5cms in 51% of the cases, 41% of the cases had an ulcer of size 6-10cms, in 41% of the cases it was of 11-20cms and in 3% of the cases it was >20cms in size.

There was no statistically significant difference in the size of ulcer across the groups and thus they stand comparable.

Table 4: Grade of Ulcers

	Amlodipine		Phenytoin		Total	
	N	%	N	%	N	%
II	22	44%	20	40%	42	42%
III	12	24%	14	28%	26	26%
IV	16	32%	16	32%	32	32%
Total	50	100%	50	100%	100	100%
Chi square test = 0.24, p= 0.88, Not statistically significant						

In the present study, 42% of the cases had a grade 2 ulcer, 26% of the cases had a grade 3 ulcer, 32% of the cases had a grade 4 ulcer. Both the groups were not different in terms of grade of ulcer and thus they stand comparable.

Table 5: Presence of Granulation tissue

	Amlodipine				Phenytoin			
	1	2	3	4	1	2	3	4
Baseline	26	21	3	0	25	22	3	0
1st week	35	13	1	0	40	8	2	0
2nd week	9	39	1	1	25	20	4	1
3rd week	1	33	14	2	16	23	10	1
4th week	0	7	38	5	6	18	23	3
P <0.001*, Statistically significant								

In the present study, it was observed that there was a significant difference between the presence of granulation tissue

Initially, the presence of granulation tissue of both the groups were nearly similar and over a time of 4 weeks the group who received phenytoin dressings were having better visual score when compared to those who received amlodipine dressings

Table 6: Wound surface area

	Amlodipine				Phenytoin			
	Nil	<5	6-10	>10	Nil	<5	6-10	>10
Baseline	0	2	26	22	0	2	25	23
1st week	0	2	26	22	0	3	19	28
2nd week	0	4	30	16	0	3	21	26
3rd week	0	7	29	14	0	4	26	20
4th week	2	16	25	7	0	6	28	16
P <0.001*, Statistically significant								

Initially, the size of the wound was comparable in both the groups. But as the time progressed and on observation in successive weeks it was observed that the wound healing was better with the group who received amlodipine when compared to those who received phenytoin dressings.

DISCUSSION

One of the most significant and devastating effects of diabetes is diabetic foot ulcer. A diabetic foot with ulceration that is also accompanied with neuropathy and/or peripheral artery disease of the lower limb is referred to as this condition. Diabetic foot ulcers affect 4–10% of diabetics, with older individuals having a higher risk of developing them. Approximately 5% of all diabetic patients have a history of foot ulceration, and diabetic patients have a 15% lifetime risk of acquiring this condition.

Within 6–18 months of the initial evaluation, the majority (60–80 percent) of foot ulcers will heal, whereas 10–15 percent will stay active and 5–24 percent will lead to limb amputation. Neuropathic wounds heal in 20 weeks more often than neuroischemic ulcers, which take longer and frequently result in limb amputation.

Patients with diabetes account for 40–70 percent of all non-traumatic lower limb amputations. Furthermore, many investigations have discovered that foot ulcers occur prior to 85 percent of all diabetic amputations[1].With age and diabetes duration, the risk of foot ulceration and limb amputation increases. Given the poor impact on a patient's quality of life and the associated cost burden on the healthcare system, diabetes foot prevention is crucial.[2,3]Diabetic ulcers are a major health problem that necessitates a multidisciplinary treatment plan. This review will provide a summary of current diabetic ulcer management strategies, ranging from prevention to treatment.

The current study was conducted as a comparison of amlodipine dressings and phenytoin dressings in diabetic ulcers of the lower limbs.

Socio demographic characteristics:

In the present study, 3% of the subjects were aged 21-30 years, 8% were aged 31-40 years, 34% were aged 41-50 years, 23% were aged 51-60 years, 27% were aged 61-70 years, 5% were aged 71-80 years.

There was no statistically significant difference in terms of age distribution in the group who received amlodipine and phenytoin.

Ulcers:

Foot ulcers are a significant complication of diabetes mellitus and often precede lower-extremity amputation. The most frequent underlying etiologies are neuropathy, trauma, deformity, high plantar pressures, and peripheral arterial disease. Thorough and systematic evaluation and categorization of foot ulcers help guide appropriate treatment.

