Techniques in Coloproctology (2023) 27:813–825
https://doi.org/10.1007/s10151-023-02825-y

REVIEW

Efficacy and safety of methylene blue injection for intractable idiopathic pruritus ani: a single-arm metaanalysis and systematic review

W. Jia[1] · Q. Li[2] · J. Ni[1] · Y. Zhang[1] · L. Wu[1] · L. Xu[1]

Received: 16 May 2022 / Accepted: 15 May 2023 / Published online: 12 June 2023

Abstract

Purpose To evaluate how effective methylene blue injection was at treating intractable idiopathic pruritus ani.

Methods A comprehensive literature search of the PubMed, Embase, Cochrane library, and Web of Science databases was conducted. All clinical studies (prospective and retrospective) that evaluated the efficacy of methylene blue in treating intractable idiopathic pruritus ani were included. Studies that reported the resolution rate, after a single injection and after a second injection, the recurrence rate, symptom scores, and transient complications of methylene blue injections in treating intractable idiopathic pruritus ani were included.

Results The seven selected studies included 225 patients with idiopathic pruritus ani. The resolution rates after a single injection and after a second injection was 0.761 (0.649–0.873, $P<0.01$, $I^2=69.06\%$) and 0.854 (0.752–0.955, $P<0.01$, $I^2=77.391\%$), respectively, the remission rates at 1, 3, and 5 years were 0.753 (0.612–0.893, $P<0.001$), 0.773 (0.675–0.871, $P<0.001$) and 0.240 (0.033–0.447, $P<0.001$), respectively, the effect value of the merger was 0.569 (0.367–0.772, $P<0.001$, $I^2=79.199\%$), and the recurrence rates at 1, 2, 3, and < 1 year were 0.202 (0.083–0.322, $P<0.001$), 0.533 (0.285–0.781, $P<0.001$), 0.437 (−0.044, 0.917, $P<0.001$) and 0.067 (0.023–0.111, $P<0.001$), respectively. The effect value of the merger was 0.223 (0.126–0.319, $P<0.001$, $I^2=75.840$).

Conclusion Using methylene blue injections to treat intractable idiopathic pruritus ani is relatively efficacious, resulting in a relatively low recurrence rate and no severe complications. However, the available literature was of poor quality. Therefore, higher quality studies are necessary to confirm that methylene blue injection is efficacious for pruritus ani, such as a randomized prospective multicenter studies.

Keywords Methylene blue · Intractable idiopathic pruritus ani · Efficacy · Safety

Introduction

In anorectal disease, pruritis ani is the second most common symptom after hematochezia [1]. The pathogenesis of pruritus ani can be described as "itch-scratch-itch behavior." When sensory nerves around the anus are stimulated, the patient incessantly scratches the surrounding skin. Excessive scratching results in skin damage [2]. Pruritus ani can be divided into idiopathic and secondary, research has revealed that idiopathic pruritus ani accounts for 50%–90% of patients with pruritus ani [3]. Secondary cases account for 25%–75% of pruritis ani, implying identifiable cause. Secondary anal pruritus can be due to local stimulation, infection, systemic inflammatory diseases, and tumors. Pruritus ani can be successfully treated if the cause is identified and suitable management is provided.

W. Jia and Q. Li are the co-first authors of the article.

✉ L. Xu
20053012@zcmu.edu.cn

[1] The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Traditional Chinese Medicine), 54 Youdian Road, Hangzhou 310006, Zhejiang Province, China

[2] School of Basic Medical Sciences, Zhejiang Chinese Medical University, 548 Binwen Road, Hangzhou 310053, Zhejiang Province, China

However, in a significant proportion of patients with idiopathic pruritus ani, the cause is unidentifiable. Patients with pruritus ani often lack standardized treatment, clean perianal skin excessively, and use over-the-counter creams and ointments, which may aggravate symptoms and further complicate treatment [4]. While medical treatments, including topical steroid ointments, antihistamines, sedatives, and other local anesthetic therapies, can be used, they are not long-term remedies and can result in high recurrence rates. Methylene blue works by severing the nerve endings of the perianal skin's unmyelinated C-fibers [5], which reduces the urge to scratch [2]. This systematic review aimed to evaluate the effectiveness of methylene blue injection in treating intractable idiopathic pruritus ani.

Methods

Search strategy

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [6] and AMSTAR (Assessing the Methodological Quality of Systematic Reviews) guidelines were followed. Inclusion criteria were established a priori. PubMed, Embase, Cochrane library, and Web of Science were searched using the phrases "methylene blue and pruritus ani," "methylenum coeruleum and pruritus ani," and "methylene blue and anal itching" from inception to December 2022. Additionally, the reference lists of all studies that met the inclusion criteria were checked for more relevant articles. Data from the included studies were extracted by two authors individually. Disagreements between both reviewers were addressed by discussing and reevaluating the trial information. The final search was conducted on 19 December 2022.

Study selection

Patients of any age or sex with unresolved pruritis ani under conservative treatment (non-invasive treatment such as sitz bath, diet control, and lifestyle changes) were included, specifically those who suffered from intractable idiopathic pruritus ani and in whom secondary causes of pruritus ani were ruled out. All clinical studies (prospective and retrospective) that evaluated the efficacy of methylene blue in treating intractable idiopathic pruritus ani were included. Clinical studies (including randomized controlled trials, non-randomized clinical studies, and observational studies) were considered for inclusion if they evaluated the efficacy of methylene blue in treating intractable idiopathic pruritus ani. However, non-English studies were excluded.

Outcomes

Studies that reported the resolution rate after a single injection and after a second injection, the the recurrence rate, symptom scores, and transient complications of methylene blue injections in treating intractable idiopathic pruritus ani were included.

Data extraction and quality assessment

Two authors first extracted the data using a standardized collection form, and disagreements were addressed by discussing and reevaluating the trial information. The form contained the following sections: characteristics of the included studies (study type, study design, study period, country, patient characteristics, including age and sex, follow-up, the Methodological Index for Non-randomized Studies (MINORS) score, and outcomes measured), resolution rate, recurrence rate, symptom scores (rate of resolution after a single and second injection, rate of resolution during follow-up, recurrence rate, and symptom scores), treatment technique, and complications (injection method, patient positioning, anesthesia used, depth of methylene blue injection, prophylactic use of antibiotics, additional measures, and transient complications).

The methodological quality of the included studies was assessed using MINORS. The study consisted of 12 projects, with the first eight devoted to non-comparative studies. The projects are scored 0 (not reported), 1 (reported, but inadequate), or 2 (reported and adequate), with an overall ideal score of 16 for non-comparative studies [7].

