

Systematic Review

# Strategies to Reduce Post-Hemorrhoidectomy Pain: A Systematic Review

Varut Lohsiriwat <sup>1,\*</sup>  and Romyen Jitmonggan <sup>2</sup> 

<sup>1</sup> Division of Colon and Rectal Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

<sup>2</sup> The Golden Jubilee Medical Center, Mahidol University, Nakhon Pathom 73170, Thailand; romyenj@gmail.com

\* Correspondence: bolloon@hotmail.com; Tel.: +66-2419-8005; Fax: +66-2412-1370

**Abstract:** *Background and Objectives:* Excisional hemorrhoidectomy is considered as a mainstay operation for high-grade hemorrhoids and complicated hemorrhoids. However, postoperative pain remains a challenging problem after hemorrhoidectomy. This systematic review aims to identify pharmacological and non-pharmacological interventions for reducing post-hemorrhoidectomy pain. *Materials and Methods:* The databases of Ovid MEDLINE, PubMed and EMBASE were systematically searched for randomized controlled trials (published in English language with full-text from 1981 to 30 September 2021) to include comparative studies examining post-hemorrhoidectomy pain as their primary outcomes between an intervention and another intervention (or a sham or placebo). *Results:* Some 157 studies were included in this review with additional information from 15 meta-analyses. Fundamentally, strategies to reduce post-hemorrhoidectomy pain were categorized into four groups: anesthetic methods, surgical techniques, intraoperative adjuncts, and postoperative interventions. In brief, local anesthesia-alone or combined with intravenous sedation was the most effective anesthetic method for excisional hemorrhoidectomy. Regarding surgical techniques, closed (Ferguson) hemorrhoidectomy performed with a vascular sealing device or an ultrasonic scalpel was recommended. Lateral internal anal sphincterotomy may be performed as a surgical adjunct to reduce post-hemorrhoidectomy pain, although it increased risks of anal incontinence. Chemical sphincterotomy (botulinum toxin, topical calcium channel blockers, and topical glyceryl trinitrate) was also efficacious in reducing postoperative pain. So were other topical agents such as anesthetic cream, 10% metronidazole ointment, and 10% sucralfate ointment. Postoperative administration of oral metronidazole, flavonoids, and laxatives was associated with a significant reduction in post-hemorrhoidectomy pain. *Conclusions:* This systematic review comprehensively covers evidence-based strategies to reduce pain after excisional hemorrhoidectomy. Areas for future research on this topic are also addressed at the end of this article.

**Keywords:** hemorrhoidectomy; postoperative pain; analgesics; anesthesia; pain; complication; hemorrhoids; review



**Citation:** Lohsiriwat, V.; Jitmonggan, R. Strategies to Reduce Post-Hemorrhoidectomy Pain: A Systematic Review. *Medicina* **2022**, *58*, 418. <https://doi.org/10.3390/medicina58030418>

Academic Editors: Gaetano Gallo, Ugo Grossi and Arcangelo Picciariello

Received: 26 January 2022

Accepted: 11 March 2022

Published: 12 March 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Hemorrhoids is the most common benign anal disease encountered by physicians and surgeons [1]. It has been estimated that a lifetime risk of hemorrhoids could be as high as 75% in the general population [2]. Although most hemorrhoids can be treated effectively by medication and/or office-based procedures, surgical treatment is indicated in high-grade hemorrhoids or complicated diseases [3–5].

A systematic review and network meta-analysis of various operations for hemorrhoids demonstrated that non-excisional surgeries, such as doppler-guided hemorrhoidal artery ligation and stapled hemorrhoidopexy, were less painful than excisional hemorrhoidectomy [6]. However, the latter had less recurrence and was associated with a lower cost of

surgical instruments. Moreover, both internal and external components of hemorrhoids can be effectively removed by hemorrhoidectomy, which is reasonably easy to learn and perform in an elective or emergency setting [2]. As a result, hemorrhoidectomy is still regarded as the mainstay operation for advanced and/or complicated hemorrhoids although post-hemorrhoidectomy pain remains a challenging problem [7,8]. The incidence of moderate to severe pain following conventional hemorrhoidectomy reported in the literature could be as high as 65% [9]. We hypothesized that some perioperative measures, together with refined surgical and anesthetic techniques, could minimize pain after hemorrhoidectomy. This study, therefore, aimed to systematically review strategies to reduce post-hemorrhoidectomy pain published in the literature.

## 2. Materials and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [10]. Literature published in English language with full text and indexed in Ovid MEDLINE, PubMed and EMBASE from 1981 to 30 September 2021 was independently searched by the two authors. The following search terms were used: (“hemorrhoidectomy” (Title) OR “haemorrhoidectomy” (Title)) AND (“postoperative pain” (All Fields) OR “posthemorrhoidectomy pain” (Title/Abstract) OR “posthaemorrhoidectomy pain” (Title/Abstract)). Synonyms of each of the terms were also used in the search. To obtain the highest level of scientific evidence, only randomized controlled trials (RCTs) and systematic reviews and meta-analyses of RCTs were included.

Fundamentally, comparative studies examining post-hemorrhoidectomy pain as their primary outcomes between an intervention and another intervention (or a sham or placebo) were included. Excisional hemorrhoidectomy was limited to open (Milligan-Morgan) technique, closed (Ferguson) technique, and semi-closed (modified Ferguson) technique. With this search strategy, 701 articles were eligible for further evaluation (168 from Ovid MEDLINE, 227 from PubMed and 306 EMBASE). References of the included studies were further reviewed to identify any additional suitable studies that may be missed by the aforementioned search strategy. Exclusion criteria included studies without extractable data, those with duplicate data, and those with sample size less than 20 patients. Finally, a total of 157 RCTs and 15 meta-analyses were included in this manuscript. Some of major guideline recommendations were also reviewed for additional information. PRISMA flow chart is shown in Figure 1.

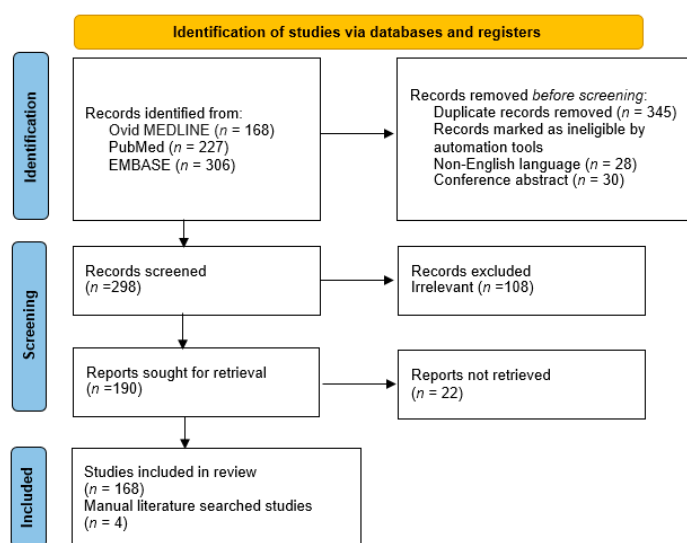


Figure 1. PRISMA flow chart.

It is worth noting that strategies to reduce pain after stapled hemorrhoidopexy, laser therapy, and radiofrequency ablation were not included in this review. Roles of conventional analgesics such as paracetamol and non-steroidal anti-inflammatory drugs on post-hemorrhoidectomy pain were not discussed in this review because the advantages of multimodal opioid-sparing analgesia are clearly evident in surgical practices including hemorrhoidectomy [11].

### 3. Results

Various strategies or interventions to reduce pain after excisional hemorrhoidectomy were identified and categorized into four groups: anesthetic methods, surgical techniques, intraoperative adjuncts, and postoperative interventions.