The Wagner and University of Texas systems are the most commonly used for foot ulcer classification, and the stage is indicative of prognosis. The mainstay of initial treatment is pressure relief with total contact casts, removable cast walkers, or "half shoes." Sharp debridement, as well as treatment of underlying infection and ischemia, are essential in the treatment of foot ulcers. Prompt and aggressive treatment of diabetic foot ulcers can often prevent the problem from worsening and eliminate the need for amputation. The goal of therapy should be to intervene early in order to allow for prompt healing of the lesion and to prevent recurrence once it has healed. Multidisciplinary management programmes that

emphasise prevention, education, regular foot examinations, aggressive intervention, and optimal use of therapeutic footwear have shown significant reductions in lower-extremity amputations[4].
In the current study, it was discovered that the ulcer was 5cms in 51% of the cases, 6-10cms in 41% of the cases, 11-20cms in 41% of the cases, and >20cms in 3% of the cases. There was no statistically significant difference in the size of ulcer across the groups and thus they stand comparable. In the present study, 42% of the cases had a grade 2 ulcer, 26% of the cases had a grade 3 ulcer, 32% of the cases had a grade 4 ulcer. Both the groups were not different in terms of grade of ulcer and thus they stand comparable.

Characteristics of ulcer and based on the outcome:

Wound healing is a well-coordinated reparative response that occurs following any surgical procedure or traumatic injury. Inflammation, cell proliferation, angiogenesis, epithelialization, wound contraction, and matrix remodelling are all part of the wound healing process[5]. This multifactorial sequence of processes begins at the time of injury and lasts for varying lengths of time depending on the extent of the injury and the health of the injured individual. The wound healing process is generally divided into three integrated and overlapping phases: the inflammatory phase, which is the establishment of homeostasis and inflammation; the non-inflammatory phase, which is the establishment of homeostasis and inflammation; and the regenerative phase, which is the establishment of homeostasis and inflammation.[6]

During the inflammation phase, inflammatory cells proliferate significantly at the wound site, producing large amounts of reactive oxygen species (ROS) in wound tissue and impairing wound healing.

The proliferative phase, which includes tissue granulation, contraction, and epithelialization, and the remodelling phase, which determines the strength and appearance of the healed tissue. Several natural and synthetic products have been shown in studies to promote wound healing by influencing one or more phases of the healing process.[7]

Phenytoin is one such agent that has been tried in wound healing. Phenytoin (diphenylhydantoin) was first introduced in 1937 to effectively control convulsive disorders.[8]

Gingival fibrous overgrowth is a common side effect of phenytoin. This apparent stimulatory effect of phenytoin on connective tissue suggested a promising application for it in wound healing. Previous clinical trials have shown that topical phenytoin promotes ulcer healing. Calcium channel blockers (CCBs) have been widely used in a variety of cardiovascular conditions and may also play a role in non-cardiac conditions.

According to some studies, cellular calcium metabolism appears to regulate extracellular matrix and collagen production, as well as wound healing. Antioxidants (vitamins A and E, Trolox) have been shown to improve wound healing. In some in vitro studies, nifedipine and amlodipine altered intracellular calcium by acting on voltage gated Ca2+ channels and had antioxidant activity. Previous research has shown that nifedipine has the potential to promote wound healing in both humans and animals.[9]

Granulation tissue:

In the present study it was observed that there was a significant difference between the presence of granulation tissue

Initially the presence of granulation tissue of both the groups were nearly similar and over a time of 4 weeks the group who received phenytoin dressings were having better visual score when compared to those who received amlodipine dressings.

Wound surface area:

Initially the size of the wound was comparable in both the groups. But as the time progressed and on observation in successive weeks it was observed that the wound healing was better with the group who received amlodipine when compared to those who received phenytoin dressings.

Split skin grafts:

There was a statistically significant difference in the application of split skin patches. In the group who received amlodipine 5 of them had a split skin graft by 3rd week, whereas 1 among the phenytoin group was ready to receive split skin graft by 4th week.