The study was registered in the international prospective database for systematic reviews (PROSPERO) with the registration number CRD42021283410.

Statistical analysis

The metaanalysis was conducted using Stata 14.0 (Stata Corp). The evaluation indices were percentages with 95% confidence intervals (CIs). Cochran's Q and the I^2 tests examined heterogeneity among individual studies [8]. Where $P \geq 0.05$ and $I^2 \leq 50\%$, suggesting homogeneity of the data from individual studies, the fixed effects model was chosen. Where $P < 0.05$ and $I^2 > 50\%$, suggesting heterogeneity between the studies, the random effects model was chosen to pool data. In addition to estimating the resolution rate in pruritus ani patients, to explore study heterogeneity, sensitivity and subgroup analyses were performed. A schematic representation (funnel plot) and quantitative analysis (Egger's

test) assessed publication bias. Statistical significance was set at $P < 0.05$.

Results

Study selection

Sixty-two articles (15 in PubMed, 25 in Embase, 1 in Cochrane library, and 21 in Web of Science) were found during the search. After removing duplicates, 34 articles were obtained; among them, 21 articles were selected based on the title and abstract. After a manual search of the reference lists and reading the full text, seven articles met our inclusion and exclusion criteria. A PRISMA diagram with full information on search results and the selection process is illustrated in Fig. 1.

Quality assessment

The quality of the studies was assessed using MINORS. All the studies had a clearly stated aim, presented endpoints to their aim, and displayed an unbiased assessment of the study endpoint. Five of the seven studies reported the inclusion of consecutive patients, prospective data collection, and loss to follow-up of < 5%. Additionally, in 85.7% (six of the seven) of the studies, the follow-up process was appropriate for the study aim. In the literature quality assessment, all included studies lacked a prospective calculation of the study size, resulting in poor MINORS scores, suggesting a relatively high risk of bias (Fig. 2).

Study characteristics

The studies included were published between 1979 and 2019 and conducted between 1977 (based on the follow-up time)

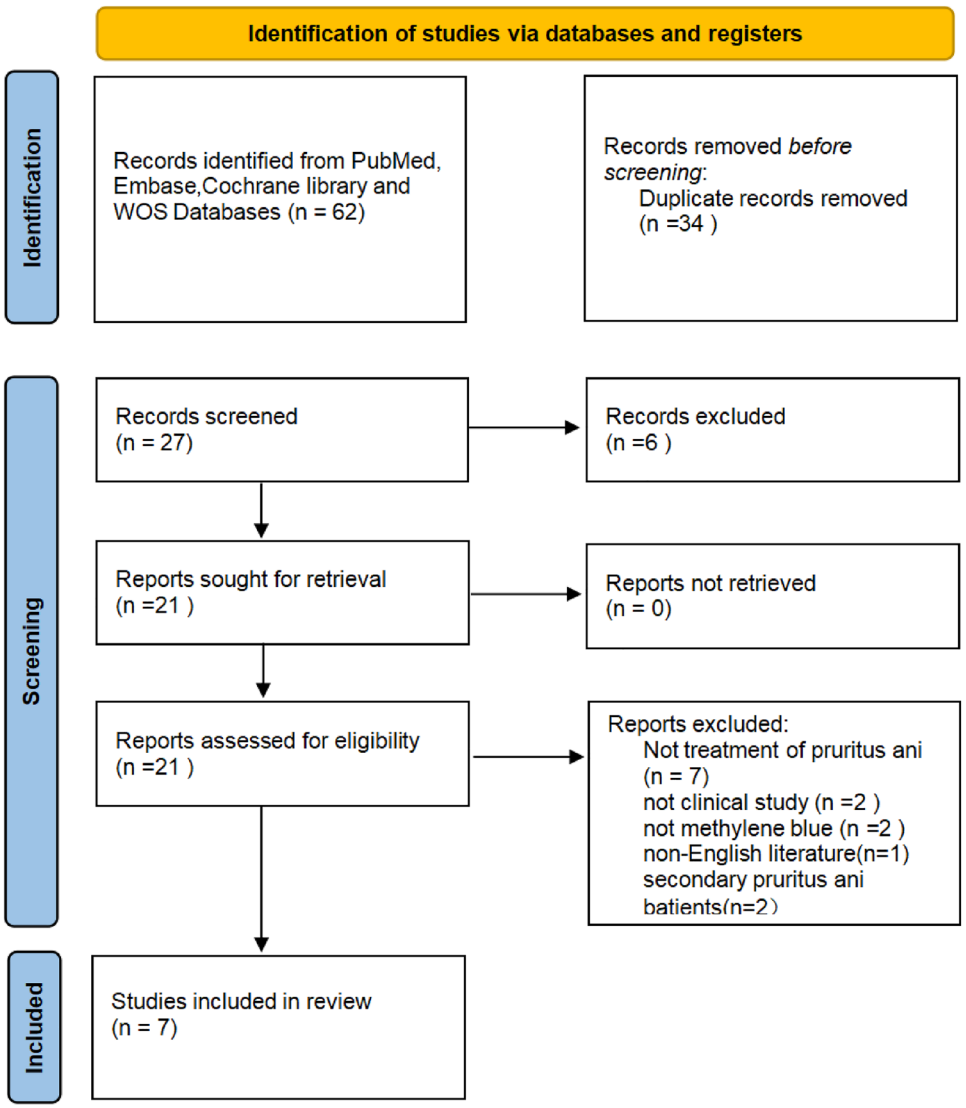

Fig. 1 PRISMA flow diagram for systematic reviews

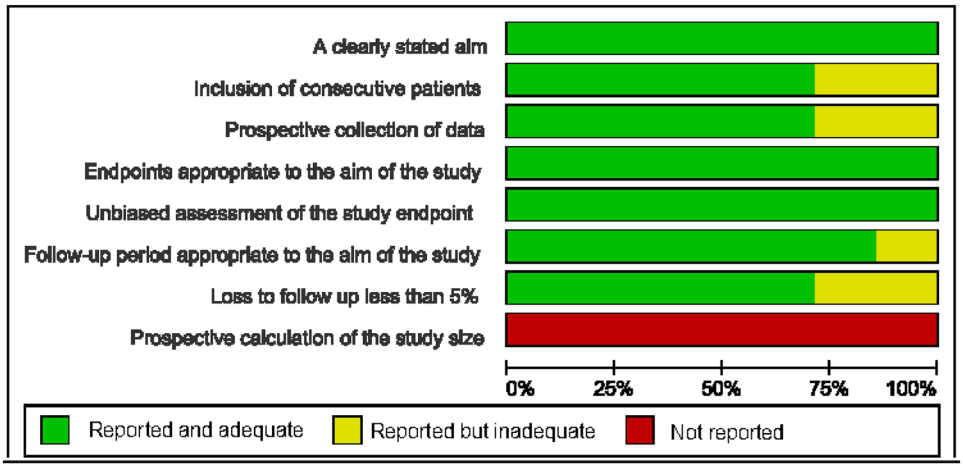

Fig. 2 Quality assessment of the studies included in the systematic review based on the Methodological Index for Nonrandomized Studies

and 2013 (Table 1). Six of the seven included studies were single-center prospective non-randomized trial case series [9–14], and one was a single-center retrospective study.

