BMC Surgery

RESEARCH

Open Access

Efficacy of metronidazole in reducing pain after hemorrhoidectomy: a meta-analysis of randomized controlled trials

Hui Dong[1], Wen-Xing Chen[1], Yue-Juan Li[1] and Deng-Chao Wang[1*]

Abstract

Objective Pain is a significant issue in post-hemorrhoidectomy. Metronidazole is being explored as an adjunctive pain management option. This meta-analysis of randomized controlled trials (RCTs) assesses metronidazole's effectiveness and safety compared to a placebo post-hemorrhoidectomy, aiming to provide evidence-based pain management guidance.

Method We conducted a systematic search of the Cochrane Library, Embase, PubMed, Web of Science, and ClinicalTrials.gov for RCTs comparing metronidazole to placebo after hemorrhoidectomy, covering the period from database inception to July 21, 2024. After screening per inclusion/exclusion criteria, study quality was assessed using Cochrane Handbook's risk of bias tool (version 5.1.0). The meta-analysis was conducted using RevMan 5.3 software, the quality of outcome indicators was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, and trial sequential analysis (TSA) was employed to verify the adequacy of the sample size.

Results A total of 9 RCTs were included. The meta-analysis results showed that the pain scores on the first day post-operation [MD=-1.07, 95% CI (-1.85, -0.30), $P=0.006$], the second day post-operation [MD=-1.72, 95% CI (-2.62, -0.81), $P=0.0002$], the seventh day post-operation [MD=-1.73, 95% CI (-2.70, -0.76), $P=0.0005$], and the fourteenth day post-operation [MD=-1.80, 95% CI (-2.67, -0.94), $P<0.0001$] in the metronidazole group were lower than those in the placebo group. Additionally, the rate of additional analgesia was reduced [RR=0.48, 95% CI (0.27, 0.84), $P=0.01$]. No statistically significant differences were found between the metronidazole and placebo groups in terms of the overall incidence of complications [RR=0.69, 95% CI (0.41, 1.16), $P=0.16$] and time to return to normal activities [MD=-1.69, 95% CI (-6.58, 3.20), $P=0.50$]. Sensitivity analysis indicated that the results for pain scores on the first day post-operation were unstable. High heterogeneity was observed in pain scores on the first, second, seventh, and fourteenth days post-operation, as well as in the time to return to normal activities. The TSA indicated that the sample size for the primary outcome measures had achieved the required information size (RIS), supporting the strength and dependability of the meta-analysis findings.

*Correspondence:
Deng-Chao Wang
wangdengchaopwk@163.com; ymx0008@svchr.edu.cn

Full list of author information is available at the end of the article

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Conclusion Metronidazole may be effective and safe in reducing postoperative pain in patients undergoing hemorrhoidectomy. However, due to the limitations of this study, further verification is needed from future large-sample, multi-center, well-designed high-quality RCTs.

Clinical trial number Not applicable.

Keywords Metronidazole, Hemorrhoidectomy, Pain, Meta-analysis

Introduction

Hemorrhoids are a common condition in proctology [1]. However, due to the unique anatomical location of the anus, which is sensitive to pain, postoperative pain is the primary symptom of hemorrhoids [2–4]. Severe anal pain can lead to complications such as difficulty in defecation, urinary retention, and elevated blood pressure [5, 6]. Moreover, the pain can impact wound healing, reduce the patient's sleep quality [7, 8], bringing significant discomfort to the patient. In severe cases, patients may even refuse to cooperate with postoperative wound management, thereby negatively impacting postoperative recovery and potentially the prognosis [9]. With the advancement of people's understanding of pain and the rising demand for quality of life, the issue of postoperative pain has been increasingly recognized and the problem of pain management after hemorrhoidectomy has emerged as a research hotspot in recent years [10–13]. However, recent research has started exploring the utilization of various other types of drugs or methods for the management of post-hemorrhoidectomy pain, showcasing many advantages. Numerous RCTs have researched the use of oral, intravenous, or local metronidazole as an adjunctive analgesic for post-hemorrhoidectomy pain management. Yet, the sample sizes of single-center studies are limited, and the reported outcomes vary among different studies [14–22]. In this study, we adopt a meta-analysis methodology incorporating RCTs on the use of metronidazole and placebo as adjunctive analgesia post-hemorrhoidectomy. By comparing their analgesic effects and safety profiles, we aim to evaluate the applicability and value of metronidazole. What sets our study apart from others is its exclusive focus on comparing the metronidazole group with the placebo group, providing more specific and detailed evidence. Through this unique research design, we seek to evaluate the actual effectiveness of metronidazole in post-hemorrhoidectomy pain management. The GRADE system is utilized to assess outcome indicators, with the goal of providing evidence-based medical guidance for pain management following hemorrhoidectomy.

Materials and methods

We conducted and reported this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols guidelines [23]. The registration number is INPLASY202390108.

Inclusion and exclusion criteria

Inclusion criteria

(1) Study subjects: Patients undergoing either open hemorrhoidectomy (Milligan-Morgan technique, also known as excision-ligation surgery) or closed hemorrhoidectomy (Ferguson hemorrhoidectomy), with no restrictions on gender. (2) Intervention measures: Patients in the metronidazole group receive metronidazole either orally, intravenously, or topically after hemorrhoidectomy, while the control group receives placebo treatment. (3) Type of study: RCTs, with language restricted to English. (4) Outcome indicators: Pain scores on the first day post-operation, pain scores on the second day post-operation, pain scores on the seventh day post-operation, pain scores on the fourteenth day post-operation, additional analgesia rate, overall incidence of complications, time to return to normal activities, with pain scores based on the Visual Analogue Scale (VAS).

Exclusion criteria

Exclusion criteria: (1) Non-RCT studies; (2) Case reports, abstracts, conference reports, and reviews; (3) Control group not receiving a placebo intervention; (4) Inability to extract relevant indicators from the literature; (5) Unavailability of full-text articles.

Retrieval strategy

The Cochrane Library, Embase, PubMed, Web of Science, and ClinicalTrials.gov databases were systematically searched. The search period spanned from the inception of each database until July 21, 2024. The following English search terms were used to search the literature: metronidazole, hemorrhoid, hemorrhoidectomy, haemorrhoidectomy, Milligan Morgan, Ferguson. Additionally, manual searches were conducted by tracing the references of relevant literature.

Literature screening and data extraction

In accordance with the set inclusion and exclusion criteria, two authors independently read the retrieved literature. When disagreements arose, a third author was involved in discussions to resolve them. If there were missing data, efforts were made to contact the original

authors for supplementation. The literature screening process involved firstly reading the title and abstract. Once clearly irrelevant literatures were excluded, the full text of the remaining literatures was read to determine the final inclusion. The extracted data primarily included: (1) General information: first author, year of publication, country, sample size, gender, age, type of surgery, intervention methods, postoperative pain management plan; (2) Outcome indicators: pain scores on the first day post-operation, pain scores on the second day post-operation, pain scores on the seventh day post-operation, pain scores on the fourteenth day post-operation, additional analgesia rate, overall incidence of complications, time to return to normal activities.

Quality assessment

Two authors independently evaluated the quality of the included studies and cross-verified the results. In the event of any disagreement during the evaluation process, the issues were resolved through discussion or adjudicated by a third author. The quality of the included RCTs was assessed using the bias risk assessment tool recommended by the Cochrane Reviewer's Handbook 5.3. This primarily includes the generation of random sequences, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each of these aspects was categorized as low risk, unclear, or high risk [24].

Statistical analysis

The Meta-analysis was conducted using RevMan 5.3 software provided by the Cochrane Collaboration. For dichotomous variables, the risk ratio (RR) was used as the measure of effect, and for continuous variables, the mean difference (MD) was used as the measure of effect. Each effect measure was expressed with a 95% confidence interval (CI). Heterogeneity between the results of the included studies was assessed with a chi-square test, combined with the I^2 statistic to quantify the magnitude of heterogeneity. If there was no statistical heterogeneity among the results of the studies ($P > 0.10$, $I^2 \leq 50\%$), a fixed-effect model was used for the meta-analysis. Conversely, after excluding obvious clinical heterogeneity, a random-effects model was used for the meta-analysis [25]. For studies with clear clinical heterogeneity, a subgroup or sensitivity analysis was performed, or only a descriptive analysis was performed. Sensitivity analysis involved conducting the meta-analysis again after each study was removed one by one to evaluate the impact of each study on the combined effect. When the number of included studies for a related indicator was ≥ 10, publication bias was examined using a funnel plot [26].