The wound closure was significant in around 60% of the subjects with phenytoin dressings in the study done by Shaw J et al., and such healing was seen with phenytoin dressings even in the current study. However, no significant difference was found between the treatment and control groups, and recurrence was seen in a few patients after a 24-week follow-up.[10]

In the study by Jeffcoate et al., 247 (55.0 percent of 449) and 295 (65.7 percent) of the ulcers healed without amputation after 6 and 12 months, respectively. The median (range) healing time was 78 (7–364) days. By the same time points, 5.8 and 8.0 percent of all index ulcers were resolved by amputation, and 6.2 and 10.9 percent by death; 27.8 and 11.6 percent remained unhealed. In contrast, patient-related outcomes revealed that only 202 (45.0 percent) of 449 patients were alive, amputation-free, and ulcer-free at 12 months. This group had been ulcer-free for 272 (1–358) days. A total of 48 patients (10.7 percent) had some form of amputation, and 75 (16.7 percent) had died. When compared to the current study, this study had a higher mortality and morbidity rate, which could be attributed to the fact that the lesions in the current study were mostly of grade 2.

Chronic nonhealing foot ulcers were observed in approximately 15% of diabetic patients in a study conducted by Andrews KL et al[11]. Diabetes-related wound healing is hampered by a variety of factors. Peripheral neuropathy, peripheral arterial disease, limited joint mobility, foot deformities, abnormal foot pressures, minor trauma, a history of ulceration or amputation, and poor visual acuity are all risk factors. A significant number of patients require amputation due to the current treatment for nonhealing diabetic foot ulcers. A multidisciplinary integrated team manages diabetic foot ulcers optimally. Offloading and preventative maintenance are critical. Dressings serve as a supplement. There is an urgent need for novel treatments to improve the healing of diabetic foot ulcers. The goal is for wounds to heal and stay healed.

According to Pendse[12] the wound area reduction was greater in the phenytoin group than in the control group. By day 7, 50% of phenytoin-treated wounds had negative cultures, compared to 17% of controls. 72.5 percent of phenytoin-treated ulcers had completely healed, compared to 28.5 percent of control ulcers. In this current study, the results were also consistent in the arm treated with phenytoin dressings.

Pai MR found that the mean percentage reduction in ulcer area was significantly greater in the experimental group than in the control group. (p 0.05.) The mean difference in ulcer area (in cm2) between pre treatment and posttreatment values was 6.45 cm2 1.53 vs 5.44 cm21.49. When compared to the control group, the phenytoin group showed a slight acceleration of effect. The average length of hospital stay in the phenytoin group was 20.04 (9.141) days, while it was 26.10 (5.701) days in the control group. This variation was statistically significant.

According to Muthukumarasamy MG[13], the mean healing time in the phenytoin group was 21 days versus 45 days in the control group, which used sterile occlusive dressing. After initial debridement or incision and drainage, the majority of patients in both the phenytoin and conventional groups required either a split thickness skin graft or delayed primary suturing as a definitive procedure. In phenytoin–treated patients, no post-operative complications were observed. These findings in terms of hospital stay were consistent with the findings of the current study.

Bhaskar et al[14]. demonstrated in 2005 that the two calcium channel blockers, nifedipine and amlodipine, would improve normal healing by increasing the tensile strength of 10-day-old granulation tissues. In the granulation tissue, neither the hydroxyproline level nor the collagen or glycosaminoglycan content changed significantly.

Microscopic examination of Phenytoin-induced gingival overgrowth biopsies revealed redundant tissue with an apparent regular composition or with an increased amount of collagen and fibroblasts[15]. A possible mechanism for phenytoin's action in wound healing is the inhibition of collagenase synthesis or secretion by fibroblasts.[12]

According to Karmai MY et al. study shows the use of CCBs should be preferred alongside the multimodality approach in ulcer healing in diabetes.[16]

Diabetes ulcer prevention is crucial to lowering the high morbidity and mortality rates associated with the disease, as well as the risk of amputation. The "at-risk foot" must be recognized through a thorough examination and physical examination of the lower limb as well as neuropathy and vascular tests.
In non-ischemic limbs, regular foot examinations, patient education, simple hygienic practices, providing proper footwear, and treating minor injuries promptly can reduce ulcer recurrence by 50% and obviate the need for amputation. Diabetic foot ulcers should be carefully assessed and the gold-standard therapies should be meticulously followed to avoid amputation. More clinical trials are needed to support the existing evidence of the therapeutic value of innovative ways for the treatment of diabetic ulcers, and these approaches should only be used if they are proven to be effective and supplements to gold-standard wound care.