Six of the seven (85.7%) studies followed up on patients for over a year, allowing assessment of the main endpoint and possible adverse events. The seven selected studies were conducted mainly in Europe and Asia, with one in Australia. Three of the seven studies reported the patients' course of illness. Studies by Botterill and Sagar [15], Mentes et al. [16], and Kim et al. [19] reported a course of 3–180 months (median 24 months), 9–120 months (median 24 months), and a mean of 9.26 ± 2.88 years, respectively. These three articles revealed that the included patients had a prolonged disease course.

Demographics

The seven selected studies included 225 patients with idiopathic pruritus ani, including 123 (54.7%) females and 102 (45.3%) males (Table 1). Kim et al.[19] selected the patients who were followed up for 6 weeks. Data on age and sex were available in all studies, and all the patients were older than 18 years.

Enrolled patients

All the patients included in the studies had received conservative therapy for long periods without benefit. They underwent detailed examination of the anal region, rectoscopy, and barium enemas to exclude hemorrhoids, fistulae, and other disorders that could cause pruritus ani. Additionally, Farouk and Lee [14], Botterill and Sagar [15], Samalavicius et al. [18], and Kim et al. [19] excluded patients with fecal incontinence, Farouk and Lee [14] excluded patients with a history of anorectal surgery, and Botterill and Sagar [15] and Samalavicius et al. [18] excluded patients with systemic dermatoses (eczema, psoriasis, lichen planus, or allergic dermatitis), local skin diseases (*herpes* simplex, worm infestations, and condylomata), and systemic diseases that cause generalized pruritus (anemia, uremia, liver disease, or diabetes mellitus). Mentes et al. [16] and Samalavicius et al. [18] measured patients' blood sugar, liver and renal function, and complete blood counts with a peripheral smear. At least two stool samples were tested for parasites. Patients with positive results from those examinations were excluded, as were those with psychiatric illnesses, such as major depressive disorder, obsessive–compulsive disorder, and alcohol or other substance use disorders. Before the conclusive diagnosis of idiopathic pruritus ani, a dermatological consultation was also acquired.

Modalities of methylene blue injection

Regarding the modalities of methylene blue injection, the main differences were the method (the concentration of methylene blue injection) and the depth of methylene blue injection. Concerning the concentration, Wolloch and Dintsman [13], Mentes et al. [16], and Samalavicius et al. [18] used 1%, Farouk and Lee [14] used 0.44%, Sutherland et al. [17] used 0.32%, and Botterill and Sagar [15] and Kim et al. [19] used 0.25%. With regard to the injection depth, Wolloch and Dintsman [13], Farouk and Lee [14], and Botterill and Sagar [15] injected subcutaneously, Mentes et al. [16] administered subcutaneous and intradermal injections, and Sutherland et al. [17], Samalavicius et al. [18], and Kim et al. [19] administered an intradermal injection.

Table 1 Characteristics of the included studies

Study	Study design	Study period	Country	Patients	Age (years)	Sex (M/F)	Follow-up	Course	MINORS score	Outcomes
Wolloch and Dintsman [9]	Single-center prospective non-randomized trial	ND	Israel	9	29–68 (mean 46)	9/0	3–15 months	ND	12	a, b, f
Farouk and Lee [10]	Single-center prospective non-randomized trial	ND	UK	6	25–76 (median 56)	5/1	2–5 years (median 3 years)	ND	14	a, c, d, f
Botterill and Sagar [11]	Single-center prospective non-randomized trial	ND	UK	25	28–85 (median 49)	15/10	2–25 months (median 11 months)	3–180 months (median 24 months)	14	a, b, f
Mentes et al. [12]	Single-center prospective non-randomized trial	ND	Turkey	30	22–70 (median 39)	13/17	25 years (1 year) 5 years (2 years)	9–120 months (median 24 months)	12	a, b, c, d, f
Sutherland et al. [13]	Single-center prospective non-randomized trial	1996–2007	Australia	49	19–67 (median 43)	19/30	at 4 and 8 weeks	ND	13	a, b, e, f
Samalavicius et al. [14]	Single-center prospective non-randomized trial	2004–2008	Lithuania	10	30–63 (median 43)	4/6	29–60 months (median 47 months)	ND	14	a, c, d, e, f
Kim et al. [15]	Retrospective study	2011–2013	Korea	96 (6 weeks) 62 (3 years)	48.34 ± 10.21 (6 weeks), 45.56 ± 9.44 (3 years)	58/38 (6 weeks), 47/15 (3 years)	96 (6 weeks), 62 (3 years)	Mean 9.26 ± 2.88 years	12	a, b, c, d, e, f

a: resolution rate after a single injection

b: resolution rate after the second injection

c: resolution rate on follow-up

d: recurrence rate

e: symptom scores

f: transient complications

Outcomes

Rate of resolution

Rate of resolution after a single injection

All the studies included recorded the rate of resolution after a single injection. Overall, the resolution rate after a single injection was 57.1%–100%, revealing a good effect (Table 2). A pooled analysis (random effects model) of the data indicated that the resolution rate after the first methylene blue injection was 0.761 (95% CI 0.649–0.873, $P < 0.01$, $I^2 = 69.06\%$) (Fig. 3). Two studies were responsible for the high heterogeneity, according to the sensitivity analyses, presumably because Asian [15] and Australian[13] patients have different eating habits and lifestyles to those in patients in other countries, and these two studies comprised over two thirds (145/225) of the total number of patients. In subgroup analyses, the pooled analysis of the five European studies indicated the same result (0.782, 95% CI 0.680–0.885, $P = 0.333$, $I^2 = 11.859\%$) (Fig. 3).

Rate of resolution after a second injection

Five of the seven studies recorded the resolution rate after a second injection [9, 11–13, 15] (Table 2). A pooled analysis (random effects model) of the data indicated that the resolution rate after the second methylene blue injection was 0.854 (95% CI 0.752–0.955, $P < 0.01$, $I^2 = 77.391\%$) (Fig. 4). According to the sensitivity analyses, for the same reason as the single injection (Sutherland et al.[17] and Kim et al.

