The Effect of Topical Timolol 0.5% Solution on the Healing of Postoperative Anal and Perianal Wounds; a Randomized Controlled Trial

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ABSTRACT
Background: Wound healing after anal surgery remains a challenging problem. May topical agents have been used to deal with this problem with variable results? Topical timolol was used successfully in the management of chronic and refractory wounds.
Aim: This study aimed to assess the effect of topical timolol 0.5% solution on healing of postoperative anal and perianal wounds.
Patients and methods: 70 participants with anal and perianal wounds were enrolled in this randomized controlled trial. Patients were randomized into two equal groups (35 in each): The timolol group where patients were treated with topical timolol maleate 0.5% solution. The control group wher patients were treated with normal saline solution.
Results: Preoperative patients' characteristics and Quality of life (QoL) were comparable between the two groups. Regarding the % of healing at postoperative 1 month, outcome data showed that there were no significant results (75.7 ± 6 % vs 75.2 ± 10.4 %, $P=0.81$) and healing time (6.2 ± 2.3 vs 5.9 ± 1.7 weeks, $P=0.54$) between the timolol and control groups respectively. Despite the significant improvement in QoL at postoperative 6 months in both groups, non-statistical significant differences were found between both groups regarding postoperative QoL scores at 1, 3, and 6 months. Pain assessment and complications were comparable between both groups and all complications were managed successfully.
Conclusion: Topical timolol 0.5% solution showed no significant advantage over routine postoperative wound care in the case of anal surgical wounds. Further studies using different forms, doses, and concentrations are required.
Keywords: Timolol solution, Surgical wounds, Healing time, Quality of life.

INTRODUCTION

One of the most difficult aspects of postoperative care following anal surgery is facilitating wound healing [1]. Surgical wounds in the anal region heal at a considerably slower rate than wounds in other parts of the body due to contamination within the wound. In addition, surgical wound infections are common and can cause discomfort, pruritus, and exudation, all of which slow healing. Therefore, it is crucial to reduce postoperative wound contamination and speed up the healing process [2].

Many topical agents have been used with variable success rates. According to **Alvandipour et al.** [3]. Individuals who had fistulotomy and were treated with sucralfate ointment (10% sucralfate) had significantly less postoperative pain and faster wound healing. Also, another study on topical metronidazole showed that Topical 10% metronidazole reduced postoperative edema, the overall healing is enhanced in comparison to the control group[4].

Wound healing was accelerated, postoperative pain was greatly reduced, and the need for analgesics was minimized in the first postoperative week when topical glyceryl trinitrate (GTN) was used [5]. Postoperative pain following open hemorrhoidectomy was also lessened by topical atorvastatin 2%, which aided in the recovery process [6]. After anal surgery, a silicate-based wound dressing was utilized in another study to promote recovery. Research demonstrated that a silicate-based wound dressing was superior at treating the wound following anorectal surgery. The average healing duration was reduced in the observation group with hemorrhoidectomy, anal fistula, and anal fissure surgery wounds compared to the control group [1].

Natural therapies, such as Aloe Vera cream applied to the surgical site, have been shown to speed up recovery time compared to a placebo group [7].

Many recent studies supported the utilization of the topical timolol to manage chronic wounds including leg ulcers [8], refractory wounds [9], and diabetic foot ulcers [10]. It has also been observed that topical timolol can speed up the healing of wounds brought on by chronic diabetes and venous insufficiency [8]. But **Dabiri et al.** [11] looked into how well topical timolol worked on fresh wounds. Previous studies demonstrated that the application of topical timolol on acute wounds enhanced cosmetic outcomes at the wound site by a factor of two. In spite of this, timolol's impact on anal surgical wound healing has not been investigated.

PATIENTS AND METHODS

Study design and setting: This study was undertaken in the Colorectal Surgery Unit of the General Surgery Department, Mansoura University Hospital between May 2021 and May 2022.