Quality of evidence assessment

According to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria, we used GRADEprofiler 3.6 to assess the quality of evidence for each outcome indicator. Based on the risk of bias in the studies, consistency, indirectness, imprecision, and publication bias, the outcome indicators were divided into four levels: high, moderate, low, and very low [27].

TSA analysis

In this study, TSA was conducted by specifying an assumed effect size, a significance level ($\alpha = 0.05$), and statistical power ($1\text{-}\beta = 0.80$). Crossing the TSA boundary suggests that the available evidence is adequate for drawing reliable conclusions, whereas failure to cross it implies that further research may be needed to confirm the meta-analysis outcomes. Using the meta-analysis results, the mean difference, variance, and heterogeneity correction values were determined to develop and assess the TSA model.

Ethical statement

All included RCTs reported obtaining ethical approval from their respective institutional review boards and informed consent from participants. As this study is a meta-analysis based on previously published studies, no additional ethical approval was required.

Results

Literature search results

Initially, a total of 136 articles were retrieved through various databases, along with an additional 2 articles identified through manual searches. After reviewing titles and abstracts, 25 duplicate articles, 83 irrelevant to the research purpose, and 12 empirical summaries and reviews were eliminated. Of the remaining 18 articles, 7 were excluded as their control groups did not use placebos, and 2 employed drug interventions for their control groups. Following the layered screening, 9 articles were finally included [14–22]. The screening process is detailed in Fig. 1. The characteristics of the studies included in this meta-analysis are provided in Table 1.

Results of literature quality evaluation

All nine studies were RCTs [14–22], seven of which [15–17, 19–22] described the specific randomization methods used. Seven studies [14–17, 20–22] used allocation concealment, and seven studies [14–17, 20–22] employed blinding for both the subjects and implementers as well as the outcome assessors. There were no missing outcome data, selective outcome reporting, or other biases in all studies [14–22]. As shown in Figs. 2 and 3.

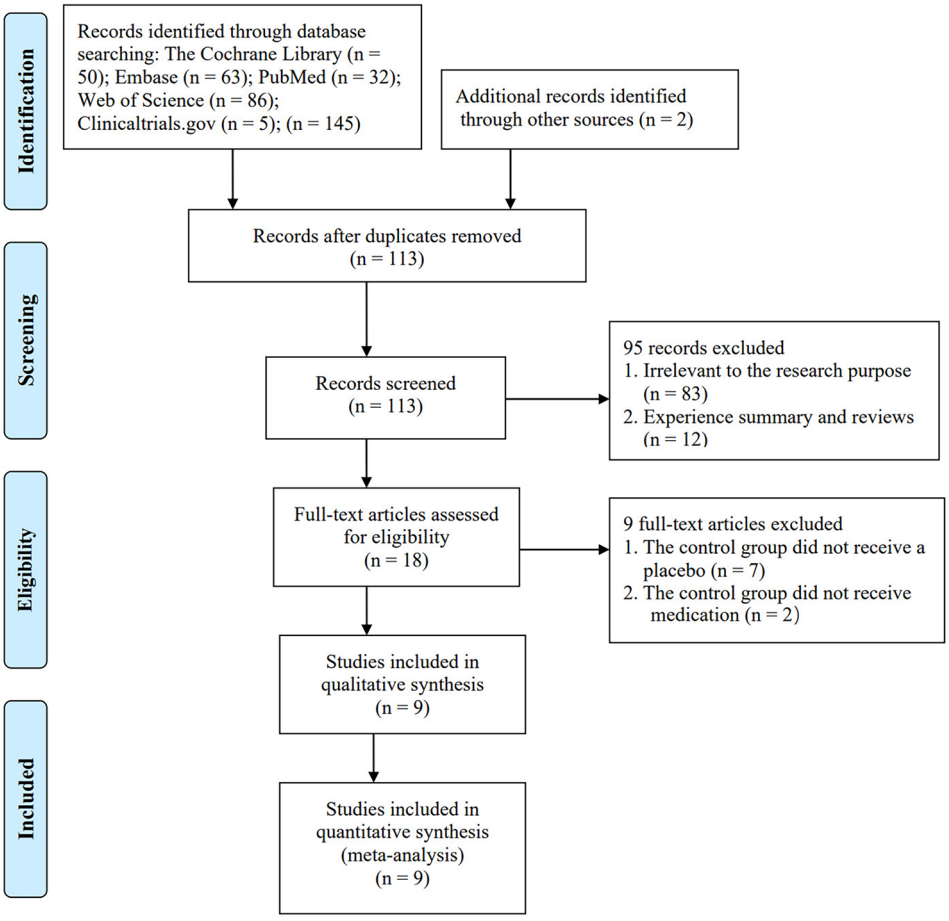

Fig. 1 Study selection

Meta-analysis results

Pain scores on the first day post-operation

Six studies [14, 16–20] reported the pain scores on the first day post-operation. Given the statistical heterogeneity among the studies ($P < 0.00001$, $I^2 = 88\%$), a random-effects model was used to conduct a meta-analysis of the effect sizes. The results suggest that the pain scores on the first day post-operation in the metronidazole group were lower than those in the placebo group [MD=-1.07, 95% CI (-1.85, -0.30), $P = 0.006$], indicating a statistically significant difference. A sensitivity analysis indicated that after excluding the study by Ala 2008 [14], the difference in the pain scores on the first day post-operation between the two groups was not statistically significant. This suggests a lack of stability in the results and it is recommended that future researchers conduct more studies on this topic, as shown in Fig. 4.

Pain scores on the second day post-operation

Five studies [14, 16–18, 20] reported the pain scores on the second day post-operation. Given the statistical heterogeneity among the studies ($P < 0.00001$, $I^2 = 88\%$), a random-effects model was used to conduct a meta-analysis of the effect sizes. The results suggest that the pain scores on the second day post-operation in the metronidazole group were lower than those in the placebo group [MD=-1.72, 95% CI (-2.62, -0.81), $P = 0.0002$], indicating a statistically significant difference. In the sensitivity analysis, excluding each study one by one did not change the direction of the combined effect value, suggesting that the results of this study are essentially stable, as shown in Fig. 5.

Pain scores on the seventh day post-operation

Seven studies [14, 16–21] reported the pain scores on the seventh day post-operation. Given the statistical heterogeneity among the studies ($P < 0.00001$, $I^2 = 96\%$), a random-effects model was used to conduct a meta-analysis of the effect sizes. The results suggest that the pain scores on the seventh day post-operation in the metronidazole group were lower than those in the placebo group [MD=-1.73, 95% CI (-2.70, -0.76), $P = 0.0005$], indicating a statistically significant difference. In the sensitivity analysis, excluding each study one by one did not change the direction of the combined effect value, suggesting that

