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ORIGINAL ARTICLE

Effect of Topical Baclofen 5% on Post-Hemorrhoidectomy Pain: Randomized Double Blind Placebo-Controlled Clinical Trial

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Abstract

Background Baclofen is an agonist for a subtype of gamma-amino butyric acid (GABA-B) receptors and traditionally been used for the systemic treatment of spasticity. Topical application of baclofen has been shown to reduce pain in patients with localized neuropathic pain.

Objectives In this study, we investigate the efficacy of baclofen cream (5%) in reducing postoperative pain and analgesic requirement after open hemorrhoidectomy.

Design The patients were randomly assigned to either baclofen (5%) cream or placebo immediately after surgery and then every 12 h for 14 days.

Patients A total of 66 patients with third- and fourth-degree hemorrhoids undergoing open hemorrhoidectomy were randomly assigned to this trial.

Setting This study was conducted at a single educational hospital.

Primary and Secondary Outcome Measures The primary outcomes were intensity of pain, measured with a visual analog scale, and the analgesic requirement, measured by the amount of the acetaminophen consumption.

Results No significant difference was found in baseline characteristics between the two groups. Postoperative pain score of the baclofen group was significantly lower on week 1 ($P = 0.01$) and week 2 ($P = 0.02$) than the placebo group. Similarly, patients in the baclofen group consumed significantly less analgesic medication on week 1 ($P = 0.025$) and week 2 ($P = 0.024$) than the control group.

Conclusion Topical application of baclofen effectively relieves pain after hemorrhoidectomy with minimal side effects.

Keywords Postoperative pain · Baclofen · Hemorrhoidectomy

Introduction

Hemorrhoids are highly vascularized tissue found within the submucosa of the anal canal.[1] Hemorrhoids are present universally in healthy individuals and consist of three main cushions located in different directions. When hemorrhoids are associated with bleeding, prolapse, or pruritus, this is considered hemorrhoidal disease (HD).[2] This complication is caused by a complex interplay between genetic and environmental factors, e.g., low-fiber diet, constipation, chronic use of laxative, pregnancy, and genetic factor absence of valve.[1] Treatment varies depending upon the severity of the hemorrhoids and ranges from dietary and lifestyle modification to radical surgery.[3] Generally, hemorrhoids can be divided into two types: internal hemorrhoid and external hemorrhoid.[4] Internal hemorrhoids are further graded based on their appearance and degree of prolapse.[5] Surgical hemorrhoidectomy is generally advocated for third-degree and fourth-degree hemorrhoid. However, postoperative pain is the most dreaded aftermath for patients undergoing the procedure.[6] The mechanism of the pain begins with an acute local inflammatory response due to tissue trauma.[7] Several factors contribute to

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this pain including spasm of the anal sphincter, delayed wound healing, and secondary infection of the exposed wound.[8] It is evident that some medications can decrease post-hemorrhoidectomy pain such as oral non-steroidal anti-inflammatory drugs[9] and gabapentin,[10] or topical administration of calcium channel blockers[11,12], nitrates[13], botulinum toxin,[14] *Aloe vera,*[15] metronidazole,[16] cholestyramine[17], sucralfate,[18,19] and atorvastatin.[20]

Baclofen is a stereospecific agonist at GABA type B (GABA-B) receptors which are abundant in the central nervous system.[21] GABA-B receptor activation prevents the release of pain-stimulating neurotransmitters such as substance P, glutamate, and calcitonin gene–related peptide (CGRP).[22] Topical baclofen has been used empirically in combination with amitriptyline and palmitoylethanolamide for vulvodynia[23,24] and has been studied as a single agent for chemotherapy-induced painful neuropathy[25], neuropathic pain as a result of acromegaly,[26] and also, there is increasing evidence of clinically relevant anti-inflammatory effects of baclofen[27,28] .

In the present study, we investigate the efficacy of baclofen cream (5%) in reducing postoperative pain and analgesic requirement after open hemorrhoidectomy.

Material and Method

Preparation of Baclofen Cream

To prepare the aqueous phase, paraben and methyl paraben as preservatives and borax were solved in autoclaved water with homogenizer and heated at 70 °C. Liquid white paraffin, baclofen powder, and beeswax were mixed and also heated at 70 °C, as the oil phase. Then the aqueous phase was added to the oil phase and mixed continuously while being cooled. Thus, after cooling, the uniform cream that was produced was placed in an aluminum tube, weighing 30 g. Placebo creams were prepared according to a similar protocol with the same ingredients and similar color and texture but without baclofen powder. The physicochemical stability of the creams was evaluated at 50, 60, 70, and 80 °C. Microbiological tests showed no evidence of bacterial growth.