Sample size calculation: With the aid of sample size calculation software (www.clinicalc.com), 64 patients were randomly assigned to one of two groups, with the goal of achieving an 80% power with an alpha of 5%. Assuming a 10% lost to follow-up and 10% dropout rate, 70 patients were included in the analysis.
Eligibility Criteria: This study included consecutive patients of both genders whose ages ranged between 18-

65 years who were scheduled for simple anal conditions including anal fissure, hemorrhoids, low anal fistula, and high anal fistula with single track.

Exclusion criteria: Patients with recurrent or complex anal fistula, secondary anal fistula, associated anorectal pathology such as neoplasms, inflammatory bowel diseases, fecal incontinence, solitary rectal ulcer syndrome, and rectal prolapse. Patients with any condition that affects wound healing such as immunosuppressive drugs, diabetes mellitus, and connective tissue disorders.

Random sequence generation and blinding: Randomization of the patients were done to be divided into 2 equal groups (each involved 35 patients): **Timolol group** where patients were treated with topical timolol maleate 0.5% solution and the **control group** in which patients were treated with normal saline solution. Randomization was done by the sealed envelope method using randomization software (www.randomization.com). This study was triple-blinded as neither the operators, the assessors, nor the patients were aware of the group to which they were enrolled.

Preoperative Assessment and Preparation:
In addition to the routine history taking and examination, short form 12 (SF-12) health survey's physical component summary (PCS) and mental component summary (MCS) were used to evaluate preoperative effects on quality of life (QoL) (MCS) [12]. All patients were given only clear fluids the day before the surgery and were informed to fast for 6 hours before the surgery. A single rectal enema two hours before the surgery was used.

Surgical Technique: The following techniques were included in the study, lay open fistulotomy in case of low anal fistula, fistulectomy with or without seton application in case of high anal fistula with single track, Milligan-Morgan hemorrhoidectomy, and open lateral internal sphincterotomy with or without skin tag excision in case of chronic anal fissure. At the end of the surgery, proper hemostasis was ensured and wound measurements (length and width) were evaluated. Using a standard measuring tape, we determined the maximum dimensions of the wound throughout its length and width. Since the wounds were elliptical, we used the linear equation to determine their surface area [length x width x 0.7854] (13,14). Then, the study drug solution was applied. Ten drops of timolol 0.5% solution or normal saline were dropped on 1cm * 1cm cotton gauze then it was applied to the anal wound for half an hour. Then, it was removed.

Postoperative care and assessment: Regular ward was used for patient monitoring. The level of pain was measured using a VAS from 0 to 10, with 0 indicating no pain and 10 indicating the worst possible pain.

Patients were discharged after 8 hours. Patients were instructed to have a sitz bath every six hours and to apply the study drug solution on the anal wound after the sitz bath twice per day.

Endpoints and Follow-up: After surgery, patients were checked on at an outpatient clinic once a week for the first two weeks, and then every two weeks until the wound had completely healed. Assessment of wound parameters during follow-up visits was in lithotomy position to ensure adequate exposure. Any patient with delayed wound healing was followed up maximally for 6 months postoperatively. Wound healing was assessed at every visit until complete healing. Complete wound healing was defined as complete epithelialization of the wound and complete closure of the wound from the bottom to the surface. Delayed wound healing was defined as a healing time longer than the mean ± 1 standard deviation of the same management group. Complications such as surgical site infection (SSI), delayed wound healing, or bleeding were recorded. QoL was reassessed at one, three, and six months postoperatively. Pain score was reassessed at every visit until complete wound healing or up to 3 months whichever is earlier. The recovery period was the primary focus of the research. Complications, pain score, and QoL were secondary objectives.

Ethical approval: The Institutional Review Board (IRB) at Mansoura University School of Medicine gave its authorization to the study with the approval number MS.21.08.1615. All participants signed informed consents after a thorough explanation of the goals of the study. The Helsinki Declaration was followed throughout the study's conduction.

Statistical Analysis
SPSST software, version 23, was used for statistical analysis (Bristol, UK). Mean ±standard deviation (SD) were used to characterize continuous variables, whereas range and median were used to characterize discrete ones. Categorical variables were described with numbers and percentages. The student t-test for paired samples was used to look for differences in means of continuous variables. The Mann-Whitney U test was used to look for differences in medians of discrete variables or non-parametric continuous variables and the Fisher exact test or Chi-square test was used to look for differences in proportions of categorical variables. $P \leq 0.05$ for significance.