#### 3.1. Anesthetic Methods

Hemorrhoidectomy could be performed under general anesthesia, spinal anesthesia, caudal block, nerve block, local anesthesia, and combined anesthesia. Preferred anesthetic techniques could vary among patients, surgeons, hospitals, and countries. Effects of anesthetic techniques on post-hemorrhoidectomy pain have been extensively examined in at least 18 RCTs with a total number of 1465 patients [12–21]. A recent systematic review and meta-analysis of seven RCTs comprising 440 patients undergoing excisional hemorrhoidectomy (222 patients with local anesthesia plus intravenous sedation, and 218 patients with spinal anesthesia) has found that local anesthesia combined with intravenous sedation had a significantly lower pain score at 6 h and 24 h after an operation—with mean difference of numerical pain rating scale  $-2.25$  (95% CI  $-3.26$  to  $-1.24$ ) and  $-0.87$  (95% CI  $-1.33$  to  $-0.40$ ), respectively [20]. Moreover, local anesthesia combined with intravenous sedation was associated with a remarkably lower risk of rescue analgesia (risk ratio (RR) = 0.18, 95% CI 0.06–0.53), urinary retention (RR = 0.17, 95% CI 0.07–0.37), and headache (RR = 0.09, 95% CI 0.03–0.33) compared with spinal anesthesia.

Another recent systematic review and meta-analysis of nine RCTs (six for local anesthesia versus regional anesthesia and the others for local anesthesia versus general anesthesia) comprising 727 patients also demonstrated that hemorrhoidectomy under local anesthesia was associated with a significant reduction in the intensity of postoperative pain and length of hospitalization compared with that under regional or general anesthesia [21]. Local anesthetic methods included pudendal nerve block [12], ischiorectal block [13], perianal block [14], posterior perineal block [15], and local anesthetic infiltration into the wound [16,17]. Regarding choices of local anesthetic agents, most investigators would prefer to use a long-acting drug such as ropivacaine, bupivacaine, and liposomal bupivacaine.

Regarding spinal anesthesia, it is worth noting that adding midazolam or morphine to bupivacaine in spinal anesthesia resulted in better pain control in the first 12–24 h after hemorrhoidectomy [18,19].

#### 3.2. Surgical Techniques

##### 3.2.1. Closed versus Open Technique

Comparison of postoperative pain between closed (Ferguson) hemorrhoidectomy and open (Milligan-Morgan) hemorrhoidectomy has been examined in a randomized fashion since early 1990s [22]. Pain following the two techniques was found to be comparable in earlier studies [23,24], but several later studies indicated less postoperative pain in closed hemorrhoidectomy [25–27]. The advantage of closed hemorrhoidectomy on postoperative pain was confirmed in a recent systematic review and meta-analysis of 11 RCTs comprising 1326 patients (663 in closed hemorrhoidectomy and 663 in open hemorrhoidectomy), in which closed technique was associated with a modest but significant reduction in post-hemorrhoidectomy pain (standardized mean difference  $-0.36$ ; 95%CI  $-0.64$  to  $-0.07$ ) [28].

### 3.2.2. Scissors, Diathermy or Other Instruments

During excisional hemorrhoidectomy, a variety of surgical instruments have been used to remove hemorrhoidal tissue, including scissors, diathermy, laser, an ultrasonic scalpel, a vascular sealing device (or bipolar electro-surgical device), and a radiofrequency device. Two prospective randomized studies demonstrated comparable postoperative pain between scissors and diathermy for 'conventional or traditional' hemorrhoidectomy [29,30]. Meanwhile, several systematic reviews and meta-analyses demonstrated that hemorrhoidectomy with a vascular sealing device (Ligasure™) had significantly less postoperative pain, shorter operative time, and decreased blood loss compared with conventional hemorrhoidectomy [31–33]. Likewise, a recent several systematic review and meta-analysis of eight RCTs comprising 468 patients (233 in the ultrasonic scalpel group) has shown that hemorrhoidectomy with an ultrasonic scalpel (Harmonic®, San Jose, CA, USA) had advantages over conventional hemorrhoidectomy in terms of reduced postoperative pain and faster recovery [34].

### 3.2.3. Hemorrhoidectomy Combined with Lateral Internal Anal Sphincterotomy

Since the spasm of the internal anal sphincter (IAS) was thought to be an aggravating factor for post-hemorrhoidectomy pain, chemical sphincterotomy, and lateral internal anal sphincterotomy (LIS) have been proposed to relieve postoperative pain. A recent systematic review of 2180 patients undergoing open or closed hemorrhoidectomy (about 43% having combined hemorrhoidectomy with LIS) has demonstrated less postoperative pain in those with LIS. However, there was a significant higher rate of fecal incontinence in patients with LIS compared with those without (7.7% versus 1.25%), although the severity of fecal incontinence was mild (e.g., flatus incontinence and fecal soiling) and improved over time [35]. In 2021, a single-institute RCT of 200 patients from India also confirmed the efficacy of LIS on better pain relief after hemorrhoidectomy, without compromising anal continence [36].

## 3.3. Intraoperative Adjuncts

### 3.3.1. Injection of Botulinum Toxin

Following the hypothesis of IAS-spasm induced post-hemorrhoidectomy pain, injection of botulinum toxin A into the IAS has been used to induce a transient relaxation of the IAS—instead of surgical division of the IAS which might cause long-term sequelae such as fecal incontinence. The effect of botulinum toxin injection on post-hemorrhoidectomy pain has been examined in a few RCTs, with conflicting results [37–39]. Although the injection of botulinum toxin reduced maximal resting pressure and maximal squeeze pressure up to 12 weeks after hemorrhoidectomy in these RCTs, only two out of the three studies reported a significant reduction in post-hemorrhoidectomy pain in patients treated with an injection of botulinum toxin [37,38]. Moreover, an intraoperative injection of botulinum toxin was shown to be more effective than repeated applications of glyceryl trinitrate in decreasing pain after hemorrhoidectomy [40].

### 3.3.2. Intradermal Injection of Methylene Blue

Methylene blue has a unique analgesic activity by temporarily interfering sensory nerve conduction at the nerve endings (pain and itch receptors) within the epidermis and dermis. Intradermal injection of 1% methylene blue 4 mL at the site of open hemorrhoidectomy was shown to reduce pain in the first three postoperative days, without increasing any complication [41].

### 3.3.3. Intrasphincteric Injection of Ketorolac

A prospective study was conducted in 1994 to compare the postoperative analgesic effect of between ketorolac injected into the anal sphincter muscle at the time of hemorrhoidectomy and taken orally thereafter versus standardized narcotic intramuscular/oral analgesics. The authors reported comparable pain intensity between the two groups—the

ketorolac group had a higher satisfaction rating—with facilitating early discharge in the setting of ambulatory hemorrhoidectomy [42].

### 3.4. Postoperative Interventions

#### 3.4.1. Topical Calcium Channel Blockers and Glyceryl Trinitrate

Aiming to decrease the spasm of IAS, calcium channel blockers (diltiazem or nifedipine) and glyceryl trinitrate (GTN) have been introduced as a topical agent applied into the anal canal and/or onto the perianal skin as an intervention to improve post-hemorrhoidectomy pain. A systematic review and meta-analysis of 12 RCTs with 1095 patients found that the topical application of GTN was associated with a significant pain reduction up to 2 weeks after hemorrhoidectomy and a faster rate of wound healing (by 4–10 days) comparing with a placebo. However, 10% of patients treated by GTN experienced headache, which could limit the extensive use of such an agent [41]. Similarly, a meta-analysis of five RCTs (227 patients) examining the effect of topical calcium channel blockers on post-hemorrhoidectomy pain indicated a significant pain reduction on postoperative day 1–4 (pooled mean difference in degree of pain score of approximately  $-3.5$ ) in those treated by diltiazem ointment. Of note, there was no significant difference in the incidence of headache between diltiazem and placebo group [43].

