Comparison of Three Treatment Methods of I-III Degree Hemorrhoids: A Meta Analysis

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ABSTRACT

Objectives: To evaluate the efficacy and safety of rubber band ligation (RBL), injection sclerotherapy(IS) and infrared coagulation(IRC) in the treatment of the internal hemorrhoids.

Methodology: Clinical studies involving comparisons between two or three of RBL, IS and IRC in the treatment of internal hemorrhoids were retrieved from PubMed, Cochrane Library and Embase database. The Cochrane risk bias assessment tool was used to Meta-analyze the efficacy and safety indicators of the three treatments using Review Manager 5.4 software. Results: A total of 379 related literatures were retrieved, and 12 literatures were included after screening. A total of 1438 patients were included, including 592 in the RBL group, 350 in the IS group, and 496 in the IRC group. Meta-analysis showed, the long-term recurrence rate of RBL group (follow up for 1 year and above) was lower than that of IS group and IRC group (P=0.0003), the effective rate of RBL group was higher than that of IS group (P=0.0003), and the complication rate of RBL group was lower than that of IRC group (P=0.01). In this study, there were no significant statistical differences in the incidence of complications between the RBL group and the IS group (P=0.42), the clinical effect between the RBL group and the IRC group (P=0.16) and the IS group and the IRC group (P=0.17), and the recurrence rate (P=0.46).

Conclusion: For the treatment of grade I-III internal hemorrhoids, the efficacy and safety of RBL group are better than those of IS group and IRC group, and there are fewer complications.

Introduction

Hemorrhoids is a common clinical disease and its pathogenesis is not yet clear. The theory of anal cushion displacement is widely accepted at present, that is, supporting tissue degeneration, including fibrous tissue fragmentation, elastic connective tissue and submucosal muscle fiber weakening, which may be related to lack of dietary fiber, constipation, improper defecation habits and lifestyle. The main clinical manifestations of hemorrhoids are bleeding during defecation, pain, anal prolapse, swelling, pruritus and perianal secretions [1]. Depending on the location of the disease, hemorrhoids can be divided into internal hemorrhoids, external hemorrhoids and mixed (internal and external) hemorrhoids. Internal hemorrhoids are formed by tissue covered by columnar epithelium, and located above the dentate line; External hemorrhoids are formed by tissue covered by squamous epithelium, and located below the dentate [2]. Mixed hemorrhoids appear at the top and bottom of the dentate line. The staging of internal hemorrhoids is not completely unified in the world. Goligher's classification is more commonly used, which divides internal hemorrhoids into gradeI-IV.

i. **Grade I**: Bleeding during defecation, but not prolapse, most patients have no obvious symptoms.

ii. **Grade II**: The hemorrhoids protrude out of the anus during defecation, and the prolapse can be returned by itself.

iii. **Grade III**: Prolapse out of the anus during defecation, fatigue, long walking, or coughing. After prolapse, internal hemorrhoids cannot be repaid by themselves, and they need to be repaid by hand.

iv. **Grade IV**: With external hemorrhoids, the hemorrhoids remain outside the anus for a long time and cannot be repaid or prolapse immediately after being repaid.

The treatment methods of internal hemorrhoids include non-surgical treatment and surgical treatment. Most internal hemorrhoids of grade I-III can be alleviated by non-surgical treatment such as drug treatment, RBL, IS, and IRC; grade IV internal hemorrhoids, internal hemorrhoids that fail or have complications should undergo surgical treatment [3]. RBL is a simple, quick and effective method for treating patients with grade I-II and part of grade III internal hemorrhoids. The method is to ligate with ligator above the dentate line, and the internal hemorrhoids are necrotic due to blood flow blockade and fall off automatically [4]. IS is an endoscopic or anal endoscopic injection of sclerosis agent into the submucosal layer of internal hemorrhoids, forming fibrosis and scars. IRC is to coagulate the hemorrhoid blood vessels or cause fibrosis of the hemorrhoid submucosa through the instant high heat generated by infrared rays, to fix the anal cushion. IRC is mainly used for the treatment of internal hemorrhoids of grade I - III [2]. The purpose of this study was to compare the efficacy and safety of RBL, IS and IRC in the treatment of internal hemorrhoids. We evaluated the evidence from the random control trial (RCT) and the research data from the systematic review of the RCT, and performed a meta-analysis, which is reported below.