RESULTS
Patients' Characteristics: Eighty-five patients were initially evaluated, however 12 were ruled out (8 did not satisfy the eligibility criteria, and 4 declined to participate), leaving a final sample size of 73 for the trial (as depicted in Figure (1) of the Consort flowchart).
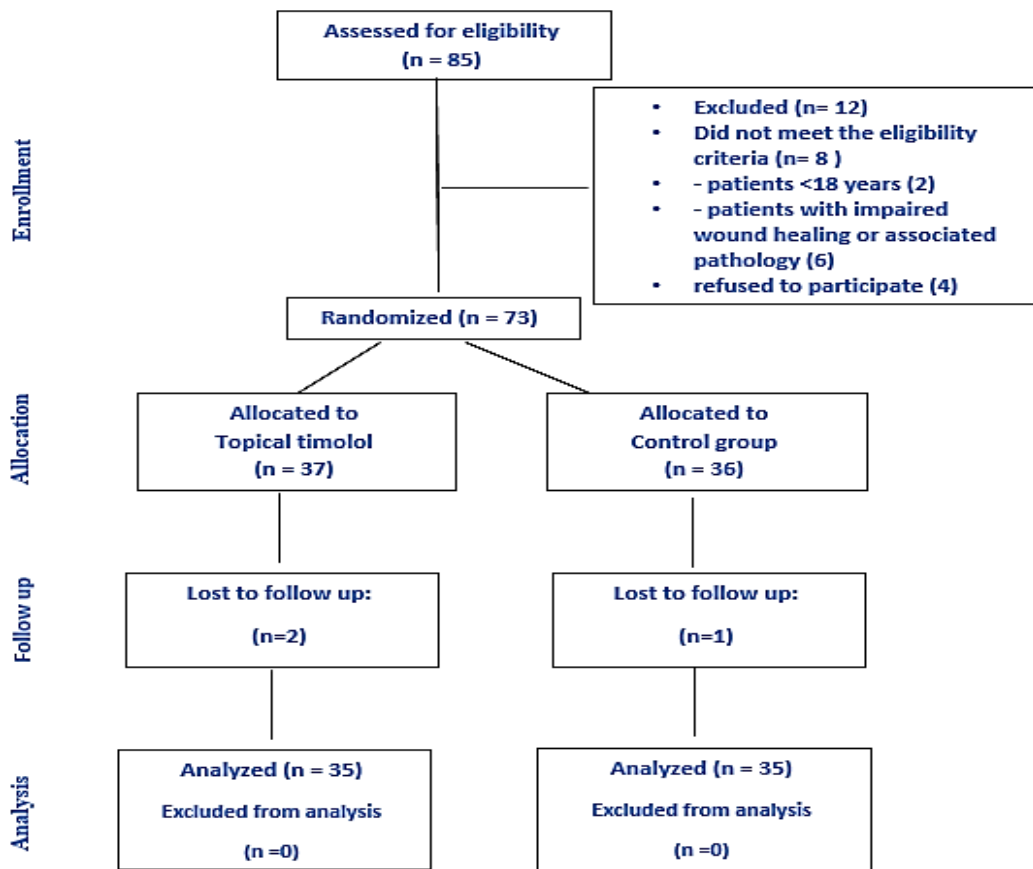
Figure (1): Consort flow chart.

The patients' mean age was 38.6 ± 10.1 years, ranged from 20 to 65 years with non-statistical significant differences regarding the gender and age of the patients. About 53% underwent anal fistulotomy, 15.7% underwent coring fistulectomy and Seton, 20 % were offered open LIS, and 11.4% underwent Milligan-Moran hemorrhoidectomy. Regarding the preoperative assessment of QoL using SF-12, both groups showed no significant difference regarding both PCS and MCS as shown in table (1).