Trial Design

This randomized, double-blinded, and placebo-controlled clinical trial was accomplished in Razi educational hospital, Mazandaran University of Medical Sciences /Iran, from September 2016 to August 2017. The study was approved by the Mazandaran University of Medical Sciences Research Ethics Committee and has been registered in the Iranian Registry of Clinical Trials with registration number 201609163014N16 (the full trial protocol is available online at http://www.irct.ir). The study was performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients after a full explanation and before their enrollment in the study.

Patient Selection

Patients ≤ 70 years of age diagnose of symptomatic third- or fourth-degree internal hemorrhoids, who were referred to the Razi Hospital, candidates for open hemorrhoidectomy, were eligible for inclusion in this study.

Patients with other disorders of anorectal function and/or structure (including perianal abscess anal fissure and fistula-in-ano), with concurrent oral baclofen and gabapentin consumption, with severe pain (VAS score ≥ 7.5) unrelated to hemorrhoidectomy, with previous or concurrent use of opioid analgesics, and blind or deaf patients were excluded from the study.

Outcome Measures

Two parameters were measured as the primary outcomes:

1- Postoperative pain on defecation measured based on the subjective report of visual analysis scale (VAS), ranging from 0, “no pain,” to 10, “very severe pain.”
2- The amount of acetaminophen consumption as painkiller by the patients during 2 weeks after surgery.

Trial Procedure

The participants were allocated to two groups (each of 33 cases) using a simple randomization procedure by a computer-generated table of random numbers. Investigators and patients were unaware of the randomization code and remained blinded to the treatment allocation throughout the study. The open hemorrhoidectomy procedure was performed according to the technique described by Milligan and Morgan[29] for all the participants under a uniform anesthesia protocol (general anesthesia) by the same surgical team including a colorectal surgeon and surgical trainees under supervision. The conventional operative technique consisted of retraction of the pile mass with an artery forceps and diathermy dissection and excision. In a substantial number of cases, surgery was three-column resection and in a very few cases, two-columns were excised. Ligature of the vascular pedicle was performed clear of the internal sphincter.

The patients received the allocated formula immediately after the surgery and then every 12 h for 2 weeks. The first dose was applied under observation of the surgeon and then self-administered by the patient under the guidance

of a trained nurse to ensure the correct use of the cream. The patients were discharged from hospital within 24 h after operation with the order of allocated formula use in the same manner every 12 h, acetaminophen tablets (500 mg) for the management of pain on a PRN (pro re nata/as required) basis and magnesium hydroxide (30 mL/day) up to 2 weeks after the surgery. Patients were visited at postoperative hours 24 and 48 and postoperative days 7 and 14. The intensity of pain and the analgesic requirements were recorded in every visit. All of the details were reported in the questionnaire.

Statistical Analysis

The statistical analysis of the data was carried out utilizing SPSS software (version 22; SPSS, IBM Corp., Armonk, NY, USA). The independent sampled *t* test and one-way analyses of variance (ANOVA) were used to compare group means for the different parameters, whereas the chi-square statistic test was utilized for the comparison of the qualitative data. Values of *P* below 0.05 were considered as a significant difference statistically.

Result

Baseline Characteristics

From 66 patients recruited in the intervention, 6 cases were excluded, 4 because of irregular use of the compound or ignoring the completion of the therapy and 2 because of oral baclofen consumption in the trial period,