Table 1 Characteristics of the studies included in this meta-analysis

Study	Country	Group	Sample size (M/F)	Age (years)	Type of operation	Intervention measures	Postoperative pain management plan	Outcome indicators
Ala 2008 [14]	Iran	Metronidazole	25 (5/20)	37 ± 11	Open hemorrhoidectomy	Topical Metronidazole 10% ointment (The duration of use is not reported.)	Patients used analgesics as needed	①②③④⑥
		Placebo	22 (7/15)	38 ± 14	Open hemorrhoidectomy	Placebo		
Balfour 2002 [15]	UK	Metronidazole	18 (8/10)	52 (31–84)	Closed hemorrhoidectomy	Metronidazole 400 mg tablet three times daily for seven days	Codeine (30 mg) combined with acetaminophen (500 mg) in a compound tablet (used as needed) and the NSAID diclofenac (50 mg, used as needed)	⑤⑥⑦
		Placebo	20 (8/12)	56 (35–82)	Closed hemorrhoidectomy	Placebo		
Carapeti 1998 [16]	UK	Metronidazole	20 (10/10)	47 (24–65)	Day-case haemorrhoidectomy	Metronidazole 400 mg tablet three times daily for seven days	Acetaminophen or Codydramol containing dihydrocodeine (30 mg) and acetaminophen (500 mg per tablet) used as needed	①②③⑤⑦
		Placebo	20 (7/13)	51 (36–64)	Day-case haemorrhoidectomy	Placebo		
Chandra 2020 [17]	Australia	Metronidazole	21 (13/8)	45 (34–60)	Milligan-Morgan or Ferguson haemorrhoidectomy	Metronidazole 400 mg tablet three times daily for seven days	1000 mg oral acetaminophen (four times daily), 50 mg diclofenac (three times daily), and 5 mg oxycodone as needed	①②③④⑥
		Placebo	19 (12/7)	44 (32–58)	Milligan-Morgan or Ferguson haemorrhoidectomy	Placebo		
Di Vita 2004 [18]	Italy	Metronidazole	15 (9/6)	35 ± 20	Milligan-Morgan haemorrhoidectomy	Metronidazole 400 mg administered intravenously 30 min before the surgical procedure, followed by metronidazole tablets 400 mg three times daily for seven days after surgery.	Intravenous diclofenac 100 mg for pain relief and oral nimesulide tablets (100 mg) as needed	①②③
		Placebo	15 (8/7)	40.6 ± 18	Milligan-Morgan haemorrhoidectomy	Placebo		
González-Ojeda 2015 [19]	México	Metronidazole	22 (17/5)	50.1 ± 16.0	Ferguson hemorrhoidectomy	500 mg of metronidazole given orally every 8 h for seven days	Diclofenac (100 mg orally, every 12 h) and acetaminophen (1 g orally, every 8 h). If the pain score exceeded 5, subcutaneous buprenorphine (150 µg) was administered	①③④⑥⑦
		Placebo	22 (11/11)	42.4 ± 18.5	Ferguson hemorrhoidectomy	Placebo		
Nicholson 2004 [20]	USA	Metronidazole	10 (6/4)	47.7 ± 3.2	Harmonic Scalpel hemorrhoidectomy	2.5 milliliter of 10% metronidazole cream to the surgical site three times daily	Oxycodone 10 mg orally every 4–6 h	①②③④
		Placebo	10 (7/3)	48.5 ± 3.1	Harmonic Scalpel hemorrhoidectomy	Placebo		

Table 1 (continued)

Study	Country	Group	Sample size (M/F)	Age (years)	Type of operation	Intervention measures	Postoperative pain management plan	Outcome indicators
Rabelo 2021 [21]	Brazil	Metronidazole	17 (6/11)	42 (37-56.5)	Excisional hemorrhoidectomy	Metronidazole 400 mg tablet every 8 h for seven days	Ephedra/Plantago seeds (once daily), scopolamine/ metamizole (four times daily), and nimesulide (twice daily)	①④
		Placebo	17 (7/10)	52 (43-60.5)	Excisional hemorrhoidectomy	Placebo		
Wilkie 2021 [22]	Australia	Metronidazole	21 (13/8)	45 (34–60)	Milligan-Morgan or Ferguson haemorrhoidectomy	Metronidazole 400 mg tablet three times daily for seven days	1000 mg oral acetaminophen (four times daily), 50 mg diclofenac (three times daily), and 5 mg oxycodone as needed	⑤⑥⑦
		Placebo	19 (12/7)	44 (32–58)	Milligan-Morgan or Ferguson haemorrhoidectomy	Placebo		

UK, United Kingdom; M, Male; F,Female; Na, not available

①pain scores on the first day post-operation; ②pain scores on the second day post-operation; ③pain scores on the seventh day post-operation; ④pain scores on the fourteenth day post-operation; ⑤additional analgesia rate; ⑥overall incidence of complications; ⑦time to return to normal activities

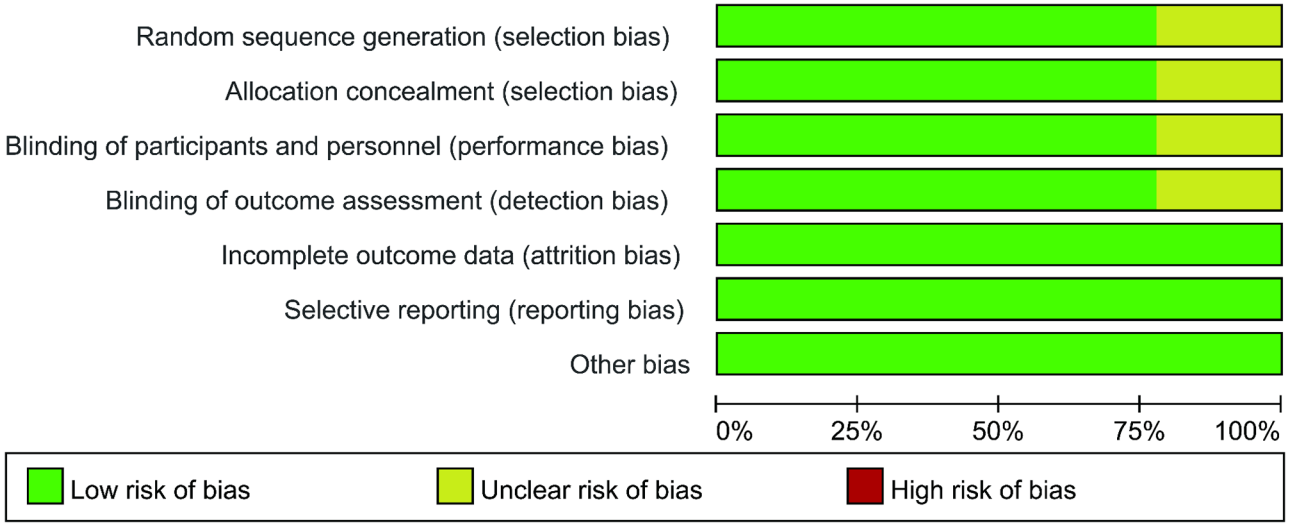

Fig. 2 Risk of bias graph for randomized controlled trials included in this study

the results of this study are essentially stable, as shown in Fig. 6.

Pain scores on the fourteenth day post-operation

Five studies [14, 17, 19–21] reported the pain scores on the fourteenth day post-operation. Given the statistical heterogeneity among the studies ($P < 0.00001$, $I^2 = 96\%$), a random-effects model was used to conduct a meta-analysis of the effect sizes. The results suggest that the pain scores on the fourteenth day post-operation in the metronidazole group were lower than those in the placebo group [MD=-1.80, 95% CI (-2.67, -0.94), $P < 0.0001$], indicating a statistically significant difference. In the sensitivity analysis, excluding each study one by one did not change the direction of the combined effect value, suggesting that the results of this study are essentially stable, as shown in Fig. 7.

Additional analgesia rate

Three studies [15, 16, 22] reported the additional analgesia rate. In the metronidazole group, the additional analgesia rate was 11/59 (18.6%), while in the placebo group, it was 23/59 (38.9%). Given the lack of statistical heterogeneity among the studies ($P = 0.23$, $I^2 = 32\%$), a fixed-effects model was used to conduct a meta-analysis of the effect sizes. The results suggest that the additional analgesia rate in the metronidazole group was lower than that in the placebo group [RR = 0.48, 95% CI (0.27, 0.84), $P = 0.01$], indicating a statistically significant difference, as shown in Fig. 8.

