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COMPARATIVE EVALUATION OF TIMOLOL VS SALINE IN THE TREATMENT OF CHRONIC VENOUS ULCER

Surgery

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ABSTRACT

Venous ulcers are open wounds mainly present in the gaiter region in lower extremities associated with venous disease. Various therapeutic modalities include dressings, topicals, systemic therapy, sclerotherapy and other alternatives. Beta 2 adrenergic receptors are highly expressed in keratinocytes and generate catecholamines that impair keratinocyte migration and wound re-epithelization. Beta blockers like timolol promote wound healing by enhancing keratinocyte migration. Our aim was to compare the effect of topical timolol with topical saline in the treatment of chronic venous ulcer.

A total of 30 clinically diagnosed chronic venous ulcer patients attending Surgery OPD were enrolled into the study after informed consent. Each patient after randomization was allotted in 2 groups. Fifteen patients received topical timolol with dressing and fifteen in the other group received saline dressing. Result was assessed on the basis of ulcer area reduction. The overall mean reduction in the ulcer area was 86.58% in the patients with timolol dressing as compared to 46.33% in the patients treated with saline dressing. Complete closure of the ulcer was observed in six patients (40%) in the timolol group. Topical timolol is recommended for treatment of venous ulcer being a non invasive, easy availability and cost effective option.

KEYWORDS

INTRODUCTION

Venous leg ulcers are open lesions predominantly seen in the gaiter region of leg usually in presence of venous disease. They account for 80-90% of all leg ulcers.[1] Risk factors include female sex, old age, trauma, obesity, immobility, deep vein thrombosis, phlebitis and congenital absence of veins.[2] Various treatment options are available but significant improvement in healing has not been seen. Search still goes on for an ideal therapeutic option. Current treatment includes compression and wound care with dressings. Wound healing involves keratinocyte migration for skin re-epithelialization and complete wound repair. Beta 2 adrenergic receptor (B2AR) is expressed on human keratinocytes.[3] Keratinocyte migration is hindered due to receptor activation hence blocking B2AR will promote wound healing via migration of keratinocyte and fibroblasts, angiogenesis and epidermal differentiation.[4] Timolol, a B2AR blocker has been shown to hasten wound healing when used in chronic leg ulcers. The purpose of this study was to assess and compare the efficacy of topical timolol in venous ulcers.

METHODS

Thirty patients diagnosed with chronic venous ulcer of lower extremities, presenting to the Surgery OPD over the study period were included in the study after obtaining informed consent.

The inclusion criteria of the study was patients who were above 18 years, venous ulcers lasting for at least 4 weeks with no improvement with good wound care, dressings and compression stockings, and patients who refused surgical treatment.

The exclusion criteria of the study included grossly infected ulcers, patients with asthma and COPD and patients on systemic β-blockers.

Each patient after randomization was allotted into 2 groups.

Group 1 Fifteen patients with chronic venous leg ulcer receiving topical timolol

Group 2 Fifteen patients with chronic venous leg ulcer receiving saline dressing.

All patients were advised to continue compression stockings.

Group 1. One milliliter of timolol contains 5mg of the drug. Each milliliter contains 20 drops. Hence, each drop contains 0.25mg of the drug. To each patient, one drop was instilled every 2 cm^2 of wound edge and then covered with sterile dressing. This was repeated every alternate day.

Group 2. One drop of saline was instilled every 2 cm^2 of wound and then covered with sterile dressing every alternate day.

Ulcer margin was measured by measuring the greatest length and the greatest width, perpendicular to the greatest length every week for a maximum period of 4 weeks.

The primary end point is to evaluate the ulcer reduction rate at the end of 4 weeks. Ulcer reduction rate in both groups was calculated at the end of 1 month after beginning the treatment. The healing rate between the groups was compared statistically using Satistical Package for Social Sciences Software Version 25.0.

RESULTS

A total of 30 patients meeting the inclusion and exclusion criteria were enrolled in the study. All the patients were suffering from chronic venous ulcers. The result was assessed on the basis of ulcer area reduction. The mean ulcer area reduction in the timolol group after 1 week was 23.31%, after 2 weeks it was 49.79%, at 3 weeks it was 72.81%, and after 4 weeks it was 86.58%. However, in the saline group, it was 13.63%, 24.58%, 35.62%, and 46.33%, respectively. The overall mean reduction in the ulcer area was 86.58% in the patients with timolol dressing as compared to 46.33% in the patients treated with saline dressing. Complete closure of the ulcer was observed in six patients (40%) in the timolol group. There was no case of complete closure of the ulcer in the saline group.

No local and systemic side effects were seen.

Table 1 Showing Percentage Of Improvement In Patients Treated With Timolol Dressing

S no	Initial measurement cm2	Measurement after 1 week	Measurement after 2 week	Measurement after 3 week	Measurement after 4 week
1	8	5.2	3	2.25	1.8
2	7.2	6.1	4.8	2.2	0
3	14.6	12.7	8	6.4	5
4	22	18.7	13.6	7.36	5.8

5	31.4	24	18.25	5.6	3
6	9	8.12	5	1.2	0
7	17	14.25	9	2.12	0
8	21.3	16	12.25	8.6	6.2
9	3	2.17	1.7	1.2	0.6
10	12	10.8	6.3	2	0
11	16.8	11.72	8.6	5	3.2
12	4.1	2.9	2.1	1.6	0.8
13	11	8.2	4.75	1.3	0
14	20.6	13	10.2	7.4	4.3
15	9.6	6	3.25	1.4	0
Mean percentage	13.84	23.31	49.79	72.81	86.58

Table 2 Showing Percentage Of Improvement In Patients Treated With Saline Dressing

