

Original Research Article

Local wound insulin infiltration (injection) and topical timolol gel versus normal saline and povidone iodine in treatment of diabetic foot ulcer

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ABSTRACT

Background: Diabetic foot ulcers (DFUs) are a common complication of diabetes mellitus, contributing significantly to patient morbidity. Effective wound management remains a challenge, prompting investigations into novel treatment methods. This randomized controlled study compares the efficacy of local wound insulin infiltration with topical timolol gel versus standard treatment with normal saline and povidone iodine for DFUs. To evaluate and compare the ulcer healing outcomes of local insulin with topical timolol gel versus normal saline with povidone iodine in treating diabetic foot ulcers.

Methods: A total of 30 patients with chronic DFUs were randomly assigned into two groups. Group 1 received local insulin infiltration (25% of daily insulin dose) and topical timolol gel, while Group 2 received normal saline and povidone iodine. Both groups followed a basal-bolus insulin regimen. The study included patients with Grade 1 or Grade 2 DFUs (Wagner classification) and excluded those with infections, osteomyelitis, or ulcers >20 cm². Outcomes assessed included healing rate, wound area reduction, time to healing, and adverse events over eight weeks.

Results: Group 1 showed a significantly higher healing rate (80% vs. 40%, $p=0.012$) and faster healing time (28.2 ± 10.5 days vs. 42.1 ± 12.1 days, $p=0.008$). Wound area reduction was significantly greater in Group 1 (75.2% vs. 40.5%, $p=0.001$). Minimal adverse events, such as hypoglycemia, were observed.

Conclusion: Local insulin infiltration combined with topical timolol gel is a safe and superior approach to enhance diabetic foot ulcer healing compared to standard treatment. This approach has the potential to improve clinical outcomes for patients with DFUs.

Keywords: Diabetic foot ulcer, Local insulin infiltration, Topical timolol gel, Ulcer healing, Wound area reduction, Randomized controlled trial

INTRODUCTION

Diabetic foot ulcers (DFUs) are a common and severe complication of diabetes mellitus, affecting approximately 15% to 25% of patients during their lifetime. Globally, an estimated 9.1 to 26.1 million new cases of DFUs are reported each year.¹ These ulcers result from various interrelated factors, including poor glycemic control, structural foot deformities, trauma, dry

skin, and compromised blood circulation. Motor, sensory, and autonomic neuropathy are pivotal contributors to DFU development, often resulting in callus formation. Repeated mechanical stress on calluses leads to hemorrhage, which eventually progresses to ulceration. Furthermore, individuals with diabetes frequently suffer from peripheral arterial atherosclerosis, which diminishes blood supply to the ulcerated area, hindering healing and increasing the likelihood of infection. Infected ulcers can

result in osteomyelitis and gangrene, potentially necessitating amputation to prevent further complications.

The management of grade-0 to grade-2 DFUs, as classified by the Wagner system, typically involves surgical or chemical debridement, application of povidone iodine, dressing, and strict glycemic control. Advanced stages of DFUs, including those with osteomyelitis or gangrenous tissue, often require more aggressive interventions such as amputation.⁷ While topical insulin has been investigated as a therapeutic option for DFUs, its application remains underexplored. Studies in burn wound healing and animal research have demonstrated that localized insulin can enhance vascularization and stimulate granulation tissue formation, which are critical for ulcer recovery.²⁻⁴ However, there is limited evidence regarding its use in human DFUs.

Timolol gel, a beta-2 antagonist widely used for glaucoma and infantile hemangiomas, has shown promise in promoting keratinocyte migration and healing chronic venous ulcers. Despite its proven efficacy in other wound types, the combination of local insulin and timolol gel has yet to be thoroughly studied in the context of DFUs. By examining this novel therapeutic approach, this study aims to expand the available treatment options for grade-1 and grade-2 DFUs.⁶

The primary objective of this study is to evaluate the efficacy of local insulin infiltration combined with timolol gel application in enhancing healing outcomes for grade-1 and grade-2 DFUs, compared to standard care methods.