#### 3.4.2. Topical Anesthetic Cream

The application of topical anesthetic cream (EMLA™ (Eutectic Mixture of Local Anesthetics) cream; mixture of 2.5% lidocaine and 2.5% prilocaine) as a preemptive analgesia to reduce pain during and after hemorrhoidectomy has been studied since 2000 [44]. Initially, it was applied over the perianal skin before infiltrating local anesthesia (perianal block) for hemorrhoidectomy. Later, the beneficial effects of topical EMLA™ cream on post-hemorrhoidectomy pain were determined when the cream was applied immediately after hemorrhoidectomy (either within the anal canal or over the perianal skin). Two double-blind RCTs demonstrated that topical EMLA cream significantly reduced pain intensity in the first 2–24 h after hemorrhoidectomy, without any adverse drug reactions [45,46].

#### 3.4.3. Other Topical Medications

**Metronidazole:** Metronidazole has antibacterial activity against enteric anaerobes (which could exert inflammatory pain after hemorrhoidectomy) and antioxidant effect (which could minimize pain and promote wound healing) [47]. A systematic review and meta-analysis of four RCTs including 149 patients (76 with 10% metronidazole ointment and the others with placebo) demonstrated that topical metronidazole significantly reduced post-hemorrhoidectomy pain, with an approximate mean difference of  $-2$  to  $-1$  in visual analog scale for pain throughout the first two weeks postoperatively [48]. There was no serious adverse drug reaction reported in patients treated by topical metronidazole although some experienced perianal burning and itching.

**Sucralfate:** Sucralfate, a complex of aluminum hydroxide and sucrose octasulfate, acts as a mucosal protective barrier and a promotor for mucosal healing [49]. It is approved by the U.S. Food and Drug Administration for the treatment of duodenal ulcers. Due to its unique mucoprotective effect of sucralfate, its topical form (10% sucralfate ointment) has been investigated whether it can reduce pain after open hemorrhoidectomy in at least three RCTs [50–52]. Applying ointment onto a hemorrhoidectomy wound once or twice daily for two weeks, topical sucralfate was shown to significantly reduce post-hemorrhoidectomy pain throughout the period of drug application and shorten time to wound healing compared with a placebo ointment.

**Diclofenac:** The application of diclofenac rectal suppository provided a better pain control in the first 24 h after hemorrhoidectomy compared with a placebo [45]. Notably, the analgesic effect of this topical non-steroidal anti-inflammatory drug lasted longer than that of EMLA™ cream.



**Baclofen:** Baclofen is a gamma-amino butyric acid (GABA) receptor agonist. It has been used traditionally as a muscle relaxant and a medication for neuropathic pain. However, it was postulated that post-hemorrhoidectomy pain could be a result of spasticity of the anal sphincter complex and injury to sensory nerves at the anoderm [53]. As a result, baclofen could be a new analgesia for controlling post-hemorrhoidectomy pain. In fact, a recent small double-blind RCT demonstrated the beneficial effect of 5% baclofen cream on pain after open hemorrhoidectomy. In this study, baclofen cream was immediately applied after surgery and then every 12 h for 2 weeks, and its analgesic effect was clearly evident after the first few days after the procedure [54].

**Cholestyramine:** Since some investigators believed that bile acids in the stool could cause skin irritation and inflammation in the perianal area as noted in an etiology peristomal dermatitis, they conducted a small double-blind RCT comprising 91 patients undergoing open hemorrhoidectomy [55]. Either 15% cholestyramine ointment or placebo was applied on perianal skin (but not inside the anus) immediately after surgery and then every 8 h for 2 weeks. Patients treated by cholestyramine ointment had a significant lower intensity of pain only in the first 48 h after an operation.

**Aloe vera:** Aloe vera was found to have anti-inflammatory activity and promote cutaneous healing [56]. The effects of Aloe vera cream on pain and wound healing after hemorrhoidectomy have been investigated in a few, small RCTs with conflicting results [57,58].

**Vitamin E:** The anti-inflammatory effect of vitamin E in dermatologic diseases was investigated in the management of post-hemorrhoidectomy pain. A small double-blind RCT in Spain included 60 patients undergoing open hemorrhoidectomy (30 with vitamin E ointment and the others with petrolatum as a placebo) [59]. Two mL of ointment was applied onto a hemorrhoidectomy wound twice daily for one week. The investigators found that vitamin E ointment significantly reduced post-hemorrhoidectomy pain—approximately with a mean difference of  $-4$  in visual analog scale for pain throughout the period of the ointment applied. Undoubtedly, more studies with larger sample sizes need to be conducted to confirm these findings.

**Trimebutine:** As an antispasmodic used orally to treat intestinal cramping and irritable bowel syndrome, Trimebutine (Proctolog<sup>®</sup>, Pfizer, New York, NY, USA) was used topically to treating anal fissures. In a RCT including 160 hemorrhoidectomies, a trimebutine suppository significantly reduced resting anal pressure but had no effect on post-hemorrhoidectomy pain [60].

#### 3.4.4. Oral Metronidazole

With its properties of anti-aerobic activity and antioxidant effect, oral metronidazole is often used to prevent surgical site infection and minimized pain following hemorrhoidectomy [47]. In the last five years, there have been at least three systematic reviews and meta-analyses of maximum nine RCTs (523 patients) examining the analgesic effect of oral metronidazole on post-hemorrhoidectomy pain [47,48,61]. With some limitations of small sample-size studies and heterogeneity among studies, these meta-analyses demonstrated that the intensity of postoperative pain at all time points of measurement (up to a week postoperatively) in patients receiving oral metronidazole was significantly less than that in comparison groups. It appeared that the analgesic effect of oral metronidazole on post-hemorrhoidectomy was slightly prominent than that of topical metronidazole [48], although there is no RCT comparing this effect between the two routes of administration. Pain intensity during the second and third week after hemorrhoidectomy between a seven-day postoperative administration of oral metronidazole and placebo was examined in a recent small RCT from Australia, in which the investigators found no significant difference in median worst pain scores and defecation-related pain [62].

#### 3.4.5. Flavonoids

Flavonoids, known as a venoactive drug, was shown to increase venous tone, decrease vascular permeability, improve lymphatic drainage, and reduced microvascular and tissue

inflammation [63]. It has been used effectively in the treatment of low-grade hemorrhoids as well as chronic venous insufficiency [3]. As it has activities against local inflammation in hemorrhoidal tissue, the effects of flavonoids on post-hemorrhoidectomy pain have been examined in several RCTs [64–66].

Systematic reviews and meta-analyses of three RCTs including 216 patients showed that postoperative administration of flavonoids reduced pain intensity after hemorrhoidectomy by approximately 1 out of 10 in visual analog scale and postoperative analgesic requirement by 46% [67,68].

#### 3.4.6. Laxatives

Bowel confinement offered no benefits in clinical and patient-reported outcomes after various anorectal operations [69]. In contrast, postoperative use of laxatives including bulk-forming agents and osmotic laxatives was associated with earlier and less painful defecation following anal surgeries including excisional hemorrhoidectomy [70–72].