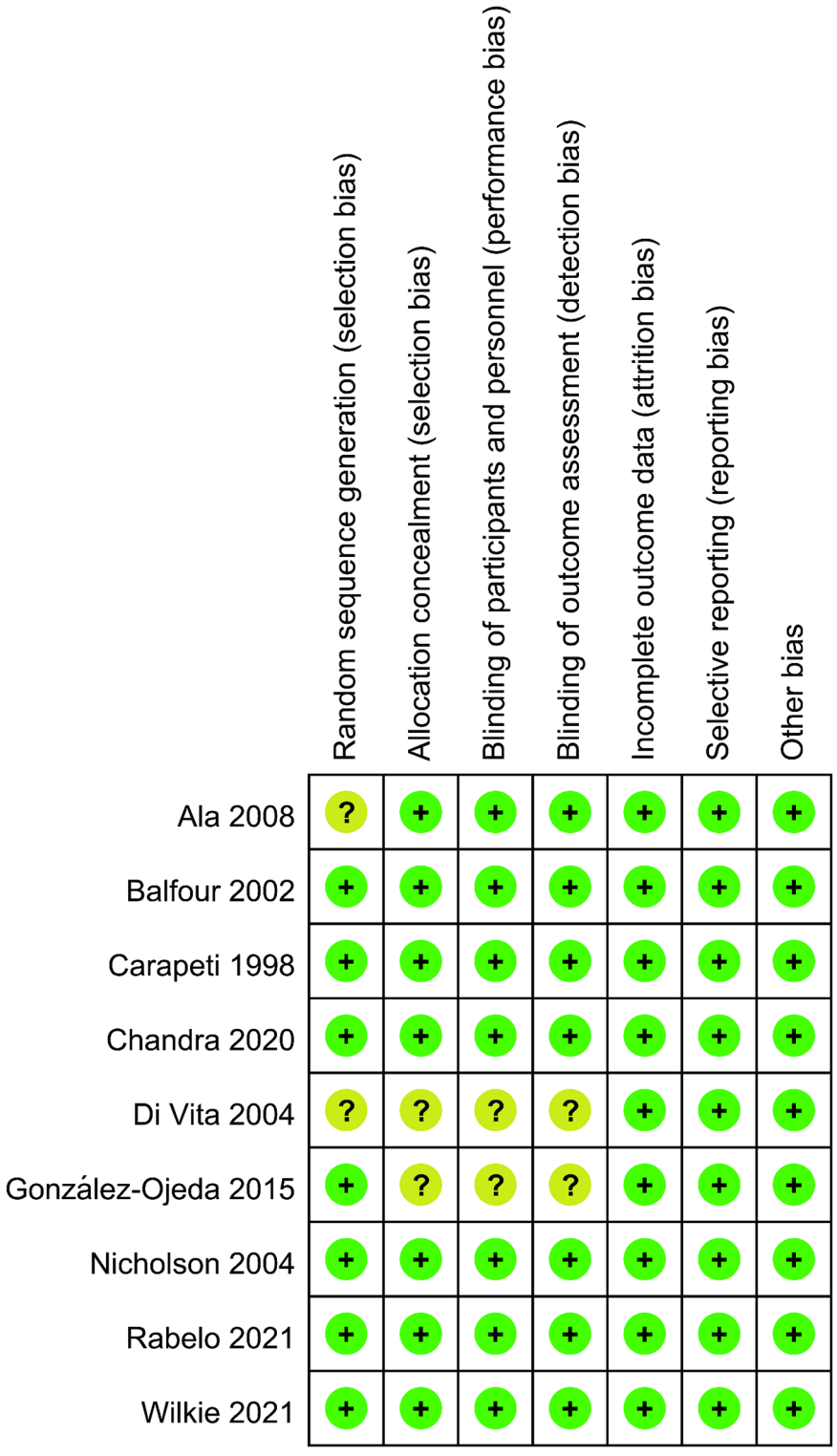

Fig. 3 Summary of the risk of bias analysis for the randomized controlled trials included in this study

Overall incidence of complications

Five studies [14–16, 19, 22] reported the overall incidence of complications, which included wound itching, urinary retention, bleeding, swelling, and tenesmus. In the metronidazole group, the overall incidence of complications was 18/107 (16.8%), while in the placebo group, it was 25/102 (24.5%). Given that there was no statistical heterogeneity among the studies ($P = 0.86$, $I^2 = 0\%$), a

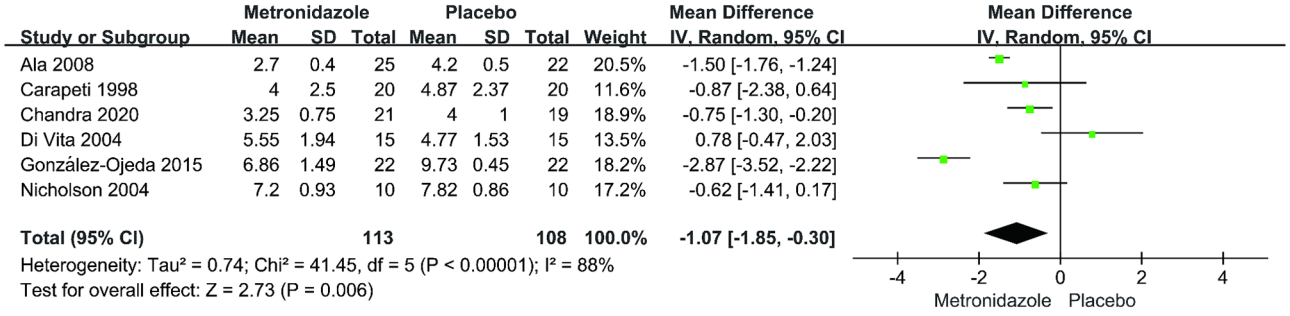

Fig. 4 Comparison of pain scores on the first day post-operation between two groups

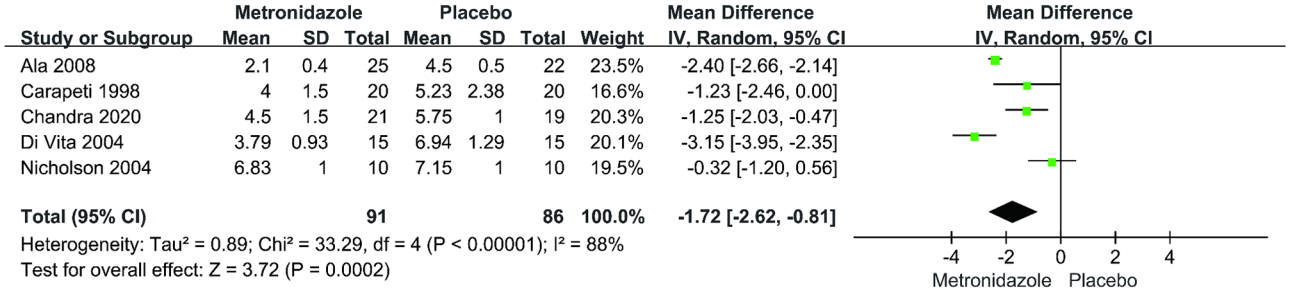

Fig. 5 Comparison of pain scores on the second day post-operation between two groups

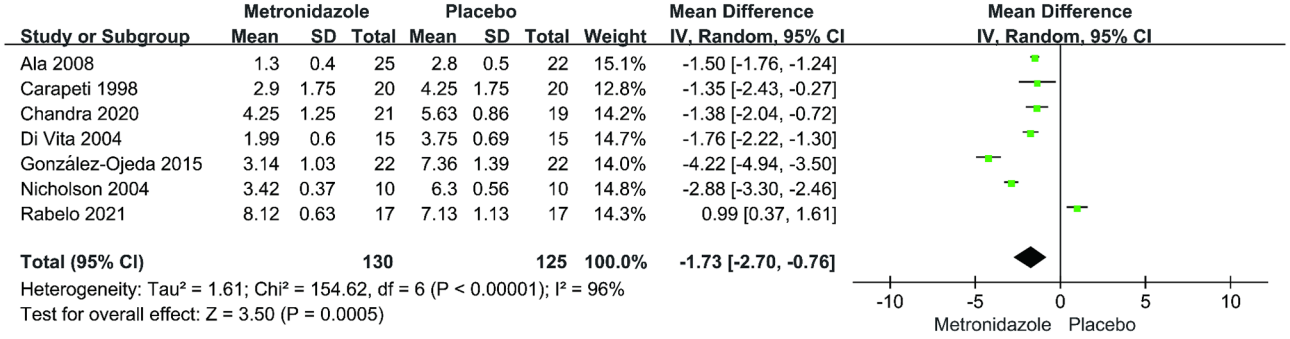

Fig. 6 Comparison of pain scores on the seventh day post-operation between two groups

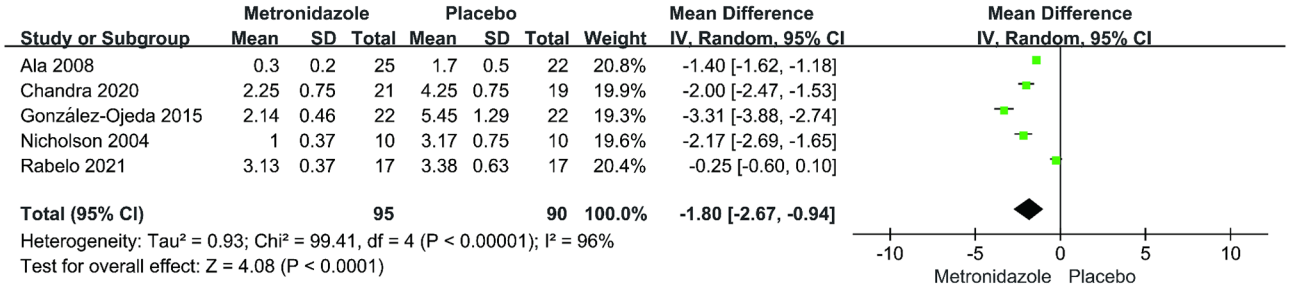

Fig. 7 Comparison of pain scores on the fourteenth day post-operation between two groups

fixed-effects model was used to conduct a meta-analysis of the effect sizes. The results suggest that the difference in the overall incidence of complications between the metronidazole group and the placebo group was not statistically significant [RR = 0.69, 95% CI (0.41, 1.16), $P = 0.16$], as shown in Fig. 9.