METHODS

Study type

This is a randomized, controlled interventional study conducted to assess the efficacy of local insulin infiltration with timolol gel compared to normal saline with povidone iodine in treating diabetic foot ulcers.

Study place

The research was conducted at GMERS Medical College and Hospital, Sola, Gujarat, India.

Study duration

The study duration was from May 2023 to January 2025.

Total number of subjects will be 30 which will be randomly divided into two groups 1 receiving local insulin and timolol and group-2 receiving normal saline and povidone iodine. Randomization will be done through lottery method.

Inclusion criteria

Patients who are above 18 years and sign the consent form. Patients having diabetes mellitus and chronic diabetic foot ulcer due to burn, physical injury, recurrence of previously healed ulcer are included. Patients who have grade 1 or grade 2 diabetic foot without infection or osteomyelitis. Diabetic foot ulcer between 0.5 sq.cm–20 sq.cm will be chosen for the study. Patient who does not have any past history of allergic reaction to insulin, asthma, bronchospasm or COPD are not included.

Exclusion criteria

Patient who are <18, neonates, pregnant females are excluded. Patients who does not have diabetes mellitus and ulcer due to other etiology such as burns, venous or arterial origin are excluded. Patients who wants to discontinue their affiliation with the research during time period in which it is conducted. Patients having infection or osteomyelitis i.e., which are Grade-4 or Grade-5 diabetic foot. Patients presenting with severe conditions (like DKA) along with diabetic foot ulcer. Patient having plantar ulcer on pressure bearing areas. Patients in which dorsalis pedis artery is not palpable are excluded. Patients having >20 sq. cm size diabetic foot ulcer are excluded. Patients who have history of allergic reaction to insulin, asthma, bronchospasm, or COPD are exclude. Patients with hypotension are excluded.

Time duration of the study will be Eight weeks. This time is deduced based on many studies involving wound healing and formation of granulation tissue which in general takes >4weeks with different approaches of treatment.

Group 1

The patients in group-1 are put of basal-bolus regime of insulin. Basal- bolus regime consists of giving long acting (basal) insulin once a day to maintain blood sugar throughout the day and giving short acting (bolus) insulin before meal to maintain increase in blood glucose after consumption of food.

Long-acting insulin glargine which acts as basal dose of insulin is given once a day while dressing in the morning for the complete duration of the study out of which 25% dose will be administered locally around the ulcer of the diabetic foot the other 75% will be administered subcutaneous route abdominally (rotation of site of injection will be done to prevent lipodystrophy).

Short acting insulin lispro dose will be administer half an hour before every meal also subcutaneously. Total insulin dosage will be calculated according to body weight and Random blood glucose levels. Before and after administrating insulin, glucose level will be check at

every 0.5, 1, 2 and 4 hours to check for hypoglycemia using Glucometer.

Topical timolol gel dosage will be 0.25 gm/1 sq.cm/day. This dosage is determined by using data from similar study using timolol drops in chronic venous ulcer and hemangioma and diabetic ulcer.

Every day during dressing, debridement of necrosed tissue, timolol gel will be applied and local insulin (insulin glargine) will be administered along with the basal insulin (insulin lispro).

Patients which develop infection during the course of therapy will be dropped from the study and transferred to medicine department for treatment.

Group 2

The patients in group 2 are also put on basal-bolus regime of insulin. Long-acting insulin glargine which acts as basal dose of insulin is given once a day during the same time every day for the complete duration of the study out of which 100% dose will be subcutaneously administered in abdomen. Short acting insulin lispro dose will be administer half an hour before every meal also subcutaneously.

Normal saline of equal quantity to 25% dose of insulin glargine dose will be given locally in group 2 patients. Every day during dressing, debridement of necrosed tissue, normal saline will be given locally around the diabetic foot ulcer and povidone iodine will be applied. Patients which develop infection during the course of therapy will be dropped from the study and transferred to medicine department for treatment.

Instrument, scheduling and dosage of insulin administration

For insulin administration Insulin syringe with gauge as shown in the Table will be used.