#### 3.4.7. Mesoglycan

Mesoglycan is a porcine-derived polysaccharide complex with antithrombotic and profibrinolytic properties. It was shown to regulate selective permeability at the microcirculatory level and restore microvascular injury [73]; thus, potentially reducing edema and pain at a surgical site. Since hemorrhoids were associated with hypervascularity and higher blood flow of the anal cushions [7], the effects of mesoglycan on post-hemorrhoidectomy pain were examined first as a pilot prospective multicenter study in Italy comprising 101 hemorrhoidectomies. The mesoglycan-treated group received mesoglycan 60 mg intramuscularly once daily for the first 5 days postoperative, followed by 50 mg (one tablet) orally twice daily for 30 days. The investigators found that patients treated by mesoglycan had less pain at 7–10 days after surgery compared with patients with no drug treatment [74]. Later, a large multicenter observational study (398 patients) supported by Italian Society of Colorectal Surgery also found that patients treated by the aforementioned course of mesoglycan experienced less post-hemorrhoidectomy pain (from the first day to 6 weeks after surgery) and earlier return to their normal activities-compared with historical control individuals [75].

#### 3.4.8. Warm Sitz Bath

Physiological studies showed that anal resting pressure diminished significantly after a warm sitz bath (40 Celsius) for 5–10 min [76]. The effects of warm water on the relaxation of IAS could last up to 70 min after exiting the bath [77]. Although a warm sitz bath is commonly advised to patients with anorectal pain and those undergoing anorectal operations [78], several systematic reviews did not find its benefit on reducing pain or enhancing wound healing in various anal disorders [79–81]. With regard to post-hemorrhoidectomy pain, a warm sitz bath did not provide better pain relief [82]. However, a small RCT showed that using surgical glove filled with warm water applied to the perianal area four times a day reduced pain in the first few days after hemorrhoidectomy [83].

#### 3.4.9. Avoidance of Spicy Foods

Capsasin, a chemical causing spiciness in chili, elicits burning pain by activating vanilloid receptors on sensory nerve endings in human skin and mucosa [84]. A small RCT from India showed that patients consuming 3 g of chili powder per day during the first week after hemorrhoidectomy had a significantly higher degree of anal burning and pain intensity than those without chili consumption [85].

#### 3.4.10. Transcutaneous Electrical Nerve Stimulation and Acupuncture

In the literature, alternative therapies for managing post-hemorrhoidectomy pain included transcutaneous electrical nerve stimulation (TENS) and acupuncture. These non-pharmacological interventions aim to modulate neurotransmitters along the nociceptive

pathway to reduce hyperalgesia [86]. TENS on the dorsal web between the first and second metacarpal bone and on the radial side of forearm was shown to reduce pain and opioid consumption after hemorrhoidectomy [87]. A recent large network meta-analysis of 101 RCTs (10,972 hemorrhoidectomies—mostly from China) confirmed the efficacy of acupuncture and its related techniques in post-hemorrhoidectomy pain relief [88]. A systematic review and network meta-analysis of RCTs evaluating all somatosensory stimulation treatments for post-hemorrhoidectomy pain is still underway [89].

#### 3.4.11. Patient's Checklist for Analgesic Consumption

High compliance with prescribed analgesic consumption would improve postoperative pain control. The benefits of medication checklist for patients taking analgesia following hemorrhoidectomy were examined in a small RCT, in which individuals in the self-checklist group had a minimal, but statistically significant, reduction in average postoperative pain between day 1 and day 14 compared with those in the control group (−2.51 versus −1.86 in visual analog scale) [90]. Nevertheless, this non-pharmacological adjunct appeared to be useful, at no cost for reducing post-hemorrhoidectomy pain especially in individuals with polypharmacy.

#### 3.5. Limitations

Although this systematic review addressed strategies to reduce post-hemorrhoidectomy pain using a systematic search of three major biomedical literature databases (Ovid MEDLINE, PubMed and EMBASE), it still has several limitations. First, other electronic sources such as Cochrane Review Library and Cumulative Index to Nursing and Allied Health Literature (CINAHL) are not included in this review. Second, only English-language articles with full text were included in this searching strategy. Third, although all studies included in this review were RCTs, their quality and number of sample size were various. Therefore, it is difficult to compare the treatment effects among these interventions. Fourth, detailed data are lacking for some interventions such as local anesthetic technique and intraoperative botulinum toxin injection.

#### 3.6. Areas for Future Research

In the era of enhanced recovery after surgery, the management of post-hemorrhoidectomy pain must include evidence-based preoperative, intraoperative, and postoperative interventions. The Prospect (procedure specific postoperative pain management) launched the recommendations for pain management after hemorrhoidectomy in 2010 and updated the recommendations in 2017 [91,92]. It is worth noting that these recommendations are mostly derived from individual interventional studies rather than multimodal studies. Interesting, recent evidence has supported a multimodal approach to post-hemorrhoidectomy pain, e.g., a combination of flavonoids and oral metronidazole had a greater degree of pain reduction after hemorrhoidectomy than either single medication [93]. Moreover, increased adherence to guideline recommendations or surgical care bundles was associated with better short-term and long-term surgical outcomes [94,95]. Whether multimodal approaches to post-hemorrhoidectomy pain and their adherence would result in better pain relief needs to be investigated. Within a care bundle for reducing post-hemorrhoidectomy pain, it is also interesting to determine which interventions have a great impact on postoperative pain. New pharmacological and non-pharmacological measures are still required to reduce post-hemorrhoidectomy pain. Moreover, the effect of surgeon's experience on pain after hemorrhoidectomy remains unknown.

## 4. Conclusions

Postoperative pain remains an unsolved and disturbing problem after excisional hemorrhoidectomy. Although there are variations in the methodology and quality of the included studies, strategies to reduce post-hemorrhoidectomy pain are presented in this systematic review and summarized in Table 1.



**Table 1.** Strategies to reduce post-hemorrhoidectomy pain.

Anesthetic methods
<ul style="list-style-type: none"> <li>Local anesthesia, alone or combined with intravenous sedation (the most preferred method), spinal anesthesia and general anesthesia</li> <li>Adding midazolam<sup>1</sup> or morphine<sup>1</sup> to bupivacaine in spinal anesthesia</li> </ul>
Surgical techniques
<ul style="list-style-type: none"> <li>Closed (Ferguson) hemorrhoidectomy</li> <li>Hemorrhoidectomy with a vascular sealing device or an ultrasonic scalpel</li> <li>Hemorrhoidectomy combined with lateral internal anal sphincterotomy</li> </ul>
Intraoperative adjunct
<ul style="list-style-type: none"> <li>Intrasphincteric injection of botulinum toxin (±)</li> <li>Intradermal injection of methylene blue<sup>1</sup></li> <li>Intrasphincteric injection of ketorolac<sup>1</sup></li> </ul>
Postoperative interventions
<ul style="list-style-type: none"> <li>Topical agents: calcium channel blockers, glyceryl trinitrate, anesthetic cream, metronidazole, sucralfate, baclofen<sup>1</sup>, cholestyramine<sup>1</sup>, trimebutine<sup>1</sup>, vitamin E<sup>1</sup>, diclofenac<sup>1</sup>, Aloe vera (±)</li> <li>Oral metronidazole</li> <li>Flavonoids</li> <li>Laxatives</li> <li>Mesoglycan<sup>1</sup></li> <li>Avoidance of spicy foods<sup>1</sup></li> <li>Transcutaneous electrical nerve stimulation</li> <li>Acupuncture</li> <li>Checklist for analgesic consumption<sup>1</sup></li> </ul>

Notes: ± = conflicting results, <sup>1</sup> = only single randomized controlled trial was identified.

**Author Contributions:** Conceptualization, V.L.; Methodology, V.L. and R.J.; Writing—Original Draft Preparation, R.J.; Writing—Review & Editing, V.L.; Supervision, V.L.; Project Administration, V.L. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Ethical review and approval were waived for this study due to the nature of this study. The identity of the subjects under this review was omitted and anonymized.