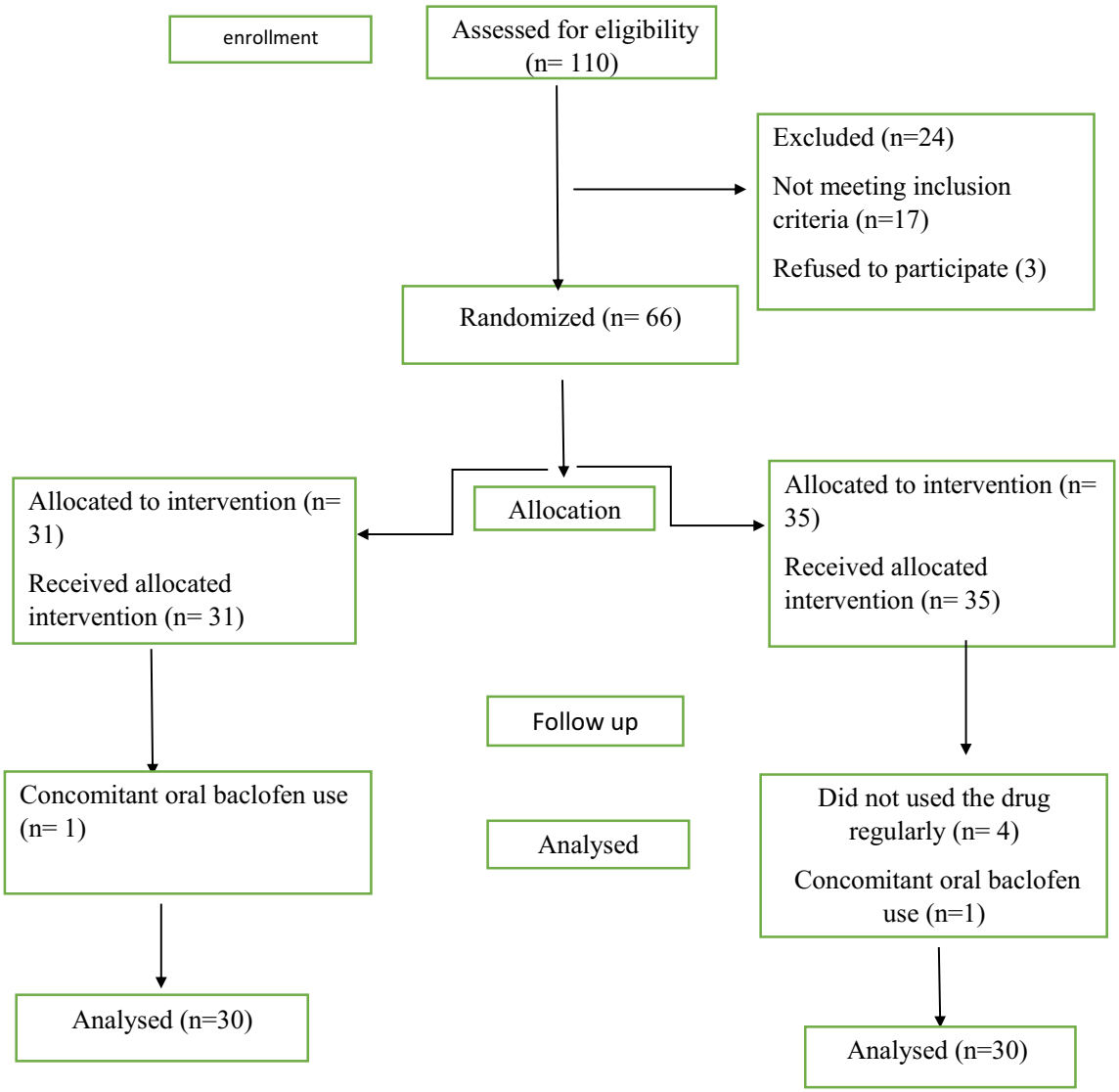

Fig. 1 Participant flow diagram (according to the Consolidated Standards of Reporting Trials (CONSORT 2010 guidelines)). Group A represents patients allocated to topical baclofen, and group B represents patients allocated to placebo

Table 1 Demographic characteristic of the patients

Parameter	Group baclofen	Group placebo	*P* value
Mean age, years	41.54 ± 15.54	43.74 ± 8.37	0.1
Sex			
Male (%)	7 (23.3%)	2 (6%)	0.07
Female (%)	23 (76.66)	28 (93.3%)	
Operation length (min)	30.16 ± 6.91	31.13 ± 6.76	0.8
Hemorrhoids grades (III/IV)	19/11	22/8	0.4

Table 3 Average analgesic consumption at different time intervals

Time	Baclofen	Placebo	*P* value
Acetaminophen			
24 h	0.6 ± 2.19	2.1 ± 1.11	0.4
48 h	0.35 ± 0.55	0.76 ± 1.57	0.1
1 week	1.47 ± 1.78	2.75 ± 2.1	0.025
2 week	0.2 ± 0.6	0.6 ± 0.64	0.024

leaving 60 patients (30 in each group) for analysis (Fig. 1). The study population ranged in age between 18 and 70 years, and there were no statistical differences in mean age ($P = 0.1$), operation length ($P = 0.8$), and grades of hemorrhoids ($P = 0.4$) (Table 1).