Time to return to normal activities

Four studies [15, 16, 19, 22] reported the time to return to normal activities. Given the statistical heterogeneity among the studies ($P < 0.0001$, I2 = 88%), a random-effects model was used to conduct a meta-analysis of the effect sizes. The results suggest that there was no statistically

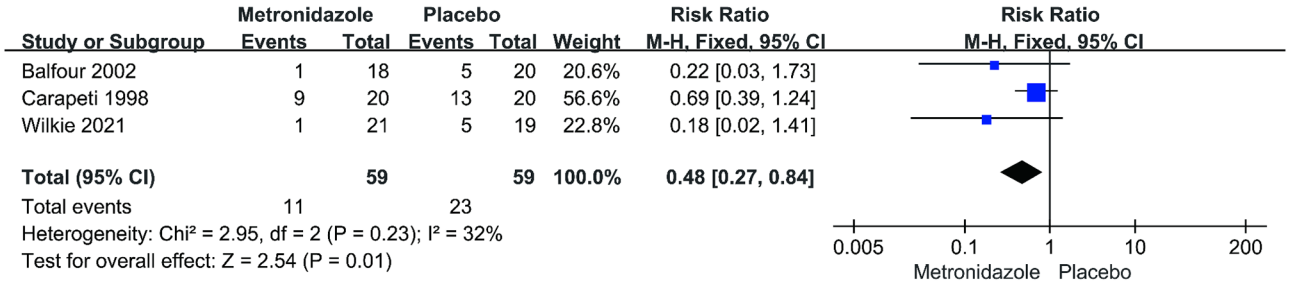

Fig. 8 Comparison of additional analgesia rate between two groups

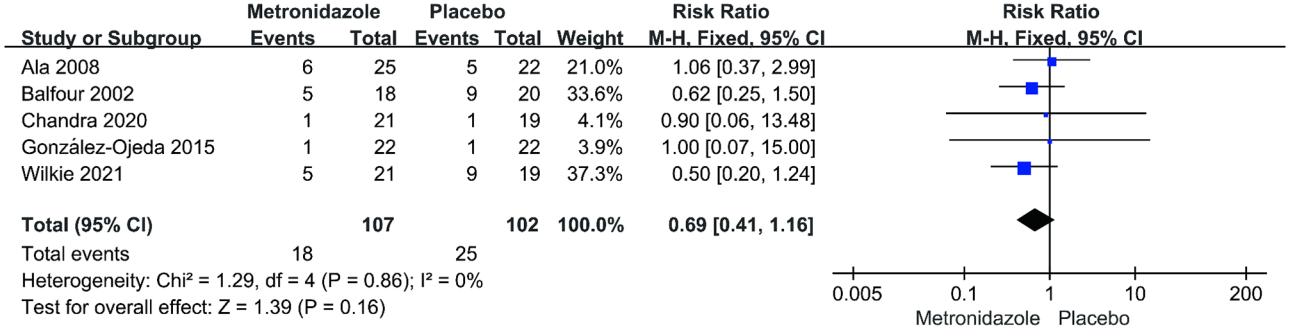

Fig. 9 Comparison of overall incidence of complications between two groups

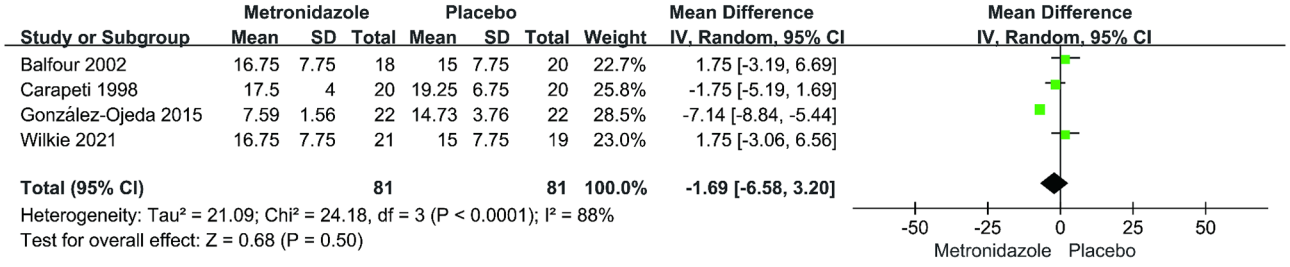

Fig. 10 Comparison of time to return to normal activities between two groups

significant difference in the time to return to normal activities between the metronidazole group and the placebo group [MD=-1.69, 95% CI (-6.58, 3.20), $P=0.50$]. A sensitivity analysis indicated that after excluding each study in turn, the direction of the combined effect size did not change, suggesting stability in the results, as shown in Fig. 10.

Subgroup analysis results

Subgroup analysis was conducted based on the randomization method, blinding method, metronidazole administration method, surgical methods, study period, and sample size in the included studies. The results are shown in Table 2.

GRADE evidence quality assessment

In this study, the evidence levels for the pain scores on the first day post-operation, pain scores on the second day post-operation, pain scores on the seventh day post-operation, pain scores on the fourteenth day post-operation, overall incidence of complications, and time to return to normal activities were low, while the evidence level for the additional analgesia rate was moderate, as shown in Table 3.

TSA results

A TSA was conducted on six studies that reported pain scores on the first day post-operation, with a two-sided type I error probability ($\alpha=0.05$) and a type II error probability ($\beta=0.20$). In the figure, after crossing the RIS, the Z-curve continues to extend with the addition of new research data and ultimately reaches the pre-specified boundary. This indicates that although there was already sufficient sample size upon crossing the RIS, subsequent data further strengthened the results, causing the Z-curve to eventually meet the significance boundary, thereby enhancing the reliability and significance of the study conclusions, as shown in Fig. 11.