Table 2 Resolution rate, recurrence rate, and symptom scores

Study	Rate of resolution after a single injection (*n*, %)[a]	Rate of resolution after the second injection (*n*, %)[b]	Rate of resolution on follow-up (*n*, %)[c]	Recurrence rate (*n*, %)[d]	Symptom scores
Wolloch and Dintsman [9]	8, 88.9	9, 100.0	9, 100.0 (3–15 months)	ND	ND
Farouk and Lee [10]	5, 83.3	ND	5, 83.3 (less than 1 year) 4, 66.7 (1 year) 3, 50.0 (3 years) 2, 33.3 (5 years)	1, 20.0 (1 years) 2, 40.0 (2 years) 3, 60.0 (3 years)	ND
Botterill and Sagar [11]	16, 64.0	22, 88.0	22, 88.0 (ND)	ND	ND
Mentes et al. [12]	24, 80.0	28, 93.3	28, 93.3 (less than 6 months) 25, 83.3 (6 months) 23, 76.7 (12 months)	3, 10.7 (6 months) 5, 17.9 (12 months)	ND
Sutherland et al. [13]	28, 57.1	32, 65.3	32, 65.3 (ND)	ND	4.53 ± 0.58[e,g] 4.61 ± 0.57[f,g]
Samalavicius et al. [14]	10, 100.0	No second injection	10, 100.0 (4 weeks) 2, 20.0 (60 months)	1, 10.0 (2 months) 3, 30.0 (1 year) 6, 60.0 (2 years) 7, 70.0 (3 years) 8, 80.0 (4 years)	3.80 ± 0.79[e,h]
Kim et al. [15]	87, 90.6 (6 weeks) 82, 85.4(2 months) 48, 77.4 (3 years)	53, 85.5 (3 years)	87, 90.6 (6 weeks) 82, 85.4 (2 months) 48, 77.4 (3 years)[e] 53, 85.5 (3 years)[f]	5, 5.7 (2 months) 4 /7.5 (3 years)	4.23 ± 0.86 (6 weeks) 4.74 ± 0.57 (3 years)[g]

ND no data

[a]Resolution rate after a single injection asymptomatic patients/total patients

[b]Resolution rate after the second Injection asymptomatic patients/total patients

[c]Resolution rate on follow-up asymptomatic patients/total patients (at corresponding time)

[d]Recurrence rate, total recurrences/asymptomatic patients (at corresponding time)

[e]After a single injection

[f]After the second injection

[g](1 much worse, 2 worse, 3 no improvement, 4 much better, 5 resolved completely)

[h](1 much worse, 2 worse, 3 same intensity of symptoms, 4 much better, 5 resolved completely)

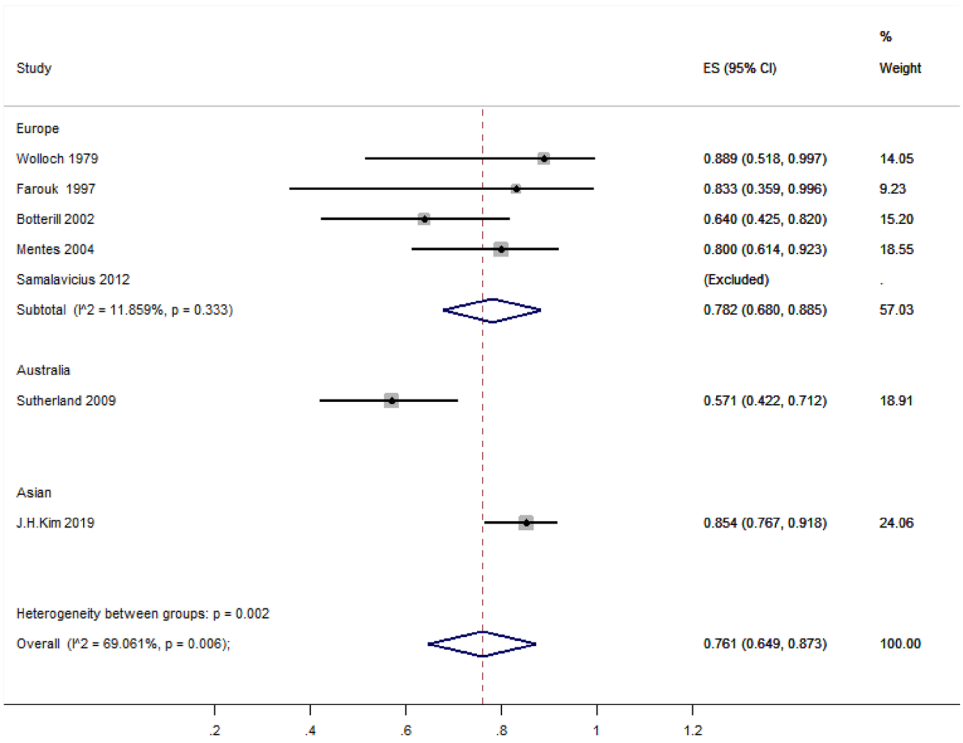

Fig. 3 Forest plot of the eligible studies for the rate of resolution after the first injection and subgroup analysis

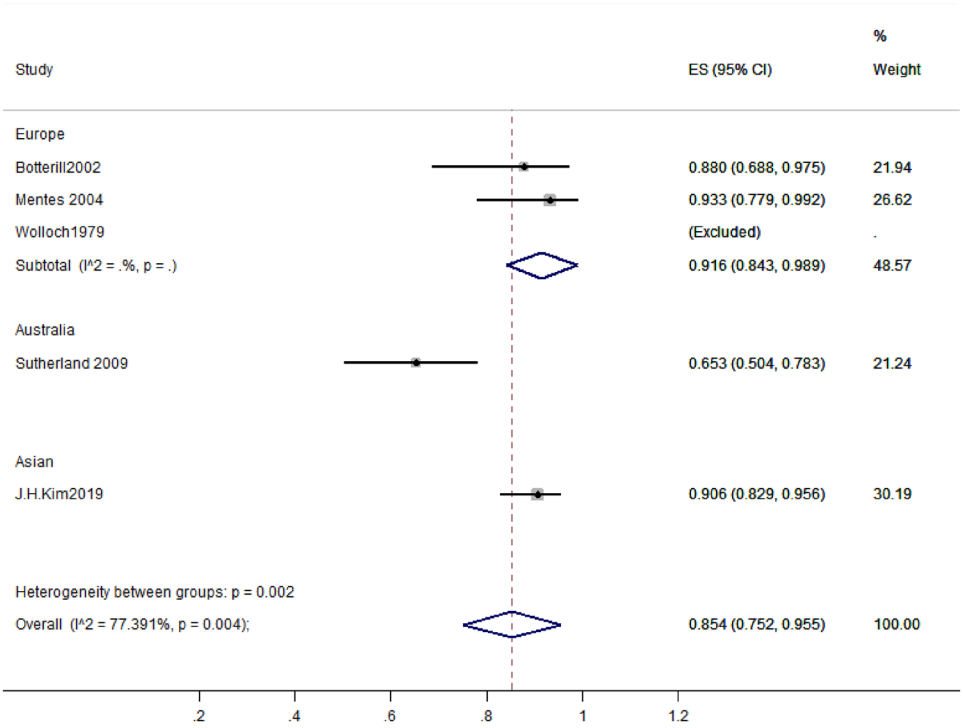

Fig. 4 Forest plot of the eligible studies for the rate of resolution after the second injection and subgroup analysis

[19]). In subgroup analyses, the pooled analysis of the three European studies indicated the same result (0.916, 95% CI 0.843–0.989, $P < 0.001$, $I^2 = 0.00\%$) (Fig. 4).