S no	Initial measure ment cm2	Measur ement after 1 week	Measur ement after 2 week	Measur ement after 3 week	Measur ement after 4 week
1	11.6	10.2	9.6	9	8.2
2	8.7	6.25	5	4.2	2.1
3	10	9.2	7.6	5	4.56
4	15.6	14	13.6	13	11.23
5	17.9	15.75	12	9.8	9
6	8.8	7.23	6	5.1	3
7	3.5	3.1	2.6	2.2	1.7
8	18	16.2	14	12.75	11.2
9	9	8.2	7.4	5.35	4
10	24.4	22.7	22.2	21.35	20.8
11	13.5	11.2	8.6	6.25	4.75
12	26.4	23	21.75	18.6	16
13	12	10.2	8.4	8	6.2
14	4.9	4.35	4.1	3.6	3.2
15	16	12.36	10.8	9	8.8
Mean percentage	13.35	13.63	24.58	35.62	46.33

Table 3 Comparing Both Groups In Terms Of Standard Deviation (SD) And P Value

	Groups	SD	P value
Initial measurement	Timolol	7.74152	0.853
	Saline	6.50614	
After 1 week	Timolol	9.57260	0.002
	Saline	5.76268	
After 2 week	Timolol	8.64716	0.000
	Saline	9.55671	
After 3 week	Timolol	11.62373	0.000
	Saline	12.69008	
After 4 week	Timolol	12.51572	0.000
	Saline	16.18985	

DISCUSSION

Venous ulcers are open wounds occurring in the presence of venous insufficiency. Chronic venous insufficiency usually is the result of defective valves in the lower limbs causing excessive pooling of blood resulting in venous hypertension.[5] Etiopathogenesis of venous ulcer includes venous hypertension, inflammatory trap theory, fibrin cuff theory, dysregulation of cytokines and other conditions like protein S or C deficiency, factor V lieden mutation, antithrombin mutation and presence of antiphospholipid antibodies. It clinically presents with brawny edema, lipodermatosclerosis, pruritus, scaling, eczema, atrophie blanche, hemosiderin deposition, tortuous capillaries and viens and inverted champagne bottle sign.[2] Therapeutic armamentarium includes dressings, topicals, systemic therapy, sclerotherapy and other conservative methods. Dressings include hydrogels, hydrocolloids, alginates, foam and antimicrobial.[6] These can be used for exudation, wound rehydration, to maintain oxygen tension and to reduce susceptibility to infection. Unfortunately not much evidence is available regarding the comparison of efficacy of various dressings. A meta-analysis of 42 randomized controlled trials with more than 1000 patients showed no significant difference among dressing types. Selection of wound dressings depends more on the cost and advertisement than any evidence supporting the use of one over another.[7] Other treatment options include debridement, compression stockings, oxygen therapy, skin grafting, negative pressure wound therapy, use of PRP and chorion and placental membrane grafts.[6]

Adequate wound healing undergoes process of inflammation, tissue remodeling and wound re-epithelialization. B2AR is highly expressed in the undifferentiated keratinocytes in the basal layer of epidermis and they also have the ability to generate catecholamine ligands upon wounding. Studies have shown that B2AR is vital for keratinocyte migration, altering fibroblast phenotype, increasing inflammatory cytokines and wound re-epithelialization.[8] Under stressful conditions, supraphysiological concentrations of catecholamine eg epinephrine is present in circulation that impairs healing and keratinocyte migration. Hence use of adrenergic receptor antagonists will reverse the inhibition and enhance keratinocyte migration resulting in wound healing. Various factors that help in the migration of keratinocytes are polarization of cells, facilitation of chemotaxis, activation of extracellular signal related kinases and galvanotaxis. B2AR like timolol has been used in recalcitrant wounds of various etiologies like chronic venous ulcer, diabetic ulcer, traumatic or sickle cell origin.[9]

A case series by Braun LR et al showed that topical application of timolol produced complete wound healing in 3 out of 5 patients.[9] A study by Rai AK et al compared timolol with saline in chronic venous ulcer and showed that timolol group (86.80%) had significant reduction in the size of the ulcer as compared to the saline group (43.82%) after 4 weeks of treatment.[1] A case report by Alsaad AMS et al observed complete healing of vasculitis ulcer by 6 weeks with topical timolol.[10] Baltazard T et al conducted a trial with results supporting the benefit and safety of using timolol maleate to manage hard-to-heal venous leg ulcers.[11] Another study conducted by Thomas B et al showed that leg ulcer healing rates were significantly better in patients who received topical timolol in addition to conventional treatment than patients who received conventional treatment alone.[12] Filoni A et al discusses the use of beta blockers like propranolol and timolol in various dermatologic disorders like hemangiomas, chronic wounds, epidermolysis bullosa, burns, pyogenic granuloma and pyoderma gangrenosum.[13] Our study compared the use of topical timolol with dressing vs saline dressing with 15 patients in each group. We observed mean ulcer area reduction of 86.58% in the patients with timolol dressing as compared to 46.33% in the patients treated with saline dressing. Complete closure was seen in 6 patients with timolol application. No side effects were observed. Our results were similar to the study by Rai AK et al where timolol is compared with saline in chronic venous ulcer.[1] Ours was an attempt to study the efficacy of topical timolol in venous ulcer and its comparison with saline dressing. We can conclude that topical timolol improves the healing of chronic venous ulcers and therefore can be used as a treatment option. Timolol also offers several advantages like cost effectiveness, easy availability as 0.5% eye drops, no adverse effects and ease of application. We accept that the study is limited in terms of sample size and follow up period. More studies are required to establish the adequacy of beta blockers in wound healing.

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