Table 2 Subgroup analysis results

Outcome indicator			Number of Studies	Heterogeneity test results		Effect	Meta-analysis results	
	Grouping method	Group		I^2 (%)	P-Value	Model	Effect Size (95% CI)	P-Value
Pain scores on the first day post-operation	Randomization method	Described	4	90	< 0.00001	Random	-1.31(-2.52,0.10)	0.03
		Not described	2	92	0.0005	Random	-0.45(-2.67,1.78)	0.7
	Blinding method	Described	4	68	0.03	Random	-1.02(-1.57,-0.47)	0.0003
		Not described	2	96	< 0.00001	Random	-1.09(-4.66,2.49)	0.55
	Metronidazole administration method	Oral/intravenous	4	92	< 0.00001	Random	-0.98(-2.50,0.53)	0.2
		Topical	2	77	0.04	Random	-1.14(-1.99,-0.29)	0.008
	Study period	Before 2010	4	81	0.001	Random	-0.66(-1.61,0.30)	0.18
		After 2010	2	96	< 0.00001	Random	-1.80(-3.88,0.27)	0.09
	Sample size	≥ 40	4	88	< 0.0001	Random	-1.56(-2.40,-0.71)	0.0003
		< 40	2	71	0.06	Random	-0.01(-1.37,1.35)	0.99
	Surgical method	Traditional	4	92	< 0.00001	Random	-1.20(-2.19,-0.21)	0.02
		Modern	2	0	0.77	Fixed	-0.67(-1.37,0.02)	0.06
Pain scores on the second day post-operation	Randomization method	Described	3	27	0.26	Fixed	-0.91(-1.44,-0.38)	0.0007
		Not described	2	67	0.08	Random	-2.67(-3.38,-1.97)	< 0.00001
	Blinding method	Described	4	89	< 0.00001	Random	-1.35(-2.42,-0.28)	0.01
		Not described	1	-	-	-	-3.15(-3.95,-2.35)	< 0.00001
	Metronidazole administration method	Oral/intravenous	3	84	0.002	Random	-1.91(-3.25,-0.56)	0.005
		Topical	2	95	< 0.00001	Random	-1.40(-3.44,0.63)	0.18
	Study period	Before 2010	4	89	< 0.00001	Random	-1.83(-2.91,-0.75)	0.0009
		After 2010	1	-	-	-	-1.25(-2.03,-0.47)	0.002
	Sample size	≥ 40	3	80	0.006	Random	-1.73(-2.66,-0.80)	0.0003
		< 40	2	95	< 0.00001	Random	-1.74(-4.51,1.03)	0.22
	Surgical method	Traditional	3	83	0.003	Random	-2.28(-3.12,-1.43)	< 0.00001
		Modern	2	28	0.24	Fixed	-0.67(-1.53,0.20)	0.13
Pain scores on the seventh day post-operation	Randomization method	Described	5	97	< 0.00001	Random	-1.77(-3.52,-0.02)	0.05
		Not described	2	0	0.34	Fixed	-1.56(-1.79,-1.34)	< 0.00001
	Blinding method	Described	5	96	< 0.00001	Random	-1.23(-2.39,-0.08)	0.04
		Not described	2	97	< 0.00001	Random	-2.97(-5.38,-0.56)	0.02
	Metronidazole administration method	Oral/intravenous	5	97	< 0.00001	Random	-1.54(-3.15,0.07)	0.06
		Topical	2	97	< 0.00001	Random	-2.18(-3.53,-0.83)	0.002
	Study period	Before 2010	4	90	< 0.00001	Random	-1.91(-2.65,-1.18)	< 0.00001
		After 2010	3	98	< 0.00001	Random	-1.53(-4.45,1.39)	0.3
	Sample size	≥ 40	4	94	< 0.00001	Random	-2.12(-3.36,-0.87)	0.0008
		< 40	3	98	< 0.00001	Random	-1.23(-3.27,0.82)	0.24
	Surgical method	Traditional	4	94	< 0.00001	Random	-2.18(-3.16,-1.20)	< 0.0001
		Modern	3	98	< 0.00001	Random	-1.23(-3.78,1.61)	0.43
Time to return to normal activities	Randomization method	Described	-	-	-	-	-	-
		Not described	-	-	-	-	-	-
	Blinding method	Described	3	0	0.37	Fixed	-0.00(-2.44,2.43)	1
		Not described	1	-	-	-	-7.14(-8.84,-5.44)	< 0.00001
	Metronidazole administration method	Oral/intravenous	-	-	-	-	-	-
		Topical	-	-	-	-	-	-
	Study period	Before 2010	2	23	0.67	Fixed	-0.61(-3.43,2.22)	0.67
		After 2010	2	91	0.0006	Random	-2.99(-11.68,5.70)	0.5
	Sample size	≥ 40	3	88	0.0002	Random	-2.73(-8.06,2.60)	0.32
		< 40	1	-	-	-	1.75(-3.19,6.69)	0.49
	Surgical method	Traditional	3	90	< 0.0001	Random	-1.51(-8.47,5.45)	0.67
		Modern	1	-	-	-	1.75(-3.19,6.69)	0.49

Since the outcome indicator "Time to return to normal activities" could not be subgrouped based on "Randomization method" and "Metronidazole administration method," a subgroup analysis was not conducted

Table 3 GRADE assessment of outcome measures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	New Comparison	Control	Relative (95% CI)	Absolute		
Pain scores on the first day post-operation (Better indicated by lower values)												
6	randomised trials	serious[1,2]	serious[3]	no serious indirectness	no serious imprecision	none	113	108	-	MD 1.07 lower (1.85 to 0.3 lower)	⊕⊕OO LOW	CRITICAL
Pain scores on the second day post-operation (Better indicated by lower values)												
5	randomised trials	serious[1,2]	serious[3]	no serious indirectness	no serious imprecision	none	91	86	-	MD 1.72 lower (2.62 to 0.81 lower)	⊕⊕OO LOW	CRITICAL
Pain scores on the seventh day post-operation (Better indicated by lower values)												
7	randomised trials	serious[1,2]	serious[3]	no serious indirectness	no serious imprecision	none	130	125	-	MD 1.73 lower (2.7 to 0.76 lower)	⊕⊕OO LOW	CRITICAL
Pain scores on the fourteenth day post-operation (Better indicated by lower values)												
5	randomised trials	serious[1,2]	serious[3]	no serious indirectness	no serious imprecision	none	95	90	-	MD 1.8 lower (2.67 to 0.94 lower)	⊕⊕OO LOW	CRITICAL
Additional analgesia rate												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	11/59 (18.6%)	23/59 (39%) 26.3%	RR 0.48 (0.27 to 0.84)	203 fewer per 1000 (from 62 fewer to 285 fewer) 137 fewer per 1000 (from 42 fewer to 192 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Overall incidence of complications												
5	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[4]	none	18/107 (16.8%)	25/102 (24.5%) 22.7%	RR 0.69 (0.41 to 1.16)	76 fewer per 1000 (from 145 fewer to 39 more) 70 fewer per 1000 (from 134 fewer to 36 more)	⊕⊕OO LOW	CRITICAL
Time to return to normal activities (Better indicated by lower values)												
4	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	81	81	-	MD 1.69 lower (6.58 lower to 3.2 higher)	⊕⊕OO LOW	IMPORTANT

[1] Specific randomization methods were not described

[2] Lack of allocation concealment and lack of blinding

[3] I2>50%

[4] Wide confdence interval

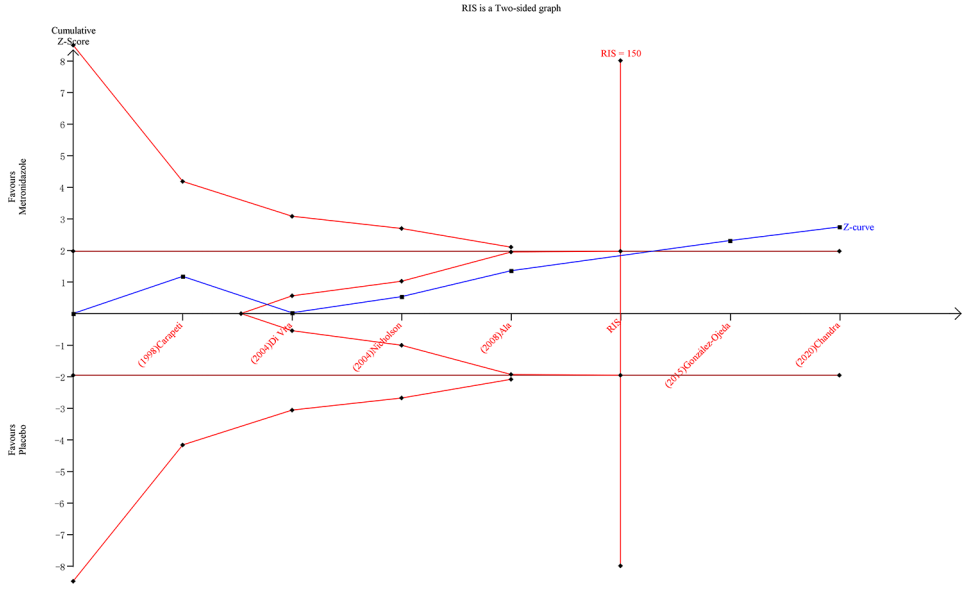

Fig. 11 TSA for pain scores on the first day post-operation

Discussion

The anatomical structure of the anus is quite unique, with the anal canal tissue and the terminal nerves of the anal part beneath the dentate line being relatively abundant, mainly controlled by the spinal nerves. The skin tissue has a high sensitivity to pain [28–30]. Incisions from hemorrhoidectomy are typically not sutured, resulting in open wounds. After the surgery, patients typically utilize gauze packing for hemostasis. The stimulation of the surgical wound by bowel movements and inflammatory substances, as well as difficulties in initial urination post-surgery and urinary retention, can all exacerbate anal sphincter spasms, leading to poor local blood circulation and intensifying pain [31, 32]. The fear of pain in patients can lead to a reduction in cooperation with postoperative treatment, which is not conducive to postoperative recovery. Therefore, it is necessary to take early measures to alleviate postoperative pain in patients [33, 34].