Table (1): Preoperative patients' characteristics

Item	Timolol (*n*=35)	Control (*n*=35)	*P* value
Age (in years), mean ± SD	39.9 ± 9.7	37.3 ± 10.6	0.29
Sex, male/female	26/9	19/16	0.13
Operation, *n* (%)			
• Fistulotomy	18 (51.4)	19 (54.3)	
• LIS	7 (20)	7 (20)	0.92
• Fistulectomy + seton	5 (14.3)	6 (17.1)	
• Haemorrhoidectomy	5 (14.3)	3 (8.6)	
Preoperative SF-12, median (range)			
• PCS	36 (33-39)	37 (33-40)	0.87
• MCS	43 (40-48)	43 (40-45)	0.88

n: number, **SD:** standard deviation, **LIS:** lateral internal sphincterotomy, **SF-12:** 12-item short-form survey, **PCS:** physical component summary, **MCS:** mental component summary.

Wound parameters and healing: There were no significant differences in immediate postoperative wound parameters including length, width, and surface area (*P*=1, *P*=0.13, *P*=0.28, respectively) between the two groups. At postoperative 1 month, despite the decline in both groups, the results of length, width, and surface area were still comparable (*P*=1, *P*=0.1, *P*=0.11, respectively) between both groups. The percentage of reduction of wound surface area after one month in both groups was 75.7 ± 6 vs. 75.2 ± 10.4 for Timolol and control groups, respectively. The percentage of healing did not differ significantly between the both groups (*P*=0.81). The mean duration to achieve wound healing was 6.2 ± 2.3 weeks in the timolol group and 5.9 ± 1.7 weeks in the control group, showing no significant difference between the two groups (P=0.54) (Table 2).

Table (2): Wound parameters and healing

Item	Timolol (*n*=35)	Control (*n*=35)	*P* value
Immediate PO wound parameters, mean ± SD			
• Length (cm)	2.4 ± 0.7	2.4 ± 0.8	1
• Width (cm)	1 ± 0.5	1.2 ± 0.6	0.13
• Surface area (cm^2)	2.1 ± 1.6	2.6 ± 2.2	0.28
1 m PO wound parameters, mean ± SD			
• Length (cm)	1.1 ± 0.4	1.1 ± 0.6	1
• Width (cm)	0.5 ± 0.2	0.6 ± 0.3	0.1
• Surface area (cm^2)	0.5 ± 0.4	0.7 ± 0.6	0.11
% of healing (reduction of wound surface area) after 1m, mean ± SD	75.7 ± 6	75.2 ± 10.4	0.81
Healing time (in weeks), mean ± SD	6.2 ± 2.3	5.9 ± 1.7	0.54

n: number, **SD:** standard deviation, **PO:** postoperative, **m:** month.

Impact on QoL: Despite the significant improvement of QoL at postoperative 6 months in both groups, the parameters of SF-12 were comparable between both groups starting from preoperative until postoperative 1, 3, and 6 months as shown in table (3).

Table (3): Quality of life assessment using SF-12 survey

Item	Timolol (*n*=35)	Control (*n*=35)	*P* value
Preoperative SF-12, median (range)			
• PCS	36 (33-39)	37 (33-40)	0.87
• MCS	43 (40-48)	43 (40-45)	0.88
1 m PO SF-12, median (range)			
• PCS	39 (34-42)	39 (36-42)	0.79
• MCS	46 (41-48)	46 (43-51)	0.25
3 m PO SF-12, median (range)			
• PCS	39 (35-42)	40 (36-43)	0.13
• MCS	46 (41-49)	46 (43-48)	0.77
6 m PO SF-12, median (range)			
• PCS	42 (37-44)	41 (37-45)	0.22
• MCS	47 (44-51)	46 (43-48)	0.07
P value (preoperative & 6m PO SF-12)			
• PCS	**<0.0001#**	**<0.0001#**	
• MCS	**<0.0001#**	**<0.0001#**	

n: number, **SD:** standard deviation, **SF-12:** 12-item short-form survey, **PCS:** physical component summary, **MCS:** mental component summary, **PO:** postoperative, **m:** month. Values (#) are statistically significant (*P*<0.05)

Pain and Complications: There was no statistically significant difference in VAS pain scores between the two groups in the first 24 hours after surgery or at the 1, 2, 4, 6, 8, 10 and 12 week follow-up visits (Table 4).