Measurement of diabetic foot ulcer

Measurement will be done by ruler method. Ulcer area is calculated by measuring greatest length and greatest width and multiplying both. Depth will be measured by putting q-tip in the deepest part of ulcer and measuring the length. Ulcer area will be calculated and noted after two consecutive days. Apart from the area, photograph of the diabetic foot with the ulcer will be archived.

Procedure

Baseline assessment and randomization

Participants who met the inclusion criteria were thoroughly assessed and their medical histories, random blood glucose levels, and baseline ulcer measurements

were documented. Eligible individuals were then randomly assigned to either group 1 or group 2 using a lottery method to ensure unbiased allocation.

Group 1 (Treatment with local insulin and timolol gel)

In group 1, patients followed a basal-bolus insulin regimen to maintain glycemic control. The long-acting insulin glargine was administered once daily, with 25% of the total dose injected locally around the ulcer and the remaining 75% administered subcutaneously in the abdominal area. To prevent lipodystrophy, the injection site was rotated daily. Short-acting insulin lispro was given subcutaneously half an hour before meals, with the dosage adjusted based on random blood glucose levels. Blood sugar levels were monitored post-insulin administration at intervals of 30 minutes, 1 hour, 2 hours, and 4 hours to detect and address hypoglycemia promptly.

For local treatment, the ulcer site was carefully debrided using surgical or hydrogen peroxide methods to remove necrotic tissue. Following debridement, timolol gel was applied at a dosage of 0.25 g per cm² of the ulcer area. This dosage was based on data from previous research involving timolol in chronic venous ulcers and hemangiomas. The ulcer was then dressed with sterile gauze and bandages. Patients who developed infections during the study period were removed from the trial and referred to the medicine department for specialized care.

Group 2 (standard care with normal saline and povidone iodine)

Group 2 participants also followed a basal-bolus insulin regimen identical to group 1, with 100% of the long-acting insulin glargine dose administered subcutaneously in the abdominal region. Short-acting insulin lispro was given before meals, with regular glucose monitoring to ensure safety and effectiveness.

For ulcer care, patients in group 2 underwent daily debridement to remove necrotic tissue. Following this, normal saline-equivalent in volume to 25% of the basal insulin dose used locally in group 1-was applied to the ulcer. Povidone iodine was then used as a disinfecting agent before dressing the site with sterile gauze and bandages. Patients with any signs of infection during the treatment were similarly excluded from the study.

Ulcer measurement and monitoring

The ulcer dimensions were measured every two days using a ruler method. The largest length and width of the ulcer were recorded to calculate the total area, while depth was determined by inserting a q-tip into the deepest part of the ulcer. These measurements were documented for progress monitoring. Photographic records of the ulcers were also maintained to visualize healing and evaluate treatment outcomes.

Ethical approval

The protocol was reviewed and approved by the Ethical Review Board of GMERS Medical College and Hospital, Sola. All participants provided written informed consent before study enrollment.

Statistical analysis

Descriptive statistics were utilized to summarize patient demographics and treatment outcomes. The chi-square test was used for categorical data, while independent t-tests analyzed continuous variables.

Logistic regression modeling assessed the impact of treatment regimens on healing rates and other outcomes. Statistical significance was set at $p < 0.05$.

RESULTS

Baseline characteristics

The baseline characteristics of the two groups were comparable, with no statistically significant differences observed. The similarity in baseline metrics ensures the validity of outcome comparisons.

Outcome measures

Interpretation

Group 1 had a significantly higher healing rate (80% vs. 40%) and a shorter time to healing (28.2 vs. 42.1 days). These differences are statistically significant, underscoring the efficacy of local insulin and timolol gel treatment.

Wound area reduction

Interpretation

Group 1 exhibited a significantly greater reduction in wound area compared to group 2. This highlights the superior ability of local insulin and timolol gel to promote granulation tissue formation and wound closure.

Adverse events

Interpretation

The incidence of adverse events was minimal in both groups, with no statistically significant differences observed. Statistical analysis was performed using SPSS (version 27.0). All p values were computed through independent t-tests for continuous variables and chi-square tests for categorical variables. A significance level of $p < 0.05$ was used to determine statistical significance.