Materials and Methods

Search strategy

Use keywords such as "Hemorrhoids", "Hemorrhoid sclerotherapy", "Injection sclerotherapy", "Rubber band ligation", "Hemorrhoid ligation", "Infrared coagulation", "Hemorrhoid infrared coagulation". Searched the literatures from PubMed, Cochrane Library, and Embase database up to 2021. The research method limited the RCT to improve the sensitivity and did not limit the language, and the related references in the included literature were manually searched, and consistent standards were used to determine the included and excluded literature.

Inclusion and Exclusion Criteria

• Participants of the study included patients ≥18 years of age who met the Goligher's grading classification criteria and patients with grade I-III internal hemorrhoids; patients diagnosed with grade IV hemorrhoids and patients with other anorectal diseases other than the study disease were excluded.

• The original text is publicly published literature; it is limited to RCT, in which patients are randomly assigned to two or more treatment groups, clinical results are recorded, and follow-up time is at least 3 months.

• The original literature provides corresponding indicators of effectiveness and safety: including effective rate, recurrence rate, complication rate, etc.

• The type of literature is limited to treatises, and literatures with incomplete original data are excluded. reviews, conference reports, reviews, case reports, etc. are excluded.

• The included RCTs are all evaluated by the Cochrane handbook to evaluate the quality of the literature.

Data Extraction

General data of the literature were extracted: including the first author, year of publication, number of patients included, observation data, etc. The extraction of all data was done independently by two researchers. For the controversial data, the third researcher participated in the discussion and decided.

Outcome Indicators

Main Outcomes: Effective Rate, Recurrence Rate.

Secondary Outcome: Complications.

Statistical Analysis

Meta-analysis was conducted with Review Manager 5.4 software to study the effective rate, recurrence rate and complication rate of RBL, IS and IRC in the treatment of patients with internal hemorrhoids. As a dichotomous variable analysis, odds ratio (OR) was used as the effect index, and 95% confidence intervals (95%CI) is calculated. The Cochrane Q test was used to evaluate the heterogeneity among studies, and the magnitude of heterogeneity among studies was determined by combining the I^2 value. Moderate to high heterogeneity was considered when I^2 was greater than 50%, and the test level was $\alpha=0.1$. The data were combined and analyzed for heterogeneity. If there was no heterogeneity ($I^2 \leq 50\%$ and $P \geq 0.1$), the fixed-effect model was selected for analysis; If there was heterogeneity ($I^2 > 50\%$ and/or $P < 0.1$), then analyze its sources and discuss, choose random effects model analysis. Meta analysis test level was $\alpha=0.05$. For highly heterogeneous variables, the single study deletion method was used to conduct sensitivity analysis to find the source of heterogeneity. If the heterogeneity decreased after deleting the document, the document was the source of heterogeneity, and the forest figure was finally made. Regarding the analysis of publication bias, by observing whether

the two sides of the funnel chart were symmetrical, if the two sides were symmetrical, there was no obvious publication bias, and if the two sides were asymmetric, there may be publication bias.