Resolution rate on follow-up

In the study by Wolloch and Dintsman [13], all nine (100%) patients were free of symptoms on follow-up from 3 to 15 months. In the study by Farouk and Lee [14], significant

reduction in symptoms was observed in five (83.3%) of six patients, and the associated skin changes subsided significantly, with only occasional mild pruritus. Three patients underwent a second injection of methylene blue due to symptom recurrence at 1, 3, and 5 years. Overall, four (66.7%), three (50.0%), and two (33.3%) of six patients were symptom-free at 1, 3, and 5 years, respectively. The study by Botterill and Sagar [15] revealed that 22 (88.0%) of 25 patients were symptom-free after injection; however, no specific duration of relief was mentioned. In the study by Mentes et al. [16], the early response rate was 80% (24 of 30) after a single injection and 93.3% (28 of 30) after a second injection. Three recurrences were recorded after 6 months, indicating an 83.3% (25 of 30) success rate. After 12 months of treatment, 23 patients (76.7%) were symptom-free. In the study by Sutherland et al. [17], symptoms improved in 95.9% (47 of 49) and resolved in 57.1% (28 of 49) of patients after a single injection. The two patients with unchanged symptom scores did not receive further treatment. Four of the 19 patients who had improved but continued to have symptoms received a second injection. All four patients were symptom-free (no complications), improving the overall resolution rate to 65.3% (32 of 49). The study by Samalavicius et al. [18] revealed resolution in all 10 (100.0%) patients at 4-week follow-up and a 20% (2 of 10) success rate after 60 months. In the study by Kim et al. [19], out of 96 patients, 9 scored ≤ 3 in their satisfaction score surveys 6 weeks post-treatment, indicating a 90.6% (87 of 96) improved symptom rate. At 3 years, 48 (77.4%) of 62 patients were symptom-free after a single injection, and 53 (85.5%) of 62 patients were symptom-free after a second injection (Table 2).

Rate of resolution after a year or more

Four studies reported the resolution rate after a year or more [10, 12, 14, 15]. Among them, in the study by Farouk and Lee [14], no patients reported pruritis at 1, 3, and 5 years after treatment, while Mentes et al. [16], Samalavicius et al. [18], and Kim et al.[19] reported improvement rates at 1, 3, and 5 years after treatment. A pooled analysis (random effects model) of the data indicated that the remission rates at 1, 3, and 5 years were 0.753 (95% CI 0.612–0.893, $P < 0.001$), 0.773 (95% CI 0.675–0.871, $P < 0.001$), and 0.240 (95% CI 0.033–0.447, $P < 0.001$), respectively, and the effect value of the merger was 0.569 (95% CI 0.367–0.772, $P < 0.001$, $I^2 = 79.199\%$) (Fig. 5).

Recurrence rate

Four of the seven studies mentioned the recurrence rate after a single injection [10, 12, 14, 15]. Overall, the recurrence rates after a single injection ranged from 5.7% to 80% (Table 2). Four studies reported cumulative recurrence rates at 1, 2, 3, and < 1 year (2 and 6 months) [10, 12, 14, 15]. A pooled analysis (random effects model) of the data indicated that the resolution rate at 1, 2, 3, and < 1 year were 0.202 (95% CI 0.083–0.322, $P < 0.001$), 0.533 (95% CI 0.285–0.781, $P < 0.001$), 0.437 (95% CI −0.044, 0.917, $P < 0.001$), and 0.067 (95% CI 0.023–0.111, $P < 0.001$), respectively. The effect value of the merger was 0.223 (95% CI 0.126–0.319, $P < 0.001$, $I^2 = 75.840$) (Fig. 6).

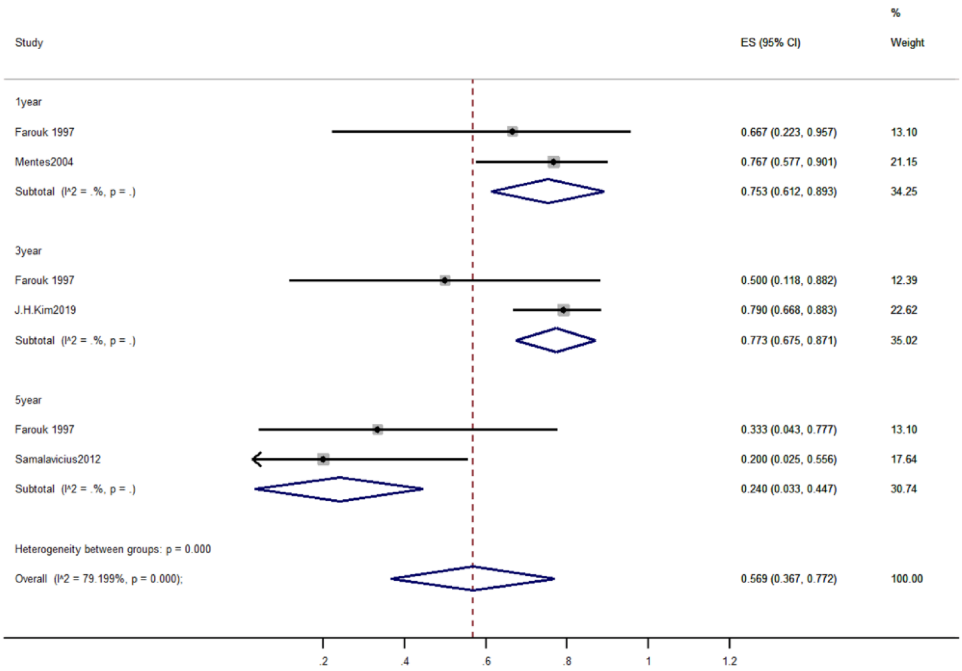

Fig. 5 Forest plot of the eligible studies for the resolution rate after 1 or more years