**Informed Consent Statement:** Patient consent was waived due to due to the nature of this study. The identity of the subjects under this review was omitted and anonymized.

**Data Availability Statement:** All data analyzed during this study are included in this published article.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

- Nelson, R.L.; Abcarian, H.; Davis, F.G.; Persky, V. Prevalence of benign anorectal disease in a randomly selected population. *Dis. Colon Rectum* **1995**, *38*, 341–344. [[CrossRef](#)] [[PubMed](#)]
- Lohsiriwat, V. Treatment of hemorrhoids: A coloproctologist's view. *World J. Gastroenterol.* **2015**, *21*, 9245–9252. [[CrossRef](#)]
- Godeberge, P.; Sheikh, P.; Zagriadskii, E.; Lohsiriwat, V.; Montaña, A.J.; Košorok, P.; De Schepper, H. Hemorrhoidal disease and chronic venous insufficiency: Concomitance or coincidence; results of the CHORUS study (Chronic venous and HemORrhoidal diseases evalUation and Scientific research). *J. Gastroenterol. Hepatol.* **2019**, *35*, 577–585. [[CrossRef](#)]
- Lohsiriwat, V. Approach to hemorrhoids. *Curr. Gastroenterol. Rep.* **2013**, *15*, 332. [[CrossRef](#)] [[PubMed](#)]
- Picciariello, A.; Tsarkov, P.V.; Papagni, V.; Efetov, S.; Markaryan, D.R.; Tulina, I.; Altomare, D.F. Classifications and Clinical Assessment of Haemorrhoids: The Proctologist's Corner. *Rev. Recent Clin. Trials* **2021**, *16*, 10–16. [[CrossRef](#)]
- Simillis, C.; Thoukididou, S.N.; Slesser, A.A.P.; Rasheed, S.; Tan, E.; Tekkis, P.P. Systematic review and network meta-analysis comparing clinical outcomes and effectiveness of surgical treatments for haemorrhoids. *Br. J. Surg.* **2015**, *102*, 1603–1618. [[CrossRef](#)] [[PubMed](#)]

7. Lohsiriwat, V. Hemorrhoids: From basic pathophysiology to clinical management. *World J. Gastroenterol.* **2012**, *18*, 2009–2017. [[CrossRef](#)]
8. Gallo, G.; Martellucci, J.; Sturiale, A.; Clerico, G.; Milito, G.; Marino, F.; Cocorullo, G.; Giordano, P.; Mistrangelo, M.; Trompetto, M. Consensus statement of the Italian society of colorectal surgery (SICCR): Management and treatment of hemorrhoidal disease. *Tech. Coloproctol.* **2020**, *24*, 145–164. [[CrossRef](#)]
9. Lohsiriwat, D.; Lohsiriwat, V. Outpatient hemorrhoidectomy under perianal anesthetics infiltration. *J. Med. Assoc. Thai.* **2005**, *88*, 1821–1824.
10. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *J. Clin. Epidemiol.* **2021**, *134*, 178–189. [[CrossRef](#)]
11. Boonnithi, W.; Lohsiriwat, V. Towards ‘zero’ postoperative pain following common anal operations by effective anesthesia and non-opioid multimodal analgesia. *J. Med. Assoc. Thai.* **2020**, *103*, 103–108.
12. Castellví, J.; Sueiras, A.; Espinosa, J.; Vallet, J.; Gil, V.; Pi, F. Ligasure™ versus diathermy hemorrhoidectomy under spinal anesthesia or pudendal block with ropivacaine: A randomized prospective clinical study with 1-year follow-up. *Int. J. Colorectal Dis.* **2009**, *24*, 1011–1018. [[CrossRef](#)] [[PubMed](#)]
13. Rajabi, M.; Hosseinpour, M.; Jalalvand, F.; Afshar, M.; Moosavi, S.S.; Behdad, S. Ischiorectal Block with Bupivacaine for Post Hemorrhoidectomy Pain. *Korean J. Pain* **2012**, *25*, 89–93. [[CrossRef](#)]
14. Kim, B.G.; Kang, H. The Effect of Preemptive Perianal Ropivacaine and Ropivacaine with Dexmedetomidine on Pain after Hemorrhoidectomy: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study. *Indian J. Surg.* **2012**, *76*, 49–55. [[CrossRef](#)]
15. Brunat, G.; Pouzeratte, Y.; Mann, C.; Didelot, J.-M.; Rochon, J.-C.; Eledjam, J.-J. Posterior Perineal Block with Ropivacaine 0.75% for Pain Control during and after Hemorrhoidectomy. *Reg. Anesth. Pain Med.* **2003**, *28*, 228–232. [[CrossRef](#)] [[PubMed](#)]
16. Gorfine, S.R.; Onel, E.; Patou, G.; Krivokapic, Z.V. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: A multicenter, randomized, double-blind, placebo-controlled trial. *Dis. Colon Rectum* **2011**, *54*, 1552–1559. [[CrossRef](#)] [[PubMed](#)]
17. Morisaki, H.; Masuda, J.; Fukushima, K.; Iwao, Y.; Suzuki, K.; Matsushima, M. Wound infiltration with lidocaine prolongs postoperative analgesia after haemorrhoidectomy with spinal anaesthesia. *Can. J. Anaesth.* **1996**, *43*, 914–918. [[CrossRef](#)] [[PubMed](#)]
18. Moreira, H.; Moreira, J.P.; Isaac, R.R.; Alves-Neto, O.; Moreira, T.A.; Vieira, T.H.; Brasil, A.M. Morphine Spinal Block Anesthesia in Patients Who Undergo an Open Hemorrhoidectomy: A Prospective Analysis of Pain Control and Postoperative Complications. *Ann. Coloproctol.* **2014**, *30*, 135–140. [[CrossRef](#)]
19. Kim, M.; Lee, Y. Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy. *Br. J. Anaesth.* **2001**, *86*, 77–79. [[CrossRef](#)]
20. Mohamedahmed, A.Y.Y.; Stonelake, S.; Mohammed, S.S.S.; Zaman, S.; Ahmed, H.; Albarade, M.; Hajibandeh, S. Haemorrhoidectomy under local anaesthesia versus spinal anaesthesia: A systematic review and meta-analysis. *Int. J. Colorectal Dis.* **2020**, *35*, 2171–2183. [[CrossRef](#)]
21. Xia, W.; MacFater, H.S.; MacFater, W.S.; Otutaha, B.F.; Barazanchi, A.W.H.; Sammour, T.; Hill, A.G. Local Anaesthesia Alone Versus Regional or General Anaesthesia in Excisional Haemorrhoidectomy: A Systematic Review and Meta-Analysis. *World J. Surg.* **2020**, *44*, 3119–3129. [[CrossRef](#)] [[PubMed](#)]
22. Reis Neto, J.A.; Quilici, F.A.; Cordeiro, F.; Reis Junior, J.A. Open versus semi-open hemorrhoidectomy: A random trial. *Int. Surg.* **1992**, *77*, 84–90. [[PubMed](#)]
23. Ho, Y.H.; Seow-Choen, F.; Tan, M.; Leong, A.F. Randomized controlled trial of open and closed haemorrhoidectomy. *Br. J. Surg.* **1997**, *84*, 1729–1730. [[PubMed](#)]
24. Arbman, G.; Krook, H.; Haapaniemi, S. Closed vs. open hemorrhoidectomy—Is there any difference? *Dis. Colon Rectum* **2000**, *43*, 31–34. [[CrossRef](#)]
25. You, S.Y.; Kim, S.H.; Chung, C.S.; Lee, D.K. Open vs. closed hemorrhoidectomy. *Dis. Colon Rectum* **2005**, *48*, 108–113. [[CrossRef](#)] [[PubMed](#)]
26. Arroyo, A.; Perez, F.; Miranda, E.; Serrano, P.; Candela, F.; Lacueva, J.; Hernández, H.; Calpena, R. Open versus closed day-case haemorrhoidectomy: Is there any difference? Results of a prospective randomised study. *Int. J. Colorectal Dis.* **2004**, *19*, 370–373. [[PubMed](#)]
27. Pokharel, N.; Chhetri, R.K.; Malla, B.; Joshi, H.N.; Shrestha, R.K. Haemorrhoidectomy: Ferguson’s (closed) vs. Milligan Morgan’s technique (open). *Nepal Med. Coll. J.* **2009**, *11*, 136–137. [[PubMed](#)]
28. Bhatti, M.I.; Sajid, M.S.; Baig, M.K. Milligan–Morgan (Open) Versus Ferguson Haemorrhoidectomy (Closed): A Systematic Review and Meta-Analysis of Published Randomized, Controlled Trials. *World J. Surg.* **2016**, *40*, 1509–1519. [[CrossRef](#)]
29. Andrews, B.T.; Layer, G.T.; Jackson, B.T.; Nicholls, R.J. Randomized trial comparing diathermy hemorrhoidectomy with the scissor dissection Milligan-Morgan operation. *Dis. Colon Rectum* **1993**, *36*, 580–583. [[CrossRef](#)]
30. Ibrahim, S.; Tsang, C.; Lee, Y.L.; Eu, K.W.; Seow-Choen, F. Prospective, randomized trial comparing pain and complications between diathermy and scissors for closed hemorrhoidectomy. *Dis. Colon Rectum* **1998**, *41*, 1418–1420. [[CrossRef](#)]
31. Mastakov, M.Y.; Buettner, P.G.; Ho, Y.-H. Updated meta-analysis of randomized controlled trials comparing conventional excisional haemorrhoidectomy with LigaSure for haemorrhoids. *Tech. Coloproctol.* **2008**, *12*, 229–239. [[CrossRef](#)]