The study compared the efficacy of local insulin and timolol gel (group 1) versus normal saline and povidone iodine (group 2) in the management of diabetic foot ulcers. Key findings include.

Ulcer healing

The healing rate in group 1 was significantly higher, with 80% (12/15) achieving complete healing compared to 40% (6/15) in group 2 ($p = 0.012$).

The average time to complete healing was notably shorter in group 1 (28.2 ± 10.5 days) compared to group 2 (42.1 ± 12.1 days) ($p = 0.008$).

Wound area reduction

Group 1 showed a significantly greater reduction in wound area ($75.2 \pm 15.1\%$) compared to Group 2 ($40.5 \pm 18.2\%$) ($p = 0.001$).

Complications

Hypoglycemia occurred in 13.3% (2/15) of group 1 participants but was mild and resolved quickly. Infections were reported in 20% (3/15) of group 2 participants, necessitating their removal from the study ($p = 0.04$).

Granulation tissue formation

Group 1 exhibited earlier and more robust granulation tissue formation, with 50% coverage within two weeks compared to three weeks in group 2 ($p = 0.02$).

Table 1: Wanger classification.

Grade	Lesion
0	No open lesions, may have deformity or cellulitis
1	Superficial diabetic ulcer (partial or full thickness)
2	Ulcer extension to the ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis
3	Deep ulcer with abscess, osteomyelitis, or joint sepsis
4	Gangrene localized to the portion of the forefoot or heel
5	Extensive gangrenous involvement of the entire foot

Table 2: Insulin syringe with following gauge.

Needle length	Needle gauge	Barrel size
3/16 inch (5 mm)	28	0.3 ml
5/16 inch (8 mm)	29, 30	0.5 ml
1/2 inch (12.7 mm)	31	1.0 ml

Table 3: Basal-bolus insulin therapy for diabetes management.

Basal-bolus insulin therapy
Discontinue oral antidiabetic drugs on admission
Start total daily insulin dose: 0.4 units · kg body wt ⁻¹ · day ⁻¹ when the admission blood glucose concentration is 140-200 mg/dl (25% dose locally in group -1 patient) 0.5 units · kg body wt ⁻¹ · day ⁻¹ when the admission blood glucose concentration is between 201-400 mg/dl (25% dose locally in group -1 patient)
Give insulin glargine once daily at the same time of the day
Give insulin lispro in three equally divided doses before each meal. Hold insulin lispro if patient is not able to eat.

Table 4: Supplemental insulin protocol.

Supplemental insulin protocol
Give supplemental insulin lispro following the “sliding-scale” protocol for blood glucose >140 mg/dl
If a patient is able and expected to eat all or most of his/her meals, give supplemental lispro insulin before each meal and at bedtime following the “usual” column.
If a patient is not able to eat, give supplemental lispro insulin every 6 h (6–12–6–12), following the “insulin-sensitive” column.

Table 5: Insulin dose adjustment strategy.

Insulin dose adjustment strategy
If the fasting or mean blood glucose during the day is >140 mg/dl in the absence of hypoglycemia, increase insulin glargine dose by 20% every day.
If patient develops hypoglycemia (<70 mg/dl), decrease glargine daily dose by 20%.

Table 6: Insulin scale.

Blood glucose (mg/dl)	Insulin sensitive	Usual	Insulin resistant
>141–180	2	4	6
181–220	4	6	8
221–260	6	8	10
261–300	8	10	12
301–350	10	12	14
351–400	12	14	16
>400	14	16	18

Table 7: Baseline characteristics.

Characteristic	Group 1 (Local Insulin+Timolol Gel)	Group 2 (Normal Saline+Povidone Iodine)	P value
Number of patients	15	15	N/A
Age (mean ± SD)	55.2±10.1	56.5±9.5	0.675
Sex (male/female)	9/6	10/5	0.732
Duration of diabetes (years)	10.2±5.1	11.1±4.9	0.642
HbA1c (%)	8.5±1.2	8.8±1.1	0.512
Ulcer size (cm²)	5.2±2.1	5.5±2.3	0.768

Table 8: Ulcer healing.

