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Research Article

The Effect of Topical Diltiazem on Post-Hemorrhoidectomy Pain: A Cohort Study

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Abstract

Background: Diltiazem is a calcium channel blocker that can prevent calcium absorption by myocytes and decrease the tone of the internal anal sphincter. Thus, it can be used for the treatment of anal fissures; however, its effect on post-hemorrhoidectomy pain is unclear. Accordingly, the current study aimed to evaluate the effect of topical diltiazem on post-hemorrhoidectomy pain.

Methods: This cohort study included 50 candidates of hemorrhoidectomy referred to Shahid Mohammadi Hospital, Bandar Abbas, Iran from March 20, 2020, to March 21, 2021. First, the characteristics of the patients, including age, gender, degree of hemorrhoid, and the number of hemorrhoid pockets were recorded based on the study purpose. One group received topical diltiazem 2% three times a day for three days after hemorrhoidectomy, and the other group received Vaseline®. Both groups also received 500 mg paracetamol tablets. Post-hemorrhoidectomy pain was assessed using a numerical rating scale (NRS) by patients on the first and third days after surgery. The cumulative amount of consumed paracetamol was also noted on the third day.

Results: Patients in both groups were comparable regarding age, gender, degree of hemorrhoids, and the number of pockets. There was no significant difference between groups in terms of pain on the first day after surgery (P=0.626), while the mean pain score was significantly lower in the diltiazem group on the third day compared to the placebo group (P<0.001). Finally, the cumulative amount of consumed paracetamol was significantly higher in the placebo group (P=0.001).

Conclusion: Overall, topical diltiazem appears to be more effective than placebo for post-hemorrhoidectomy pain reduction.

Keywords: Pain, Hemorrhoidectomy, Diltiazem

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Background

Hemorrhoids are among the most common ailments of the anal region, especially in adults, and hemorrhoidectomy is the most common method of treatment (1). Hemorrhoidectomy is recommended for patients with severe internal or external hemorrhoids or a combination of the two. There are multiple surgical methods for hemorrhoidectomy (2). Hemorrhoidectomy is accompanied by severe pain in the anal region due to the removal of a portion of skin in this area (3).

Pain at the site of surgery can cause anxiety, constipation, urinary retention, and increased hospital length of stay (4). Moreover, post-surgical pain can increase the risk of atelectasis, thromboembolism, myocardial ischemia, cardiac arrhythmia, water and electrolyte disturbance, and ileus (5). Post-hemorrhoidectomy pain has been reported to occur in 75% of the patients, and 80% of these patients experienced average to high levels of pain. Therefore, post-hemorrhoidectomy pain is one of the reasons why patients avoid surgery (6). The mechanism of pain following hemorrhoidectomy is not clear; nevertheless, internal anal sphincter spasm has an important role in post-surgical pain. Increased anal pressure has been reported in recovering patients and is assumed to be one of the primary causes of post-hemorrhoidectomy pain (7). Post-hemorrhoidectomy pain appears to be multifactorial, including anal sphincter spasm, type of anesthesia, surgical method, type of pain control medication used after surgery, and the patient's pain tolerance (8-10).

Non-steroidal anti-inflammatory drugs and opioids have been suggested for pain reduction after hemorrhoidectomy; however, the use of these agents should be limited as they are associated with multiple side effects (10). Other topical drugs such as nitroglycerine and botulinum toxin have also been used for anal sphincter relaxation and pain reduction (6). Nonetheless, the use of nitroglycerin has been associated with headaches, resulting in the increased use of sedatives (11). Diltiazem is a calcium channel blocker that can be administered both orally and topically to relieve pain in patients with anal diseases (12, 13). Calcium channel blockers can relax the

smooth muscles of the digestive system, potentially leading to decreased anal sphincter pressure (14). In fact, diltiazem decreases the reabsorption of calcium by myocytes, preventing the contraction of the internal anal sphincter; therefore, it can be used to treat an anal fissure, but its effect on post-hemorrhoidectomy pain is unclear (15).