32. Milito, G.; Cadeddu, F.; Muzi, M.G.; Nigro, C.; Farinon, A.M. Haemorrhoidectomy with Ligasure vs conventional excisional techniques: Meta-analysis of randomized controlled trials. *Colorectal Dis.* **2010**, *12*, 85–93. [[CrossRef](#)] [[PubMed](#)]
33. Nienhuijs, S.; de Hingh, I. Pain after conventional versus Ligasure haemorrhoidectomy. A meta-analysis. *Int. J. Surg.* **2010**, *8*, 269–273. [[CrossRef](#)] [[PubMed](#)]
34. Mushaya, C.D.; Caleo, P.J.; Bartlett, L.; Buettner, P.G.; Ho, Y.H. Harmonic scalpel compared with conventional excisional haemorrhoidectomy: A meta-analysis of randomized controlled trials. *Tech. Coloproctol.* **2014**, *18*, 1009–1016. [[CrossRef](#)] [[PubMed](#)]
35. Emile, S.H.; Youssef, M.; Elfeki, H.; Thabet, W.; El-Hamed, T.M.A.; Farid, M. Literature review of the role of lateral internal sphincterotomy (LIS) when combined with excisional hemorrhoidectomy. *Int. J. Colorectal Dis.* **2016**, *31*, 1261–1272. [[CrossRef](#)] [[PubMed](#)]
36. Vijayaraghavalu, S.; Rajkumar, S. The Role of Lateral Internal Sphincterotomy in Haemorrhoidectomy: A Study in a Tertiary Care Center. *Cureus* **2021**, *13*, e15630. [[CrossRef](#)]
37. Davies, J.; Duffy, D.; Boyt, N.; Aghahoseini, A.; Alexander, D.; Leveson, S. Botulinum toxin (botox) reduces pain after hemorrhoidectomy: Results of a double-blind, randomized study. *Dis. Colon Rectum* **2003**, *46*, 1097–1102. [[CrossRef](#)]
38. Patti, R.; Almasio, P.L.; Muggeo, V.; Buscemi, S.; Arcara, M.; Matranga, S.; Di Vita, G. Improvement of Wound Healing After Hemorrhoidectomy: A Double-Blind, Randomized Study of Botulinum Toxin Injection. *Dis. Colon Rectum* **2005**, *48*, 2173–2179. [[CrossRef](#)]
39. Singh, B.; Box, B.; Lindsey, I.; George, B.; Mortensen, N.; Cunningham, C. Botulinum toxin reduces anal spasm but has no effect on pain after haemorrhoidectomy. *Colorectal Dis.* **2009**, *11*, 203–207. [[CrossRef](#)]
40. Patti, R.; Almasio, P.L.; Arcara, M.; Sammartano, S.; Romano, P.; Fede, C.; Di Vita, G. Botulinum Toxin vs. Topical Glyceryl Trinitrate Ointment for Pain Control in Patients Undergoing Hemorrhoidectomy: A Randomized Trial. *Dis. Colon Rectum* **2006**, *49*, 1741–1748. [[CrossRef](#)]
41. Sim, H.-L.; Tan, K.-Y. Randomized single-blind clinical trial of intradermal methylene blue on pain reduction after open diathermy haemorrhoidectomy. *Colorectal Dis.* **2014**, *16*, O283–O287. [[CrossRef](#)]
42. O'Donovan, S.; Ferrara, A.; Larach, S.; Williamson, P. Intraoperative use of toradol<sup>®</sup> facilitates outpatient hemorrhoidectomy. *Dis. Colon Rectum* **1994**, *37*, 793–799. [[CrossRef](#)]
43. Huang, Y.-J.; Chen, C.-Y.; Chen, R.-J.; Kang, Y.-N.; Wei, P.-L. Topical diltiazem ointment in post-hemorrhoidectomy pain relief: A meta-analysis of randomized controlled trials. *Asian J. Surg.* **2017**, *41*, 431–437. [[CrossRef](#)] [[PubMed](#)]
44. Ho, K.S.; Eu, K.W.; Heah, S.M.; Seow-Choen, F.; Chan, Y.W. Randomized clinical trial of haemorrhoidectomy under a mixture of local anaesthesia versus general anaesthesia. *Br. J. Surg.* **2000**, *87*, 410–413. [[CrossRef](#)]
45. Rahimi, M.; Kazemeini, A.R.; Pourtabatabaei, N.; Honarmand, A.R. Comparison of topical anesthetic cream (EMLA) and diclofenac suppository for pain relief after hemorrhoidectomy: A randomized clinical trial. *Surg. Today* **2012**, *42*, 1201–1205. [[CrossRef](#)]
46. Shiau, J.M.; Su, H.P.; Chen, H.S.; Hung, K.C.; Lin, S.E.; Tseng, C.C. Use of a topical anesthetic cream (EMLA) to reduce pain after hemorrhoidectomy. *Reg. Anesth. Pain Med.* **2008**, *33*, 30–35. [[CrossRef](#)] [[PubMed](#)]
47. Lyons, N.J.R.; Cornille, J.B.; Pathak, S.; Charters, P.; Daniels, I.; Smart, N.J. Systematic review and meta-analysis of the role of metronidazole in post-haemorrhoidectomy pain relief. *Colorectal Dis.* **2017**, *19*, 803–811. [[CrossRef](#)] [[PubMed](#)]
48. Xia, W.; Manning, J.P.R.; Barazanchi, A.W.H.; Su'A, B.; Hill, A.G. Metronidazole following excisional haemorrhoidectomy: A systematic review and meta-analysis. *ANZ J. Surg.* **2018**, *88*, 408–414. [[CrossRef](#)]
49. Nagashima, R. Mechanisms of action of sucralfate. *J. Clin. Gastroenterol.* **1981**, *3*, 117–127.
50. Ala, S.; Saeedi, M.; Eshghi, F.; Rafati, M.; Hejazi, V.; Hadianamrei, R. Efficacy of 10% sucralfate ointment in the reduction of acute postoperative pain after open hemorrhoidectomy: A prospective, double-blind, randomized, placebo-controlled trial. *World J. Surg.* **2013**, *37*, 233–238. [[CrossRef](#)] [[PubMed](#)]
51. Gupta, P.J.; Heda, P.S.; Kalaskar, S.; Tamaskar, V.P. Topical Sucralfate Decreases Pain After Hemorrhoidectomy and Improves Healing: A Randomized, Blinded, Controlled Study. *Dis. Colon Rectum* **2008**, *51*, 231–234. [[CrossRef](#)] [[PubMed](#)]
52. Vejdani, A.K.; Khosravi, M.; Amirian, Z.; Daneshmand, M.; Babak, B.; Samira, K.; Azin, S.; Kosar, S.; Razie, K. Evaluation of the efficacy of topical sucralfate on healing haemorrhoidectomy incision wounds and reducing pain severity: A randomised clinical trial. *Int. Wound J.* **2020**, *17*, 1047–1051. [[CrossRef](#)] [[PubMed](#)]
53. Emile, S.H. Evidence-based review of methods used to reduce pain after excisional hemorrhoidectomy. *J. Coloproctol.* **2019**, *39*, 81–89.
54. Ala, S.; Alvandipour, M.; Saeedi, M.; Mansourifar, M.; Monajati, M.; Shiva, A. Effect of Topical Baclofen 5% on Post-Hemorrhoidectomy Pain: Randomized Double Blind Placebo-Controlled Clinical Trial. *J. Gastrointest. Surg.* **2019**, *24*, 405–410. [[CrossRef](#)] [[PubMed](#)]
55. Ala, S.; Eshghi, F.; Enayatifard, R.; Fazel, P.; Rezaei, B.; Hadianamrei, R. Efficacy of Cholestyramine Ointment in Reduction of Postoperative Pain and Pain during Defecation after Open Hemorrhoidectomy: Results of a Prospective, Single-center, Randomized, Double-blind, Placebo-controlled Trial. *World J. Surg.* **2012**, *37*, 657–662. [[CrossRef](#)]
56. Sánchez, M.; González-Burgos, E.; Iglesias, I.; Gómez-Serranillos, M.P. Pharmacological Update Properties of Aloe Vera and its Major Active Constituents. *Molecules* **2020**, *25*, 1324. [[CrossRef](#)]