Outcome	Group 1 (Local Insulin+Timolol Gel)	Group 2 (Normal Saline+Povidone Iodine)	P value
Ulcer healing rate (%)	80% (12/15)	40% (6/15)	0.012
Time to healing (days)	28.2±10.5	42.1±12.1	0.008

Table 9: Wound area reduction.

Outcome	Group 1 (Local Insulin+Timolol Gel)	Group 2 (Normal Saline+Povidone Iodine)	P value
Wound area reduction (%)	75.2±15.1	40.5±18.2	0.001

Table 10: Adverse events.

Outcome	Group 1 (Local Insulin+Timolol Gel)	Group 2 (Normal Saline+Povidone Iodine)	P value
Hypoglycemia	2 (13.3%)	0 (0%)	0.157
Allergic reactions	0 (0%)	1 (6.7%)	0.315

DISCUSSION

The findings of this study highlight the significant efficacy of combining local insulin infiltration and topical timolol gel in managing diabetic foot ulcers, demonstrating superior results compared to conventional treatment with normal saline and povidone iodine. The combination therapy in group 1 resulted in faster healing rates, a greater reduction in wound size, and fewer complications compared to group 2. These observations align with earlier findings from Martínez-Jiménez et al, and Madibally et al, which demonstrated that local insulin enhances vascularization and granulation tissue formation, critical processes for wound healing. Zhang et al, further emphasized the role of insulin in promoting angiogenesis and tissue regeneration, which was corroborated in our study by the improved ulcer healing outcomes in group 1.³⁻⁵

The use of timolol gel as an adjunct in this study contributed additional benefits, including capillary stabilization, improved oxygenation, and inflammation modulation. Similar effects have been reported in previous studies on chronic venous ulcers.⁶ The combined effect of local insulin and timolol addresses multiple pathological mechanisms in diabetic foot ulcers, including poor glycemic control, impaired blood flow, and slow tissue regeneration. This dual-action approach underscores its therapeutic potential, offering a marked improvement over standard antiseptic treatment. In contrast, group 2 patients exhibited slower healing rates and a higher incidence of complications. While normal saline and povidone iodine are effective antiseptics, they lack the regenerative properties required for rapid wound closure. The higher infection rates in this group are consistent with reports by Rai et al and Wagner et al, highlighting the limitations of conventional treatments in addressing the multifactorial nature of diabetic ulcers.^{6,7}

Comparison of study outcomes

Healing rates

The faster healing rates observed in Group 1 align with prior findings by Jiménez et al and Zhang et al, who reported similar effects of local insulin on wound closure and vascularization.^{4,5}

Reduction in wound area

The greater reduction in ulcer size in group 1 supports the findings of Bhattani et al, who emphasized the benefits of insulin therapy in reducing wound dimensions.²

Complication rates

Fewer complications in group 1, compared to higher infection rates in group 2, echo the observations of Armstrong et al, who highlighted the role of enhanced angiogenesis and tissue repair in reducing infection risks.¹ This study is not without limitations. The small sample size of 30 participants limits the generalizability of the results. Larger studies are required to confirm these findings across diverse populations. The short eight-week duration provided sufficient data on initial healing but did not allow for the assessment of long-term outcomes, such as ulcer recurrence or sustained improvements in quality of life.

Additionally, the single-center design restricts the applicability of the results to other healthcare settings. Selection bias due to the inclusion and exclusion criteria may have further influenced the outcomes, potentially favoring patients with better wound-healing potential. Future studies should explore long-term outcomes, cost-effectiveness, histological changes, and patient satisfaction with this therapeutic approach.

CONCLUSION

The combination of local insulin infiltration and topical timolol gel offers a superior therapeutic strategy for managing diabetic foot ulcers, significantly improving healing rates, reducing wound area, and lowering infection risks compared to normal saline and povidone iodine.

This dual-action treatment addresses multiple pathological factors in diabetic ulcers and holds promise as an adjunct to standard care. The study demonstrates the potential of this novel approach in enhancing wound healing, but further research with larger sample sizes, multicenter designs, and extended follow-up periods is necessary to establish its long-term efficacy and broader applicability.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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