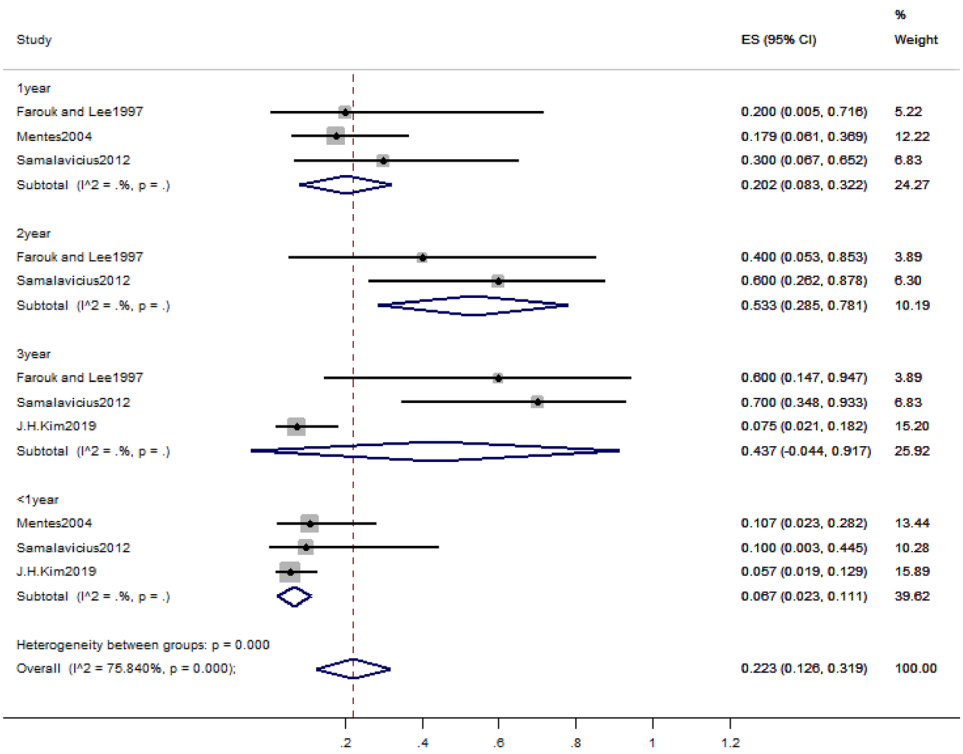

Fig. 6 Forest plot of the eligible studies for the cumulative recurrence rate of pruritus ani

Symptom scores

Three of seven studies included symptom scores [13–15]. In the study by Sutherland et al. [17], symptom scores were 1 much worse, 2 worse, 3 no improvement, 4 much better, and 5 complete resolution. The mean symptom score was 4.53 ± 0.58 after a single injection, while it was 4.61 ± 0.57 after a second injection. Samalavicius et al. [18] reported symptom scores of 3.80 ± 0.79 after a single injection, and Kim et al. [19] reported 4.23 ± 0.86 at 6 weeks and 4.74 ± 0.57 at 3 years (Table 2).

Transient complications

All patients noted temporary staining of the perianal skin, urine discoloration, and perianal area numbness. In the study by Wolloch and Dintsman [13], apart from one patient who reported a pyrexia of 39 ℃ for 1 day and recovered without treatment, no other complications were observed. In the study by Farouk and Lee [14], one patient reported urinary retention that necessitated temporary catheterization, another had a superficial abscess, and one experienced transient incontinence. Botterill and Sagar [15] reported a patient who had involuntary fecal seepage for 2 days post-injection. In the study by Mentes et al. [16], self-limited cellulitis was reported in two patients, which resolved after a few days of warm sitz baths. In the study by Sutherland et al. [17], seven patients complained of incontinence, including four patients with incontinent flatus, one patient with incontinence, one patient with incontinent stool, and one patient with impaired continence, all which resolved within 10 days to 6 weeks. The perianal sensation was reduced in two individuals, causing them distress. In the study by Samalavicius et al. [18], two patients experienced minor swelling that lasted up to 2 months, which did not require any therapy. In the study by Kim et al. [19], subcutaneous hematoma occurred in 6 (9.7%) of the 62 patients, spontaneously resolving after 2 weeks. Overall, methylene blue injection resulted in no severe complications.

Publication bias

Figure 7 illustrates a funnel plot for the resolution rate after the first injection (seven studies), demonstrating no publication bias ($t = -0.81$, $\Pr > |t| = 0.465$, $P > 0.05$).

Discussion

In 1890, Ehrlich discovered that the local use of methylene blue in high concentrations could dye nerve terminals and destroy their function. He worked with German psychiatrists to successfully use it to treat neuritis and rheumatic diseases. In 1891, Ehrlich observed methylene blue as an effective malaria treatment, and it was gradually used to treat other infections. Although 100 years have passed, methylene blue

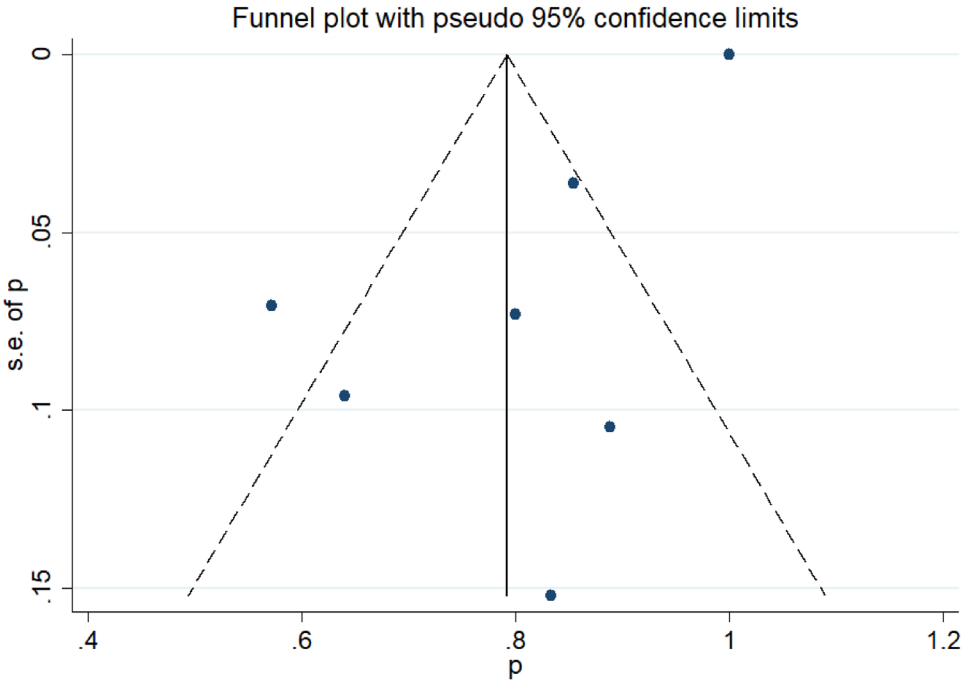

Fig. 7 Funnel plot of the seven eligible studies that reported the rate of resolution after the first injection

remains widely used in clinical diagnosis and treatment, mainly related to methemoglobinemia, ifosfamide-induced encephalopathy, malaria, shock, analgesia, and intraoperative localization [16, 17].