Meta Analysis Results

A total of 379 relevant literatures were retrieved, 159 duplicate literatures were excluded, 155 were excluded after reading the title, 39 were excluded after reading the abstract, and 14 were excluded after reading the full text. A total of 12 literatures were screened according to the inclusion criteria (Figure 1). A total of 1438 patients were included, including 592 patients in the RBL group, 350 patients in the IS group, and 496 patients in the IRC group. The detailed data of the included literatures were shown in Table 1 (Figure 2).
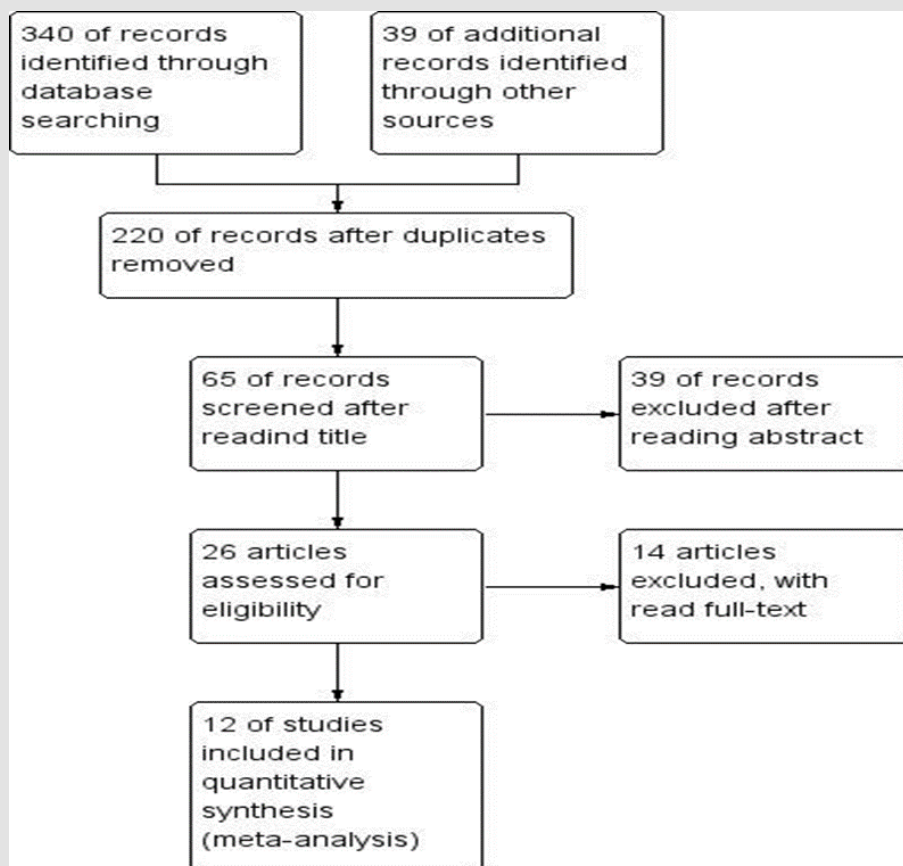

Figure 1: Literature retrieval process and results Table 1 Features of the included literatures.
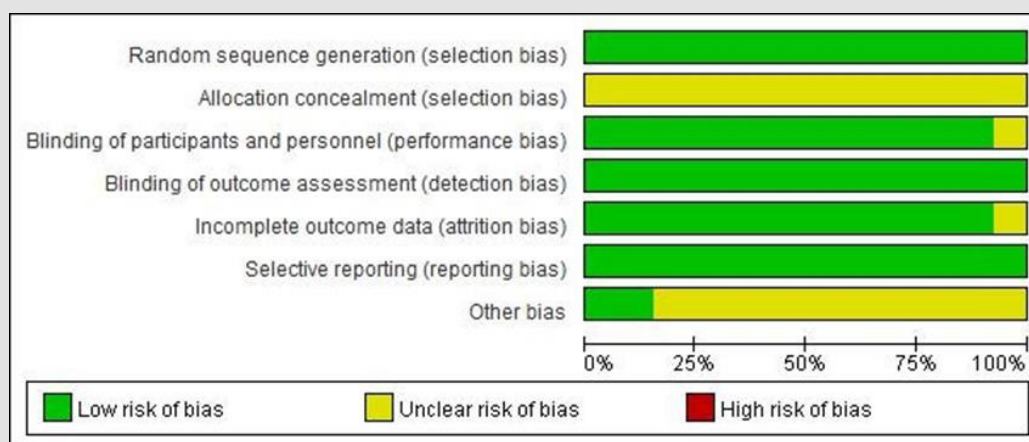

Figure 2: Risk assessment of inclusion literature.

Table 1.