In this study, we included nine RCTs involving a total of 333 patients who underwent hemorrhoidectomy, with 169 in the metronidazole group and 164 in the placebo group. From this meta-analysis, it can be seen that the metronidazole group showed better results in reducing patient's pain scores on the first, second, seventh, and fourteenth day post-operation, compared to the placebo group. This suggests that metronidazole may be effective in alleviating postoperative pain following hemorrhoidectomy. The mechanism by which metronidazole alleviates postoperative pain has not been fully elucidated [35]. Its action may be related to the following aspects: (1) Persistent stimulation from trauma after hemorrhoidectomy and the release of inflammatory mediators from tissue damage, termed "pain-causing factors," can lead to postoperative anal sphincter spasm and perianal edema, making postoperative anal pain more significant than pain after other surgeries. Metronidazole may inhibit the release of these inflammatory mediators, thereby relieving pain [28, 36]. (2) Infection in the surgical area can easily occur after hemorrhoidectomy, potentially leading to symptoms such as pain, fever, and swelling. Metronidazole can inhibit the growth and reproduction of bacteria, exhibiting direct antibacterial properties, thereby reducing the infection of the anal wound or the formation of "micro abscesses," ultimately alleviating postoperative pain in patients [20, 37, 38]. (3) When pain occurs, neurons release inflammatory mediators and other neurotransmitters to transmit pain signals. Metronidazole may inhibit the release of these inflammatory mediators and neurotransmitters to a certain extent, thereby blocking the conduction of nociceptive stimuli by neurons, and hence regulating the perception and transmission of pain [39, 40]. (4) The inflammatory response following hemorrhoidectomy can lead to the production of a series of free radicals and oxidants. These chemicals can further exacerbate tissue damage and neuroinflammation in the surgical area. The antioxidant properties of metronidazole can neutralize these harmful molecules, thereby reducing the inflammatory response and tissue damage, and consequently alleviating the sensation of pain [41–44]. In addition to alleviating postoperative pain, this meta-analysis also suggests that metronidazole can reduce the rate of additional analgesia, which could potentially reduce the use of analgesics, thereby preventing issues such as drug misuse and dependence. The metronidazole group demonstrated a trend towards lower overall incidence of complications and shorter time to return to normal activities compared to the placebo group. However, these differences were not statistically significant. Given the

small sample size of the studies, it is necessary to validate these findings through further high-quality, large-scale, multi-center randomized double-blind trials.

While metronidazole demonstrates some effectiveness in alleviating postoperative pain from hemorrhoidectomy, with increasing awareness regarding the significance of antibiotic use, we should recognize that unless the antibiotic treatment provides substantial and irreplaceable clinical benefits, it should not be used as an auxiliary means for analgesia. Metronidazole is a cornerstone in the global treatment of anaerobic bacterial infections; misuse could contribute to the emergence of drug resistance in pathologically significant bacteria [45–47]. Although the analgesic effect of metronidazole may be related to its antibacterial properties, there is currently a lack of direct evidence to support whether other antibiotics with similar antimicrobial activity can also alleviate postoperative pain through the same mechanism. For example, a study comparing intravenous cefoxitin with no antibiotic prophylaxis found no significant effect of cefoxitin on postoperative pain, wound edema, or other postoperative complications [48]. This finding suggests that the selection of antibiotics may be crucial for postoperative pain management, and the unique effects of metronidazole may extend beyond its broad-spectrum antibacterial activity, potentially involving antioxidant and anti-inflammatory mechanisms [41–44]. In this study, the routes of metronidazole administration included local application, intravenous injection, and oral intake. Since local administration may reduce systemic toxicity of the drug and mitigate the risk of bacterial resistance, future research could compare the analgesic effectiveness of local use with oral or intravenous metronidazole after hemorrhoidectomy. Alternatively, it could be compared with other methods of pain relief (such as local anesthetic infiltration in the surgical area, regional blockade, oral administration of non-steroidal anti-inflammatory drugs) to find a superior postoperative pain management method for hemorrhoidectomy. Additionally, future studies should consider directly comparing the relative efficacy of metronidazole with other antibiotics in postoperative pain management to determine whether metronidazole has a unique advantage in analgesia. The aim is to alleviate the degree of postoperative pain for patients, improve their postoperative quality of life, and minimize potential drug adverse reactions and the emergence of drug resistance as much as possible.

This study has several limitations: (1) Due to the limited number of studies included, no further comparison of the efficacy and safety of metronidazole between local administration and oral or intravenous administration was conducted. (2) The TSA results revealed that while the sample size reached the RIS, the significance boundary was only reached after including additional studies. This suggests that despite sufficient sample size, more data was necessary to confirm the robustness and reliability of the findings. (3) Differences in the analgesic effects of metronidazole after different surgical methods were not analyzed. (4) Some outcome indicators showed considerable heterogeneity, which persisted even after performing subgroup analyses. (5) The inconsistencies in postoperative pain management protocols among the included studies may have a potential impact on the evaluation of metronidazole or placebo as an adjunct analgesic. (6) Some studies did not place adequate importance on the significance of double-blinding randomization and allocation concealment in randomized controlled trials. (7) The GRADE evidence level for the majority of outcome indicators is low, mainly because the specific randomization methods were not described, allocation concealment and blinding were lacking, $I^2 > 50\%$, and the confidence interval was wide. Therefore, these findings should be interpreted with caution, and further high-quality RCTs are needed to validate the results.

In conclusion, current evidence suggests that metronidazole may significantly alleviate postoperative pain following hemorrhoidectomy. However, due to limitations, the conclusions of this study still need to be confirmed by large-scale, multicenter, rigorously designed high-quality RCTs.

Acknowledgements
None.

Author contributions
Hui Dong: Hui Dong was involved in study design, data interpretation, and discussion of results. She also assisted in conductingthe systematic literature review and data extraction. Primarily responsible for revisions and language polishing.Wen-Xing Chen: Wen-Xing Chen was responsible for data collection and analysis, drafting the initial manuscript, and revising it.He also participated in literature screening and quality assessment.Yue-Juan Li: Yue-Juan Li was involved in study design, data interpretation, and discussion of results.Deng-Chao Wang (Corresponding Author): As the corresponding author, Deng-Chao Wang designed the study protocol, reviewed, and approved the final version of the manuscript for publication. He also provided substantial intellectual content and supervised the entire project.

Funding
No funding was received for this study.

Data availability
The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of General Surgery, Zigong Fourth People's Hospital, 19 Tanmulin Road, Zigong, Sichuan 643000, China

Received: 14 November 2024 / Accepted: 18 February 2025
Published online: 08 March 2025