Table (4): Pain assessment using VAS score

Item	Timolol (*n*=35)	Control (*n*=35)	*P* value
VAS score, median (range)			
• Preoperative	2 (1-6)	2 (1-5)	0.96
• 8 hour	6 (5-8)	6 (5-8)	0.18
• 1 week	3 (1-5)	3 (2-5)	0.81
• 2 week	2 (1-3)	2 (1-3)	0.09
• 4 week	1 (0-2)	1 (0-2)	0.07
• 6 week	1 (0-2)	1 (0-1)	0.7
• 8 week	0 (2-2)	0 (0-1)	0.95
• 10 week	0 (0-1)	0 (0-1)	0.99
• 12 week	0 (0-1)	0 (0-1)	0.99

n: number, **VAS:** visual analog scale

Regarding postoperative complications, 16 patients developed wound infections (9 in the Timolol group and 7 in the control group) in the form of unhealthy granulation tissue at the base of the wound. Bleeding was reported in 4 patients (2 in each group) after hemorrhoidectomy. Recurrence was reported in 4 patients (1 in the Timolol group and 3 in the control group). None of the patients in the study suffered from fecal incontinence. No significant differences were noticed between the two groups about postoperative complications. Among the 16 patients with wound infection, 13 patients were managed conservatively and three patients required curettage and frequent dressing. All patients managed to heal completely within 4-10 weeks. Regarding the four patients with bleeding, they were managed conservatively without any further intervention, using local hemostatics and careful wound dressing. The pathology of the four patients who suffered from recurrence was high anal fistula. They were managed by second-stage surgery (re-setton or mucosal advancement flap). **(Table 5)**.

Table (5): Complications among the studied cases

Item	Timolol (*n*=35)	Control (*n*=35)	*P* value
Complications, *n* (%)			
• SSI	9 (25.7)	7 (20)	0.78
• Bleeding	2 (5.7)	2 (5.7)	1
Recurrence, *n* (%)	1 (2.9)	3 (8.6)	0.61

n: number **SSI:** surgical site infection

DISCUSSION

Post-operative care following anal surgery is complicated by wound healing. It is widely accepted that reducing postoperative pain can hasten a patient's discharge and allow them to get back to their regular routines and activities sooner [1]. The healing phase of an anal surgical wound is substantially slower than that of a wound in any other part of the body due to contamination within the incision. It is also common for surgical wounds to get infected, which can cause pain, pruritus, and exudation and, ultimately, slow the healing process. Therefore, it is crucial to reduce postoperative wound contamination and speed up the healing process [2]. Attempts to promote healing after anal surgery using different topical agents have been described in the literature. Topical sucralfate, metronidazole, GTN, Aloe Vera, atorvastatin, and silicate-based wound dressing have been applied with variable results and variable methods of assessment [1, 3-7].

Many recent studies supported the use of topical timolol for the treatment of chronic leg ulcers, refractory wounds, diabetic foot ulcers, and chronic wounds in patients with diabetes or chronic venous insufficiency (8–10). On the other hand, the effect on the healing of acute wounds was studied by **Dabiri and coworkers** [11] who reported that topical timolol improved the aesthetic results twice more in the wound sites compared to previous studies. Here we studied the effect of topical timolol on the healing of anal surgical wounds.

Previous studies used topical timolol in the form of drops or gel (0.5%). The drops form isn't applicable in case of anal wounds while gel or cream form is hardly commercially available in the local markets, so we used another method to lengthen the contact time with the drug and to provide a fixed dose among the patients. Our method was to apply 10 drops of timolol 0.5% solution on 1cm * 1cm cotton gauze and then it was applied to the anal wound for half an hour. Then, it was removed.