Objectives

The present study sought to evaluate the effect of topical diltiazem on post-hemorrhoidectomy pain relief.

Methods

Participants

In this cohort study, we evaluated the candidates for hemorrhoidectomy referred to Shahid Mohammadi Hospital, Bandar Abbas, Iran from March 20, 2020, to March 21, 2021. The inclusion criterion was patients with 3- and 4th-degree hemorrhoids. On the other hand, the exclusion criteria were the presence of anal fissure, history of diltiazem ointment administration for the treatment of anal-related diseases, cardiac diseases, pregnancy, severe or toxic hypertension, and history of cardiac arrhythmias.

The sample size was estimated using the formula for the comparison of means in a two-sample parallel group as follows :

$$n_{\text{در هر گروه}} = \frac{2\sigma^2(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

$$\sigma^2 = \frac{(n_1-1)S_1^2 + (n_2-1)S_2^2}{n_1 + n_2 - 2}$$

Accordingly, the sample size was calculated as at least 25 patients in each group.

In the above-mentioned formula, n is the size of the sample, and S1 and S2 represent the standard deviations (SD) of the first and second sample groups, respectively. In addition, α and 1-β denote the type 1 error and the test power, respectively. Further, μ1 and μ2 are the means of groups one and two, respectively. In this study, α: 0.01 and 1-β: 0.9. According to a double-blind randomized clinical trial study by Wong et al (6), the mean of visual analogue scale (VAS) score in the control group was 4.32 ± 2.13 in the 72nd hour. This score was 0.84 ± 0.92 in the active group in the 72nd hour. By implementing these numbers in the above formula and considering volume loss, the size of each sample was obtained as 25 and 25 for the two groups.

Study Design

All the included patients were initially evaluated by the attending physician the night before the surgery. They did not eat or drink anything for at least 8 hours before the surgery. All participants received spinal anesthesia for the operation. They were then placed in the lithotomy position, and their anal region underwent an examination. The hemorrhoid pockets were removed, and the wound was closed using 2-0 chromic surgical sutures.

Patients in groups A (n=25) and B (n=25) received topical diltiazem 2% (Sobhan Darou Company, Iran) and Vaseline® three times a day for three days after hemorrhoidectomy, respectively. As an oral sedative, an equal number of 500 mg paracetamol tablets were prescribed for all patients. Post-hemorrhoidectomy pain was assessed using a numerical rating scale (NRS) by the patients ("0" and "10" indicated no pain and the worst pain, respectively) on the first and third days after surgery. The cumulative amount of the consumed paracetamol was also noted on the third day.

Data Analysis

The Statistical Package for the Social Sciences (SPSS) software (version 25.0, Armonk, NY: IBM Corp., USA) was used for data analysis. The means and SDs, as well as frequencies and percentages, were used to describe quantitative and qualitative variables, respectively. Based on the results of the Kolmogorov-Smirnov normality test, the independent t-test was applied to compare quantitative variables between groups. The chi-square test was employed to compare qualitative variables, and *P* values ≤0.05 were considered statistically significant.

Results

The general characteristics of patients are provided in Table 1. Patients in both groups were comparable in terms of age, gender, hemorrhoid degree, and the number of hemorrhoid pockets.

The mean pain score did not differ between groups on the 1st day after surgery (*P*=0.626); however, on the 3rd day, the mean pain score was significantly lower in the diltiazem group compared to the placebo group (*P*<0.001). Further, the cumulative amount of paracetamol consumption was significantly lower in the diltiazem group (*P*=0.001, Table 2).