References

1. Emile SH, Elfeki H, Sakr A, Shalaby M. Transanal hemorrhoidal dearterialization (THD) versus stapled hemorrhoidopexy (SH) in treatment of internal hemorrhoids: a systematic review and meta-analysis of randomized clinical trials. Int J Colorectal Dis. 2019;34:1–11.
2. Brusciano L, Gambardella C, Terracciano G, Gualtieri G, Schiano di Visconte M, Tolone S, del Genio G, et al. Postoperative discomfort and pain in the management of hemorrhoidal disease:laser hemorrhoidoplasty, a minimal invasive treatment of symptomatic hemorrhoids. Updates Surg. 2020;72(3):851–7.
3. Lie H, Lukito PP, Sudirman T, Purnama AA, Sutedja R, Setiawan A, et al. Utility of botulinum toxin injection for post-operative pain management after conventional hemorrhoidectomy: a systematic review and meta-analysis of clinical trials. Scand J Gastroenterol. 2023;58(2):116–22.
4. Zobeiri M, Parvizi F, Rahimi R, Heydarpour F, Sheikhan HR, Navabi J, et al. Efficacy and safety of hemoheal cream in patients with hemorrhoids: a randomized double-blind placebo controlled clinical trial. J Tradit Chin Med. 2021;41(2):301.
5. Jeong H, Hwang S, Ryu KO, Lim J, Kim HT, Yu HM, et al. Early experience with a partial stapled hemorrhoidopexy for treating patients with grades III–IV prolapsing hemorrhoids. Ann Coloproctol. 2017;33(1):28.
6. Pickering TG. Pain and blood pressure. J Clin Hypertens. 2003;5(5):359.
7. Karanlik H, Akturk R, Camlica H, Asoglu O. The effect of Glyceryl trinitrate ointment on posthemorrhoidectomy pain and wound healing: results of a randomized, double-blind, placebo-controlled study. Dis Colon Rectum. 2009;52(2):280–5.
8. Wu J, Chen B, Yin X, Yin P, Lao L, Xu S. Effect of acupuncture on post-hemorrhoidectomy pain: a randomized controlled trial. J Pain Res. 2018;11:1489–96.
9. Feng J, Cheng J, Xiang F. Management of intractable pain in patients treated with hemorrhoidectomy for mixed hemorrhoids. Ann Palliat Med. 2021;10(1):479–83.
10. Chierici A, Frontali A. Post-Hemorrhoidectomy pain management: the latest news. Rev Recent Clin Trials. 2021;16(1):32–8.
11. Balciscueta Z, Balciscueta I, Uribe N. Post-hemorrhoidectomy pain: can surgeons reduce it? A systematic review and network meta-analysis of randomized trials. Int J Colorectal Dis. 2021;36(12):2553–66.
12. Zhao-Fleming H, Hand A, Zhang K, Polak R, Northcut A, Jacob D, et al. Effect of non-steroidal anti-inflammatory drugs on post-surgical complications against the backdrop of the opioid crisis. Burns Trauma. 2018;6:25.
13. Schug SA, Manopas A. Update on the role of non-opioids for postoperative pain treatment. Best Pract Res Clin Anaesthesiol. 2017;21(1):15–30.
14. Ala S, Saeedi M, Eshghi F, Mirzabeygi P. Topical metronidazole can reduce pain after surgery and pain on defecation in postoperative hemorrhoidectomy. Dis Colon Rectum. 2008;51:235–8.
15. Balfour L, Stojkovic SG, Botterill ID, Burke DA, Finan PJ, Sagar PM. A randomized, double-blind trial of the effect of metronidazole on pain after closed hemorrhoidectomy. Dis Colon Rectum. 2002;45:1186–90.
16. Carapeti EA, Kamm MA, McDonald PJ, Phillips RKS. Double-blind randomised controlled trial of effect of metronidazole on pain after day-case haemorrhoidectomy. Lancet. 1998;351(9097):169–72.
17. Chandra MR, FCSSANZ MF, Jonathon M, Chua M, Lam MDCS, Paratz ED. Efficacy of post-operative oral metronidazole for haemorrhoidectomy pain: a randomised double-blind, placebo-controlled trial. Colorectal Dis. 2020;23(1):274–82.
18. Di Vita G, Patti R, Arcara M, Petrone R, Davi V, Leo P. A painless treatment for patients undergoing Milligan-Morgan haemorrhoidectomy. Ann Ital Chir. 2004;75(4):471–4.
19. González-Ojeda A, Rendón-Félix J, García-Rentería J, Chávez-Tostado M. Efficacy of metronidazole versus placebo in pain control after hemorrhoidectomy. Results of a controlled clinical trial. Revista Española De Enfermedades Digestivas. 2015;107(11):681–5.
20. Nicholson TJ, Armstrong D. Topical metronidazole (10%) decreases posthemorrhoidectomy pain and improves healing. Dis Colon Rectum. 2004;47:711–8.
21. Rabelo FEF, Lacerda-Filho A, Mansur ES, de Oliveira FH, de Queiroz FL, França-Neto PR, et al. Benefits of flavonoid and metronidazole use after excisional hemorrhoidectomy: a randomized double-blind clinical trial. Tech Coloproctol. 2021;25(8):949–55.
22. Wilkie BD, Chandra R, Chua J, Lam DCS, Paratz ED, An V, et al. Efficacy of post-operative oral metronidazole for haemorrhoidectomy pain: a randomized double-blind, placebo-controlled trial. Colorectal Dis. 2021;23(1):274–82.
23. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264–9.
24. Higgins JPT, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:343–d5928.
25. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
26. Sedgwick P, Marston L. How to read a funnel plot in a meta-analysis. BMJ. 2015;351.
27. Zhang Y, Akl EA, Schünemann HJ. Using systematic reviews in guideline development: the GRADE approach. Res Synthesis Methods. 2019;10(3):312–29.
28. Emile SH. Evidence-based review of methods used to reduce pain after excisional hemorrhoidectomy. J Coloproctology (Rio De Janeiro). 2019;39:81–9.
29. Huang H, Gu Y, Ji L, Li Y, Xu S, Guo T, et al. A new mixed surgical treatment for grades Iii and Iv hemorrhoids: modified selective hemorrhoidectomy combined with complete anal epithelial retention. ABCD Arquivos Brasileiros De Cirurgia Digestiva (São Paulo). 2021;34:e1594.
30. Sindou M, Joud A, Georgoulis G. Usefulness of external anal sphincter EMG recording for intraoperative neuromonitoring of the sacral roots-a prospective study in dorsal rhizotomy. Acta Neurochir. 2021;163:479–87.
31. Mishra N, Hall JF. Operative management of hemorrhoids. Seminars in Colon and rectal surgery. WB Saunders. 2013;24(2):86–90.
32. Lohsiriwat V, Jitmungngan R. Strategies to reduce post-hemorrhoidectomy pain: a systematic review. Medicina. 2022;58(3):418.
33. Zhao Y, Zhang L, Wang Y, Liao C, Chen Y, Zhen Q, et al. Acupuncture therapy for postoperative pain of anorectal diseases: A systematic review protocol. Medicine. 2020;99(7):e19112.
34. 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. 2020;24:405–10.
35. Garg P, Yagnik VD, Kaur G. Increased risk of bleeding with topical metronidazole in a postoperative wound after anal fistula and hemorrhoid surgery: A propensity Score-Matched Case–Control study. Clin Pract. 2022;12(1):133–9.
36. Nienhuijs SW, de Hingh I. Pain after conventional versus Ligasure haemorrhoidectomy. A meta-analysis. Int J Surg. 2010;8(4):269–73.
37. Wanis KN, Emmerton-Coughlin HM, Coughlin S, Foley N, Vinden C. Systemic metronidazole May not reduce posthemorrhoidectomy pain: a meta-analysis of randomized controlled trials. Dis Colon Rectum. 2017;60(4):446–55.
38. Xia W, Manning JPR, Barazanchi AWH, Su'a B, Hill AG. Metronidazole following excisional haemorrhoidectomy: a systematic review and meta-analysis. ANZ J Surg. 2018;88(5):408–14.
39. Puri V. Metronidazole neurotoxicity. Neurol India. 2011;59(4):4–5.
40. Tasca T, Borges FP, Bonan CD, De Carli GA, Battastini AMO, Sarkis JJF. Effects of metronidazole and Tinidazole on NTPDase1 and ecto-5'-nucleotidase from intact cells of Trichomonas vaginalis. FEMS Microbiol Lett. 2003;226(2):379–84.
41. Lyons NJR, Cornille JB, Pathak S, Charters P, Daniels IR, Smart NJ. Systematic review and meta-analysis of the role of metronidazole in post-haemorrhoidectomy pain relief. Colorectal Dis. 2017;19(9):803–11.
42. Rao CM, Ghosh A, Raghothama C, Bairy KL. Does metronidazole reduce lipid peroxidation in burn injuries to promote healing? Burns. 2002;28:427–9.
43. Miyachi Y, Imamura S, Niwa Y. Anti-oxidant action of metronidazole: a possible mechanism of action in rosacea. Br J Dermatol. 1986;114(2):231–4.
44. Miyachi Y. Potential antioxidant mechanism of action for metronidazole: implications for rosacea management. Adv Ther. 2001;18:237–43.
45. Löfmark S, Edlund C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections. Clin Infect Dis. 2010;50(Supplement1):S16–23.
46. Smith A. Metronidazole resistance: a hidden epidemic? Br Dent J. 2018;224(6):403–4.
47. Ghotaslou R, Baghi HB, Alizadeh N, Yekani M, Arbabi S, Memar MY. Mechanisms of Bacteroides fragilis resistance to metronidazole. Infect Genet Evol. 2018;64:156–63.
48. Liu J, Lv L, Qian HH, Sun PL, Zhang D. Role of antibiotics in Milligan-Morgan hemorrhoidectomy for grade III to IV hemorrhoids: A randomized clinical trial. Asian J Surg. 2024;47(1):169–75.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.