57. Eshghi, F.; Hosseinimehr, S.J.; Rahmani, N.; Khademloo, M.; Norozi, M.S.; Hojati, O. Effects of Aloe vera Cream on Posthemorrhoidectomy Pain and Wound Healing: Results of a Randomized, Blind, Placebo-Control Study. *J. Altern. Complement. Med.* **2010**, *16*, 647–650. [[CrossRef](#)] [[PubMed](#)]
58. Kanlıöz, M.; Ekici, U. The Effects of Using Liposomal Bupivacaine and Aloe Vera Cream after Haemorrhoidectomy on Postoperative Pain, Need for Analgesics, Hospitalisation Period and Return to Work and Social Life. *Turk. J. Colorectal Dis.* **2020**, *30*, 184–190. [[CrossRef](#)]
59. Ruiz-Tovar, J.; Duran, M.; Alias, D.; Manso, B.; Moreno, A.; Nevado, C.; Lopez, S.; Jimenez, M.; Garia-Olmo, D. Reduction of postoperative pain and improvement of patients' comfort after Milligan-Morgan hemorrhoidectomy using topical application of vitamin E ointment. *Int. J. Colorectal Dis.* **2015**, *31*, 1371–1372. [[CrossRef](#)]
60. Ho, Y.H.; Seow-Choen, F.; Low, J.Y.; Tan, M.; Leong, A.P. Randomized controlled trial of trimebutine (anal sphincter relaxant) for pain after haemorrhoidectomy. *Br. J. Surg.* **1997**, *84*, 377–379.
61. Di Re, A.; Toh, J.W.T.; Iredell, J.; Ctercteko, G. Metronidazole in the Management of Post-Open Haemorrhoidectomy Pain: Systematic Review. *Ann. Coloproctol.* **2020**, *36*, 5–11. [[CrossRef](#)]
62. Wilkie, B.D.; Chandra, R.; Chua, J.; Lam, D.C.S.; Paratz, E.D.; An, V.; Keck, J.O. Efficacy of postoperative oral metronidazole for haemorrhoidectomy pain: A randomized double-blind, placebo-controlled trial. *Colorectal Dis.* **2021**, *23*, 274–282. [[CrossRef](#)] [[PubMed](#)]
63. Lyseng-Williamson, K.A.; Perry, C.M. Micronised purified flavonoid fraction: A review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. *Drugs* **2003**, *63*, 71–100. [[CrossRef](#)] [[PubMed](#)]
64. Colak, T.; Akca, T.; Dirlik, M.; Kanik, A.; Dag, A.; Aydin, S. Micronized Flavonoids in Pain Control After Hemorrhoidectomy: A Prospective Randomized Controlled Study. *Surg. Today* **2003**, *33*, 828–832. [[CrossRef](#)] [[PubMed](#)]
65. La Torre, F.; Nicolai, A.P. Clinical use of micronized purified flavonoid fraction for treatment of symptoms after hemorrhoidectomy: Results of a randomized, controlled, clinical trial. *Dis. Colon Rectum* **2004**, *47*, 704–710. [[CrossRef](#)] [[PubMed](#)]
66. Lee, H.W.; Lee, W.Y.; Chun, H.K. Clinical effects of Venitol on complications after hemorrhoidectomy prospective randomized and placebo-controlled trial. *J. Korean Soc. Coloproctol.* **1998**, *14*, 761–766.
67. Perera, N.; Liolitsa, D.; Iype, S.; Croxford, A.; Yassin, M.; Lang, P.; Ukaegbu, O.; van Issum, C. Phlebotonics for haemorrhoids. *Cochrane Database Syst. Rev.* **2012**, *8*, CD004322. [[CrossRef](#)]
68. Sheikh, P.; Lohsiriwat, V.; Shelygin, Y. Micronized Purified Flavonoid Fraction in Hemorrhoid Disease: A Systematic Review and Meta-Analysis. *Adv. Ther.* **2020**, *37*, 2792–2812. [[CrossRef](#)] [[PubMed](#)]
69. Nessim, A.; Wexner, S.D.; Agachan, F.; Alabaz, O.; Weiss, E.G.; Noguerras, J.J.; Daniel, N.; Lee Billotti, V. Is bowel confinement necessary after anorectal reconstructive surgery? A prospective, randomized, surgeon-blinded trial. *Dis. Colon Rectum* **1999**, *42*, 16–23. [[CrossRef](#)] [[PubMed](#)]
70. Mahony, R.; Behan, M.; O'Herlihy, C.; O'Connell, P.R. Randomized, Clinical Trial of Bowel Confinement vs. Laxative Use After Primary Repair of a Third-Degree Obstetric Anal Sphincter Tear. *Dis. Colon Rectum* **2004**, *47*, 12–17. [[CrossRef](#)]
71. Johnson, C.D.; Chir, M.; Budd, J.; Ward, A.J. Laxatives after hemorrhoidectomy. *Dis. Colon Rectum* **1987**, *30*, 780–781. [[CrossRef](#)] [[PubMed](#)]
72. Kecmanovic, D.M.; Pavlov, M.J.; Ceranic, M.; Kerkez, M.D.; Rankovic, V.I.; Masirevic, V.P. Bulk agent *Plantago ovata* after Milligan-Morgan hemorrhoidectomy with Ligasure™. *Phytother. Res.* **2006**, *20*, 655–658. [[CrossRef](#)]
73. Tufano, A.; Arturo, C.; Cimino, E.; Di Minno, M.; Di Capua, M.; Cerbone, A.M.; Di Minno, G. Mesoglycan: Clinical Evidences for Use in Vascular Diseases. *Int. J. Vasc. Med.* **2010**, *2010*, 390643. [[CrossRef](#)] [[PubMed](#)]
74. Gallo, G.; Mistrangelo, M.; Passera, R.; Testa, V.; Pozzo, M.; Perinotti, R.; Lanati, I.; Lazzari, I.; Tonello, P.; Ugliono, E.; et al. Efficacy of Mesoglycan in Pain Control after Excisional Hemorrhoidectomy: A Pilot Comparative Prospective Multicenter Study. *Gastroenterol. Res. Pract.* **2018**, *2018*, 6423895. [[CrossRef](#)] [[PubMed](#)]
75. Gallo, G.; Di Saverio, S.; Clerico, G.; Sturiale, A.; Manigrasso, M.; Luc, A.; Trompetto, M.; Sammarco, G. Mesoglycan for pain control after open excisional HAEMORrhoidectomy (MeHAEMO): An observational multicentre study on behalf of the Italian Society of Colorectal Surgery (SICCR). *BMC Surg.* **2020**, *20*, 251.
76. Dodi, G.; Bogoni, F.; Infantino, A.; Pianon, P.; Mortellaro, L.M.; Lise, M. Hot or cold in anal pain? A study of the changes in internal anal sphincter pressure profiles. *Dis. Colon Rectum* **1986**, *29*, 248–251. [[CrossRef](#)] [[PubMed](#)]
77. Shafik, A. Role of Warm-Water Bath in Anorectal Conditions. The “thermosphincteric reflex”. *J. Clin. Gastroenterol.* **1993**, *16*, 304–308. [[CrossRef](#)]
78. Lohsiriwat, V.; Lohsiriwat, D. Ambulatory anorectal surgery under perianal anesthetics infiltration: Analysis of 222 cases. *J. Med. Assoc. Thail.* **2007**, *90*, 278–281.
79. Lang, D.S.; Tho, P.C.; Ang, E.N. Effectiveness of the Sitz bath in managing adult patients with anorectal disorders. *Jpn. J. Nurs. Sci.* **2011**, *8*, 115–128. [[CrossRef](#)] [[PubMed](#)]
80. Siew Ping, D.L.; Chi, T.P.; Li, G.M.; Nk, E.A. The effectiveness of sitz bath in managing adult patients with anorectal disorders: A systematic review. *JBI Libr. Syst. Rev.* **2010**, *8*, 447–469. [[CrossRef](#)]
81. Tejirian, T.; Abbas, M.A. Sitz Bath: Where Is the Evidence? Scientific Basis of a Common Practice. *Dis. Colon Rectum* **2005**, *48*, 2336–2340. [[CrossRef](#)] [[PubMed](#)]
82. Gupta, P.J. Warm Sitz Bath Does Not Reduce Symptoms in Posthaemorrhoidectomy Period: A Randomized, Controlled Study. *ANZ J. Surg.* **2008**, *78*, 398–401. [[CrossRef](#)] [[PubMed](#)]