Table 1. General Characteristics of Patients in Diltiazem and Placebo Groups

Variables	Diltiazem (n=25)	Vaseline (n=25)	*P* Value[a]
Age (y), mean ± SD	45.04 ± 16.37	40.28 ± 11.18	0.236[b]
Gender, n (%)			
Male	17 (54.8)	14 (45.2)	0.382
Female	8 (42.1)	11 (57.9)	
Hemorrhoid degree, n (%)			
3rd Degree	18 (72.0)	20 (80.0)	0.508
4th Degree	7 (28.0)	5 (20.0)	
Number of pockets, n (%)			
1 Pocket	6 (24.0)	8 (32.0)	0.812
2 Pockets	13 (52.0)	12 (48.0)	
3 Pockets	6 (24.0)	5 (20.0)	

Note. N: Number; SD: Standard deviation.
[a] Analyzed by the chi-square test. [b] Analyzed by the independent *t* test.

Table 2. Comparison of Pain and Cumulative Paracetamol Consumption Between Diltiazem and Placebo Groups

Variables	Diltiazem (n=25)	Vaseline (n=25)	*P* Value[a]
Pain (NRS), mean ± SD			
1st day	5.00 ± 1.29	4.72 ± 1.51	0.626
3rd day	1.68 ± 1.24	3.28 ± 1.48	<0.001
Paracetamol (mg), mean ± SD	1360.00 ± 860.23	2360.00 ± 1104.15	0.001

Note. N: Number; SD: Standard deviation; NRS: Numerical rating scale.
[a] Analyzed by the independent *t* test.

Discussion

The results of the current study revealed that on the third day after hemorrhoidectomy, the pain was significantly lower with diltiazem compared to placebo. Moreover, the cumulative amount of consumed paracetamol was significantly lower with diltiazem, highlighting the effect of diltiazem on post-hemorrhoidectomy pain reduction. In line with our findings, Rodríguez-Wong et al compared topical diltiazem 2% gel with placebo for post-hemorrhoidectomy pain and reported significantly lower pain and analgesic dose with diltiazem at 24, 48, and 72 hours after surgery (6). They used a visual analogue scale for pain assessment, which is comparable with the NRS used in our study. However, the pain was only significantly lower with diltiazem on the third day in our study. This discrepancy between their results and ours can be explained by the difference in the demographic features, hemorrhoid grade, and the number of pockets. Meanwhile, in another study by Yadav et al, pain scores were lower in the diltiazem group in comparison to controls at 6, 24, and 48 hours and one week after surgery; nevertheless, the difference between groups was not significant at 6 hours (4). Patients in the diltiazem group of the above-mentioned study used the ointment twice a day for a week, which might account for the difference between their findings and those of our study.

Furthermore, in a meta-analysis of randomized controlled trials performed by Huang et al, including 5 trials and a total of 227 patients, diltiazem ointment usage resulted in a statistically significant pain reduction within 48, 72, and more than 96 hours after surgery compared to placebo (14). Other studies have also reported the efficacy of topical diltiazem for post-hemorrhoidectomy pain reduction (1,11,13,16,17). On the contrary, by comparing pain scores during defecation and the number of consumed analgesic tablets between the diltiazem and placebo groups, Sugimoto et al found no statistically significant differences (15). Moreover, the total number of complications was significantly higher with topical diltiazem in their study. Their patients were older than our patients; older age may have reduced the efficacy of diltiazem. Nonetheless, the impact of age on the efficacy of diltiazem needs further investigations.

This study had some limitations. First, the sample size was relatively small, limiting the generalizability of our findings. Second, the follow-up period was quite short; thus, we could not determine the mid- and long-term effects of topical diltiazem on post-hemorrhoidectomy pain.

Conclusion

Topical diltiazem was effective in pain reduction after hemorrhoidectomy, especially on the 3rd day after surgery. In addition, topical diltiazem three times a day for three days after hemorrhoidectomy was associated with reduced sedative consumption.

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Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

This study has received approval from the Ethics Committee of Hormozgan University of Medical Sciences (under the ethics code: IR.HUMS.REC.1399.186) and is in accordance with the statements of the Declaration of Helsinki. Written informed consent forms were obtained from all participants, and they were informed about the purpose of the research and its stages and assured of the confidentiality of their information. Moreover, the subjects were free to withdraw from the study at any stage. They were also informed that they would be provided with the results of the research.

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