As reported in this article, methylene blue injections can treat intractable idiopathic pruritus ani. Rygick first reported the use of methylene blue to treat intractable idiopathic pruritus ani in 1968 and reported that local nerve terminal necrosis was observed through clinical observation and electron-microscopic observation of skin biopsies of the injection site. The nerve terminal necrosis caused by methylene blue was thought to block the conduction of local sensation for 26–28 days [18]. No significant differences in normal tissue structure were observed on electron microscopy 1 and 7 years after methylene blue injection, confirming that methylene blue causes reversible nerve damage [19]. In the study by Botterill and Sagar [15], blue skin discoloration lasted ≤ 2 weeks. The short retention time of the blue tattoo could indicate that methylene blue was injected too deeply. Effective injections require skin tattoos lasting between 2 and 6 weeks. This period of perianal anesthesia appears necessary for the denervation of the perianal skin, allowing for the interruption of the itch-scratch-itch cycle. Therefore, Mentes et al. [16] administered subcutaneous and intradermal injections, whereas Sutherland et al., Samalavicius et al. [18], and Kim et al. [19] injected intradermally. However, Sutherland et al. [17] did not report this association. However, Kim et al. [19], like Botterill and Sagar [15], discovered a lower recurrence rate of methylene blue tattooing around the anus over a long period. Therefore, further studies are needed to verify whether the duration of blue skin discoloration correlates with the recurrence rate. Regarding the concentration of methylene blue injection, there was no authoritative standard. Among the seven included studies, the resolution rates following the first and second injections, and the outcomes observed during the long-term follow-up, recurrence rates, and symptom scores, were not significantly linked with various concentrations.

Regarding complications, Botterill and Sagar [15] hypothesized that transient incontinence might be caused by the local dispersal of lignocaine, which may cause pudendal neuropathy. Sutherland et al. [17] hypothesized that it may be due to sensory changes within the anal canal owing to the dye's proximal spread. The concentration of methylene blue, the injection depth, and antibiotics used, or additional measures used before or during surgery, were not significantly correlated with the occurrence or severity of complications (Table 3). However, the sterility of the solutions and skin preparation are paramount. Mentes et al. [16] and Samalavicius et al. [18] noted that the injection should not be administered superficially or deeply, risking skin necrosis and pelvic sepsis, respectively. Local anesthesia resulted in fewer and less severe complications than general or no anesthesia.

Breaking the itch-scratch-itch cycle is the primary goal in managing intractable idiopathic pruritus ani. Treatments other than methylene blue include topical steroids, topical capsaicin ointment, and tacrolimus ointment. Long-term use of topical steroids is ill-advised due to skin and secretory gland atrophy risk [20]. Topical capsaicin was a safe and effective treatment for severe intractable idiopathic pruritus ani in a double-blind, placebo-controlled,

Table 3 Treatment technique and complications

Study	Method (methylene blue %)	Position	Anesthesia	Depth of methylene blue injection	Prophylactic use of antibiotics	Additional measures	Transient complications
Wolloch and Dintsman [9]	10–15 ml 1% methylene blue (1%)	Lithotomy position	Local anesthesia	Infiltrated subcutaneously	ND	AP codeine analgesia	1/9 Pyrexia (39 ℃) (1 day)
Farouk and Lee [10]	10 ml 1% methylene blue + 7.5 ml 0.25% marcaine with 1:200,000 adrenaline + 5 ml 0.9% sodium chloride (0.44%)	Lithotomy position	General anesthesia	Infiltrated intradermally	Intravenous cefuroxime 750 mg + metronidazole 500 mg	ND	1.1/6 Urinary retention (temporary catheterization), 2.1/6 superficial abscess, 3.1/6 transient incontinence
Botterill and Sagar [11]	5 ml 1% methylene blue + 100 mg hydrocortisone + 15 ml 1% lignocaine (0.25%)	Lithotomy position	General anesthesia (23), intravenous sedation (2)	Infiltrated intradermally	No antibiotic prophylaxis	One patient partially improved: topical barrier creams	1/25 involuntary fecal seepage (2 days)
Mentes et al. [12]	7–8 ml 2% methylene blue + 7–8 ml 0.5% lidocaine (1%)	Prone jack-knife position	No anesthesia or sedation	Intracutaneously and subcutaneously	No antibiotic prophylaxis	Warm sitz baths, dietary and hygienic guidelines	2/30 self-limited cellulitis (resolved within a few days with warm sitz baths)
Sutherland et al. [13]	10 ml 1% methylene blue + 20 ml 0.5% marcaine with 1:200,000 adrenaline + 1 ml methylprednisolone (0.32%)	ND	General anesthesia	Intradermally	ND	Overnight stay with patient-controlled narcotic infusion and discharged with paracetamol as required	1.7/49 incontinence (10 days–6 weeks), 2.2/49 distressed by decreased perianal sensation
Samalavicius et al. [14]	10 ml 2% methylene blue + 5 ml saline + 5 ml 2% lidocaine (1%)	prone jack-knife position	No general or intravenous anesthesia	Intradermally	No premedication, but during operation 1500 mg metronidazole + 1.5 g cefuroxime intravenously	Petroleum jelly ointment to decrease the sensation of underwear touching the numb perianal area	All 10 slight swelling (8 cases 3–4 weeks, 2 cases 2 months)
Kim et al. [15]	5 ml 1% methylene blue + 15 ml 1% lidocaine (0.25%)	Prone jack-knife position	Saddle block anesthesia	Intradermally	ND	ND	6/62 subcutaneous hematoma (2 weeks)

ND no data

crossover research. Thirty-one of the 44 patients who participated in the study experienced relief after capsaicin treatment [21]. A randomized double-blind clinical trial including 21 patients with intractable idiopathic pruritus ani treated with tacrolimus 0.1% ointment reported symptom improvement in 68% of the patients after 2 weeks of treatment, suggesting that it may be an effective treatment for intractable idiopathic pruritus ani [22]. A conference abstract of a randomized crossover study on topical tacrolimus in 16 patients revealed significant reductions in the recorded Eczema Area and Severity Index (EASI), dermatology life quality index (DLQI), and itching scores at weeks 4 and 6 of treatment compared with the placebo group ($P < 0.05$) [23].