CONCLUSION

- In the present study, it was observed that there was a significant difference between the presence of granulation tissue.
- Initially, the presence of granulation tissue of both the groups were nearly similar and over a time of 4 weeks the group who received phenytoin dressings were having better visual score when compared to those who received amlodipine dressings.
- Initially, the size of the wound was comparable in both the groups. But as the time progressed and on observation in successive weeks it was observed that the wound healing was better with the group who received amlodipine when compared to those who received phenytoin dressings.
- There was a statistically significant difference in the application of split skin patches. In the group who received amlodipine 5 of them had a split skin graft by 3rd week, whereas 1 among the phenytoin group was ready to receive split skin graft by 4th week.

REFERENCES

1. Moxey PW, Gogalniceanu P, Hinchliffe RJ, et al. Lower extremity amputations—a review of global variability in incidence. Diabet Med. 2011; 28:1144–1153. doi: 10.1111/j.1464-5491.2011.03279. x.
2. Prompers L, Huijberts M, Schaper N, et al. Resource utilisation and costs associated with the treatment of diabetic foot ulcers. Prospective data from the Eurodiale Study. Diabetologia. 2008; 51:1826–1834. doi: 10.1007/s00125-008-1089-6.
3. Malgrange D, Richard JL, Leymarie F, French Working Group on The Diabetic Foot Screening diabetic patients at risk for foot ulceration. A multi-centre hospital-based study in France. Diabetes Metab. 2003; 29:261–268. doi: 10.1016/S1262-3636(07)70035-6.
4. Frykberg RG. Diabetic foot ulcers: pathogenesis and management. American family physician. 2002 Nov 1;66(9):1655.
5. Singer AJ, Clark RA. Cutaneous wound healing. N Engl J Med. 1999;341(10):738–46. doi: 10.1056/NEJM199909023411006.
6. Mantle D, Gok MA, Lennard TW. Adverse and beneficial effects of plant extracts on skin and skin disorders. Adverse Drug React Toxicol Rev. 2001;20(2):89–103.
7. Phillipson JD. Phytochemistry and medicinal plants. Phytochemistry. 2001;56(3):237–43.
8. Bhatia A, Prakash S. Topical phenytoin for wound healing. Dermatol Online J. 2004;10(1):5.
9. Lee RC, Ping JA. Calcium antagonists retard extracellular matrix production in connective tissue equivalent. J Surg Res. 1990;49(5):463–6.
10. J. Shaw, C. M. Hughes, K. M. Lagan, M. R. Stevenson, C. R. Irwin, and P. M. Bell. Diabetic medicine. 2011 Oct;28(10):1154-7.
11. Andrews KL, Houdek MT, Kiemele LJ. Wound management of chronic diabetic foot ulcers: from the basics to regenerative medicine. Prosthetics and orthotics international. 2015 Feb;39(1):29-39.
12. Pendse AK, Sharma A, Sodani A, Hada S. Topical phenytoin in wound healing. Int J Dermatol. 1993; 32:214–7.
13. Muthukumarasamy MG, Sivakumar G, Manoharan G. Topical phenytoin in diabetic foot ulcers. Diabetes Care. 1991; 14:909–11.
14. Bhaskar HN, Udupa SL, Udupa AL. Effect of nifedipine and amlodipine on dead space wound healing in rats. Indian J Exp Biol. 2005;43(3):294–296.
15. Mendes JJ, Marques-Costa A, Vilela C, Neves J, Candeias N, Cavaco-Silva P, et al. Clinical and bacteriological survey of diabetic foot infections in Lisbon. Diabetes Res Clin Pract. 2012; 95:153–61.
16. Karami MY, Mansournia N, Bagherian N, Makarem A, MoeinVaziri N, Borna S, Pourdavood AH, Shamohammadi I. Effects of Azelnidipine-Carboxymethylcellulose Gel on Healing of Full-Thickness Skin Wounds in Streptozotocin Induced Diabetic Rats. Veterinary Medicine: Research and Reports. 2019; 10:215.