83. Balta, A.Z.; Ozdemir, Y.; Sucullu, I.; Filiz, A.I.; Yucel, E.; Akin, M.L. The effect of early warm plastic bag application on postoperative pain after hemorrhoidectomy: A prospective randomized controlled trial. *Am. Surg.* **2015**, *81*, 182–186. [[CrossRef](#)] [[PubMed](#)]
84. Fischer, M.J.M.; Ciotu, C.I.; Szallasi, A. The Mysteries of Capsaicin-Sensitive Afferents. *Front. Physiol.* **2020**, *11*, 554195. [[CrossRef](#)]
85. Gupta, P.J. Effect of red chili consumption on postoperative symptoms during the post-hemorrhoidectomy period: Randomized, double-blind, controlled study. *World J. Surg.* **2007**, *31*, 1822–1826. [[CrossRef](#)] [[PubMed](#)]
86. Kocot-Kępska, M.; Zajackowska, R.; Zhao, J.; Wordliczek, J.; Tomasik, P.; Przeklasa-Muszyńska, A. The role of complementary and alternative methods in the treatment of pain in patients with cancer—Current evidence and clinical practice: A narrative review. *Contemp. Oncol.* **2021**, *25*, 88–94. [[CrossRef](#)]
87. Chiu, J.H.; Chen, W.S.; Chen, C.H.; Jiang, J.K.; Tang, G.J.; Lui, W.Y.; Lin, J.K. Effect of transcutaneous electrical nerve stimulation for pain relief on patients undergoing hemorrhoidectomy: Prospective, randomized, controlled trial. *Dis. Colon Rectum* **1999**, *42*, 180–185. [[CrossRef](#)] [[PubMed](#)]
88. Qin, D.; Zhang, A.-M.; Chen, M.; Tang, T.-C.; Du, Y.-J.; Zheng, H. Acupuncture and related techniques for postoperative pain after hemorrhoidectomy: A systematic review and network meta-analysis. *Eur. J. Integr. Med.* **2020**, *37*, 101112. [[CrossRef](#)]
89. Zhang, A.M.; Chen, M.; Tang, T.C.; Qin, D.; Yue, L.; Zheng, H. Somatosensory stimulation treatments for postoperative analgesia of mixed hemorrhoids: Protocol for a systematic review and network meta-analysis. *Medicine* **2019**, *98*, e14441. [[CrossRef](#)] [[PubMed](#)]
90. Huang, J.; Rickard, M.J.F.X.; Keshava, A.; Suen, M.K.L. Impact of post-haemorrhoidectomy pain relief checklists on pain outcomes: A randomized controlled trial. *ANZ J. Surg.* **2020**, *90*, 580–584. [[CrossRef](#)]
91. Joshi, G.P.; Neugebauer, E.A.M. Evidence-based management of pain after haemorrhoidectomy surgery. *Br. J. Surg.* **2010**, *97*, 1155–1168. [[CrossRef](#)] [[PubMed](#)]
92. Sammour, T.; Barazanchi, A.W.H.; Hill, A.G.; On Behalf of the PROSPECT Group (Collaborators). Evidence-Based Management of Pain After Excisional Haemorrhoidectomy Surgery: A PROSPECT Review Update. *World J. Surg.* **2016**, *41*, 603–614. [[CrossRef](#)] [[PubMed](#)]
93. Rabelo, F.E.F.; Lacerda-Filho, A.; Mansur, E.S.; de Oliveira, F.H.; de Queiroz, F.L.; França-Neto, P.R.; Misson, N. Benefits of flavonoid and metronidazole use after excisional hemorrhoidectomy: A randomized double-blind clinical trial. *Tech. Coloproctol.* **2021**, *25*, 949–955. [[CrossRef](#)] [[PubMed](#)]
94. Lohsiriwat, V. High Compliance with Surgical Site Infection (SSI) Prevention Bundle Reduces Incisional SSI after Colorectal Surgery. *Ann. Coloproctol.* **2021**, *37*, 146–152. [[CrossRef](#)] [[PubMed](#)]
95. Lohsiriwat, V.; Lertbannaphong, S.; Polakla, B.; Riansuwan, W. Implementation of enhanced recovery after surgery and its increasing compliance improved 5-year overall survival in resectable stage III colorectal cancer. *Updates Surg.* **2021**, *73*, 2169–2179. [[CrossRef](#)] [[PubMed](#)]