Individual studies on intractable idiopathic pruritus ani treatment are frequently limited by a paucity of patients and the control group design. Thus, this metaanalysis aimed to systematically analyze the efficacy and safety of methylene blue in adult patients with intractable idiopathic pruritus ani. The pooled data suggest that methylene blue is effective and well tolerated for intractable idiopathic pruritus ani.

To our knowledge, this is the first systematic review of methylene blue's clinical efficacy and safety in intractable idiopathic pruritus ani treatment. Furthermore, the study participants were from various countries, ensuring that the sample was broadly representative.

Nevertheless, there were several limitations to this review. First, significant heterogeneity was observed, most likely attributable to the varying backgrounds of patients and the varied doses and treatment techniques used. Second, while Egger's test revealed no significant publication bias in the literature, this metaanalysis included few studies and a small sample size, potentially limiting the review's strength. Therefore, there may be potential publication bias due to the low statistical efficiency of quantitative tests. As a result, the findings should be viewed with caution. Third, the studies included in this metaanalysis were diverse, including non-randomized clinical and observational studies. Although all were eligible for inclusion, only single-arm data of methylene blue were collected, and all included studies lacked a prospective calculation of the study size, resulting in poor MINORS scores and suggesting a relatively high risk of bias. Since all the included studies were single-arm studies, methylene blue could not be compared with other treatments such as topical and intradermal steroids, topical capsaicin ointment, and tacrolimus ointment. Therefore, further randomized controlled trials should be conducted to validate the clinical efficacy of methylene blue compared with that of other treatments. Finally, the studies were published over 40 years, between 1979 and 2019, which is also a potential source of bias, as the treatment technique has developed over time.

Conclusion

Based on the existing literature, using methylene blue injections to treat intractable idiopathic pruritus ani is relatively efficacious, resulting in a relatively low recurrence rate and no severe complications. However, the available literature is of poor quality. Therefore, higher quality studies are necessary to confirm that methylene blue injection is efficacious in treating pruritus ani, such as a randomized prospective multicenter study, which may provide definitive results.

Funding This study was supported by the National Natural Science Foundation of China [grant number 81704082], the Medical Scientific Research Foundation of Zhejiang Province, China [grant number 2020RC086], the Zhejiang Traditional Chinese Medicine Scientific Research Foundation [grant number 2020ZB095], and the Zhejiang Provincial Natural Science Foundation of China [grant number LQ20G030015].

Declarations

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

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

References

1. Abramowitz L, Benabderrahmane M, Pospait D, Philip J, Laouénan C (2014) The prevalence of proctological symptoms amongst patients who see general practitioners in France. Eur J Gen Pract 20(4):301–306
2. Hsieh JC, Hägermark O, Ståhle-Bäckdahl M, Ericson K, Eriksson L, Stone-Elander S, Ingvar M (1994) Urge to scratch represented in the human cerebral cortex during itch. J Neurophysiol 72(6):3004–3008
3. Nasseri YY, Osborne MC (2013) Pruritus ani: diagnosis and treatment. Gastroenterol Clin North Am 42(4):801–813
4. Oueidat D, Bou Assi T, Jurjus A (2014) Pruritus ani: more than a decade of personal experience in Lebanon. J med liban Leb med J 62(4):203–206
5. Etter L, Myers SA (2002) Pruritus in systemic disease: mechanisms and management. Dermatol Clin 20(3):459–472
6. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71
7. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J (2003) Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 73(9):712–716
8. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560

9. Wolloch Y, Dintsman M (1979) A simple and effective method of treatment for intractable pruritus ani. Am J Proctol Gastroenterol Colon Rectal Surg 30(1):34–36
10. Farouk R, Lee PW (1997) Intradermal methylene blue injection for the treatment of intractable idiopathic pruritus ani. Br J Surg 84(5):670
11. Botterill ID, Sagar PM (2002) Intra-dermal methylene blue, hydrocortisone and lignocaine for chronic, intractable pruritus ani. Col Dis 4(2):144–146
12. Mentes BB, Akin M, Leventoglu S, Gultekin FA, Oguz M (2004) Intradermal methylene blue injection for the treatment of intractable idiopathic pruritus ani: results of 30 cases. Tech Coloproctol 8(1):11–14
13. Sutherland AD, Faragher IG, Frizelle FA (2009) Intradermal injection of methylene blue for the treatment of refractory pruritus ani. Col Dis 11(3):282–287
14. Samalavicius NE, Poskus T, Gupta RK, Lunevicius R (2012) Long-term results of single intradermal 1 % methylene blue injection for intractable idiopathic pruritus ani: a prospective study. Tech Coloproctol 16(4):295–299
15. Kim JH, Kim DH, Lee YP (2019) Long-term follow-up of intradermal injection of methylene blue for intractable, idiopathic pruritus ani. Tech Coloproctol 23(2):143–149
16. Oz M, Lorke DE, Hasan M, Petroianu GA (2011) Cellular and molecular actions of methylene blue in the nervous system. Med Res Rev 31(1):93–117
17. Wainwright M, Crossley KB (2002) Methylene blue a therapeutic dye for all seasons? J Chemother 14(5):431–443
18. An R (1968) Atlas of the Operations on the Rectum and Colon. Moscow Meduch Posovie. 14:431
19. Eusebio EB, Graham J, Mody N (1990) Treatment of intractable pruritus ani. Dis Colon Rectum 33(9):770–772
20. Ortega AE, Delgadillo X (2019) Idiopathic pruritus ani and acute perianal dermatitis. Clin Colon Rectal Surg 32(5):327–332
21. Lysy J, Sistiery-Ittah M, Israelit Y, Shmueli A, Strauss-Liviatan N, Mindrul V, Keret D, Goldin E (2003) Topical capsaicin–a novel and effective treatment for idiopathic intractable pruritus ani: a randomised, placebo controlled, crossover study. Gut 52(9):1323–1326
22. Suys E (2012) Randomized study of topical tacrolimus ointment as possible treatment for resistant idiopathic pruritus ani. J Am Acad Dermatol 66(2):327–328
23. Ucak H, Demir B, Cicek D, Dertlioglu SB, Akkurt ZM, Ucmak D, Halisdemir N (2013) Efficacy of topical tacrolimus for the treatment of persistent pruritus ani in patients with atopic dermatitis. J Dermatolog Treat 24(6):454–457