We encountered a wide range of anal surgeries that leave variable wound sizes, so we choose comparable post-operative anal wounds including open sphincterotomy, fistulotomy, coring fistulectomy, and hemorrhoidectomy. These entire wounds resulted from the use of electrocautery. Usually, anal wounds are elliptical in shape. Hence, we used a formula to measure the surface area of the wound elliptical in shape. This may not be the most accurate method but it is a reliable and repeatable method. Despite its importance, it was difficult to assess the wound volume due to variable wound topography.

The two groups were comparable regarding age, sex, and type of operation. In addition, the triple-blinded nature of the study helped to avoid most of the study bias. Regarding the assessment of Qol, there was no valid specific Qol score to assess the anal wound, so the use of a general tool as the SF-12 questionnaire was suitable. The time required to achieve complete wound healing was comparable between the two groups so there was no advantage of using timolol as an anal wound healing promoter. This may be attributed to the form of the drug, dose, concentration, and/or application duration. Other forms of the drug like cream, ointment, or gel are easier to apply, more stable, and have longer application duration. Other studies are required to assess the optimum dose and concentration.

Timolol maleate solution pH is nearly neutral (pH is about 7). It is worth noting that the absorption of topical timolol can be affected by the pH of the wound environment. Wound pH may be lowered in the presence of infection so absorption may be adversely affected [15, 16]. This may partly explain the lack of significant positive effect of timolol on wound healing in some circumstances as demonstrated in our study, although we did not evaluate the pH of our postoperative wound.

In a previous meta-analysis, patients treated with advanced bipolar sealing devices (LigaSure) had a significantly shorter wound healing time and time off from work than the patients submitted to conventional excisional techniques did. Conventional electrocautery causes more thermal injury and tissue damage and this leads to delayed wound healing [17].

Compared to other topical agents, the use of topical 10% sucralfate achieved better more rapid wound healing compared to the control group $(5.9 \pm 0.8$ vs 8.15 ± 1 weeks, $P<0.001)$ [3]. Also, topical 10% metronidazole caused overall wound healing ranked significantly better (4.0 vs 7.0, $P=0.03$) than in controls [4]. Topical 0.2% GTN resulted in significantly greater wound healing at

the end of the third compared to the control group (76.7% vs. 46.7%, *P*=0.02) [5]. Topical 2% atorvastatin on the post-hemorrhoidectomy wound resulted in significantly better wound healing by the 2nd postoperative week compared to the control group (*P*=0.04) [18]. Patients with anal fistulas took an average of 23.72 days to recuperate from surgery, whereas those with mixed hemorrhoids took an average of 19.04 days, and those with anal fissures took an average of 21.14 days, which were shorter than the controls (by an average of 23.25 days for patients with mixed hemorrhoid, 27.76 days for patients with anal fistula, and 24.32 days for patients with a fissure in ano respectively) [1]. Also, the use of natural remedies such as topical Aloe Vera cream showed significantly better wound healing at the end of the second postoperative week compared with the control group (*P*<0.001) [7].

Regarding the assessment of postoperative pain, topical timolol did not help to reduce postoperative pain as the two groups had similar pain scores one week after surgery. Mostly due to comparable healing duration and wound parameters. Also, the complications were minor and comparable between the two groups and were managed successfully either by conservative methods or simple bedside maneuvers. It is of the utmost importance to assess our results based on patient-reported outcome measures. In this study, it was a QoL assessment using SF-12. The two groups were comparable regarding SF-12 score by its two components MCS and PCS. These results are in accordance with the previously discussed values including pain, healing time, complications, and incidence of recurrence.

Limitations of this study: The single-center nature of the study and the small number of patients included in each group. Finally, we used timolol in the form of a solution, which may have compromised its delivery to the tissues, and thus minimized its healing-promoting effect. It would have been optimal to use timolol in ointment or cream form, however these topical forms are hardly commercially available in the Egyptian drug market.

CONCLUSION

The use of topical timolol solution did not significantly promote anal and perianal wound healing in our study. Further larger trials evaluating topical timolol in other topical forms are recommended to ascertain the results of the present trial.

- **Sponsoring financially:** Nil.
- **Competing interests:** Nil.

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