Post-Hemorrhoidectomy Pain

Postoperative pain score based on VAS did not differ between the two groups at 24 h after surgery (baclofen group, 5.92 ± 2.59 vs placebo group, 6.53 ± 2.07; $P = 0.3$) or at 48 h after surgery (baclofen group, 4.89 ± 2.51 vs placebo group, 5.27 ± 2.33; $P = 0.5$). Results shown in Table 2 demonstrate significant reduction on pain score in the baclofen group from week 1 ($P = 0.01$) to week 2 ($P = 0.02$), as compared to the placebo group.

The average amounts of analgesic consumption were correlated with the average pain scores for each visit and were found to be significant from week 1 ($P_{24\ h} = 0.4$, $P_{48\ h} = 0.1$ and $P_{week\ 1} = 0.025$, $P_{week\ 2} = 0.024$) (Table 3).

No significant complications or allergic reactions were reported by any of the patients during the trial period. A similar number of patients reported slight bleeding and itching with both treatments. The intervention was well tolerated in all patients and no patient discontinued treatment due to adverse events.

Discussion

Today, the open hemorrhoidectomy technique is still considered to be the mainstay and global gold standard procedure for third- and fourth-degree internal hemorrhoids.[30] But unfortunately, operative hemorrhoidectomy is usually associated with significant postoperative complications which may be potentially life-threatening if massive postoperative bleeding or severe perianal infection intervene.[31] The common post-hemorrhoidectomy complications are severe pain, stenosis, fissure, bleeding, skin tag, thrombosis, papillary hypertrophy, fecal urgency, staples problems, gas flatus, and fecal incontinence.[20,32,33] Post-hemorrhoidectomy pain originating from the surgical incision and tissue inflammation is caused by bacterial infiltration of the wound.[19] Subsequent pain-related complications and infective complications are often the key factors that prolong hospital stay, delay patient recovery, and may be involved in the greater post-operative opioid and analgesic demand.[34,35] Therefore, minimizing postoperative pain is essential.

Table 2 Average postoperative pain scores at different times after hemorrhoidectomy

Time	Baclofen	Placebo	*P* value
24 h	5.92 ± 2.59	6.53 ± 2.07	0.3
48 h	4.89 ± 2.51	5.27 ± 2.33	0.5
1 week	2.89 ± 2.31	4.41 ± 2.54	0.01
2 week	1.65 ± 1.6	2.81 ± 2.18	0.02

The present double-blind, randomized clinical trial study evaluates the efficacy of topical baclofen 5% for post-hemorrhoidectomy pain. Sixty patients (9 males, 51 females) were enrolled in this study. The greater proportion of participants were female (85%). This distribution shift may be influenced by surgeon gender.

The result of this study showed that a significant pain reduction was achieved from the first week of treatment, and also significant difference in analgesic consumption occurred in a similar pattern. The effectiveness of topical baclofen in neuropathic pain has been described in three case reports.[24,26,36] A study found that the combination of amitriptyline, ketamine, and baclofen can improve pain in patients with chemotherapy-induced neuropathy (CIPN).[25] In another retrospective study, 38 patients with vulvodynia received topical baclofen 2% and amitriptyline 2% for 33 weeks. Negative symptom severity significantly decreased in more than half of patients compared to baseline measures.[23] Barton et al. also showed that a combination product of topical baclofen, amitriptyline, and ketamine can improve sensory and motor function in patients with CIPN.[25]

A possible mechanism for the anti-nociceptive effect of baclofen is the inhibition of excitatory neurotransmitters released from primary afferent fibers. The main mechanism is thought to be the glutamate release inhibition from Aδ and C primary afferent terminals in substantia gelatinosa.[37]

Moreover, baclofen inhibits the NK-1 receptor expression in the spinal dorsal horn. Except for the central nervous system, GABAB receptors are found in cutaneous layers on C fibers and keratinocytes.[38]

Conclusions

In conclusion, we demonstrate the effectiveness of topical baclofen in relieving of postoperative pain and reduction of analgesic consumption after hemorrhoidectomy, for the first time.

The main limitation of this study was that the majority of the participants were females, which might have biased the results. Further and larger studies are desirable.

Author Contributions Study design: Shahram Ala, Mina Alvandipour
Implementation: Mina Alvandipour, Majid Saeedi, Mohaddeseh Mansourifar
Data acquisition: Mina Alvandipour, Mohaddeseh Mansourifar, Mahila Monajati
Drafting of manuscript: Shahram Ala, Afshin Shiva
Critical revision of manuscript: Shahram Ala, Afshin Shiva

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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