Study	Year	Enrolled	No. of Patient of Treatment	Follow- Up	Mean Page	Males	Females	Hemorrhoid/ Grade		Treatment
								01-Feb	3	
Ayomide Makanjuola [5]	2020	74	RBL=37 IS=37	12W	43.84±13.8	42	32	54	20	RBL,IS
Greca [6]	1981	82	RBL=39 IS=43	1y	45	50	32	74	8	RBL,IS
Gartell [14]	1985	214	RBL=105 IS=109	2.75y	49.5	171	98	177	42	RBL,IS
Sim [15]	1981	46	RBL=22 IS=24	1y	45	33	13	46		RBL,IS
Cheng [16]	1981	60	RBL=30 IS=30	12m	44	64	56		60	RBL,IS
Ricci MP [9]	2008	48	RBL=23 IRC=25	4w	54.3	25	23	42	6	RBL,IR C
P J Gupta [17]	2003	100	RBL=54 IRC=46	12m	38	68	32	100		RBL,IR C
A C Poen [12]	2000	124	RBL=60 IRC=64	19.2m	48	73	60	124	9	RBL,IR C
Templeton [18]	1983	122	RBL=62 IRC=60	1y	46.3	97	40	137		RBL,IR C
Ambrose [19]	1983	268	RBL=127 IRC=141	12m	45.9	149	119	255	13	RBL,IR C
Walker [20]	1990	165	RBL=33 IS=45 IRC=87	12m	47	132	68	165		RBL IS IRC
Ambrose [21]	1985	135	IS=62 IRC=73	12m	45	74	61	135		IS IRC

Effective Rate

a. RBL vs IRC: A total of 782 cases are included in 6 literatures, and heterogeneity analysis indicates no heterogeneity (P=0.60, I^2=0%). The fixed-effect model analysis is carried out, and the results shows that there is no significant difference in the effective rate between the RBL group and the IRC group (OR=1.36, 95%CI:0.89-2.09, P=0.16), indicating that the treatment effect of the two groups is similar, as shown in Figure 3.
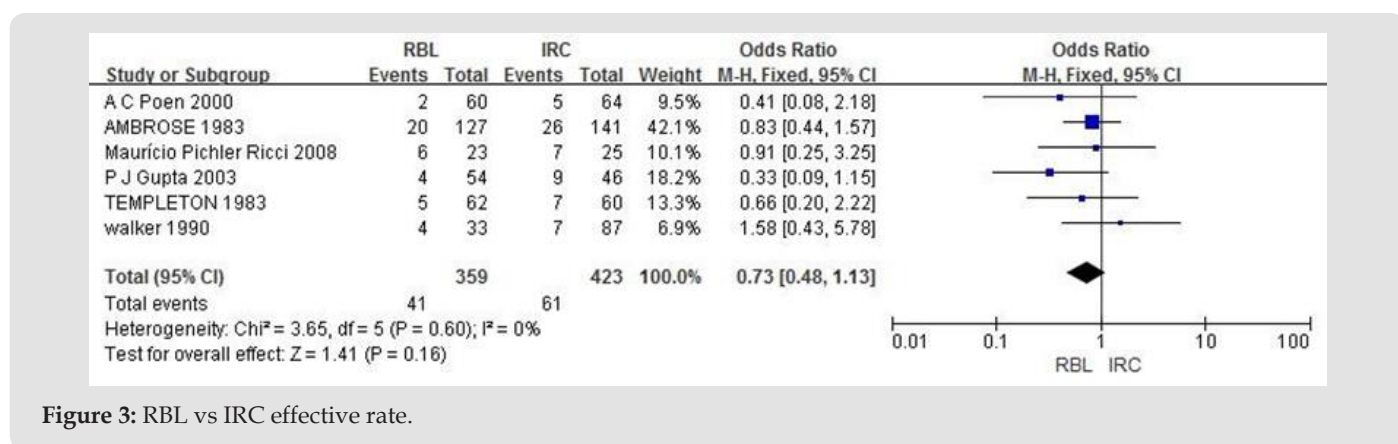

Figure 3: RBL vs IRC effective rate.

b. RBL vs IS8: A total of 480 patients are included in 5 literatures. Fixed effect model analysis is used, and the heterogeneity analysis indicates that there is heterogeneity (P=0.06, I^2=55%). By eliminating literatures one by one, it is found that the heterogeneity decreases after eliminating literatures Greca.1981, with statistical difference (OR = 2.56, 95% CI: 1.53-4.27, I^2 = 46%, P = 0.0003). It suggests that the effective rate of RBL group is better than that of IS group, as shown in Figure 4.
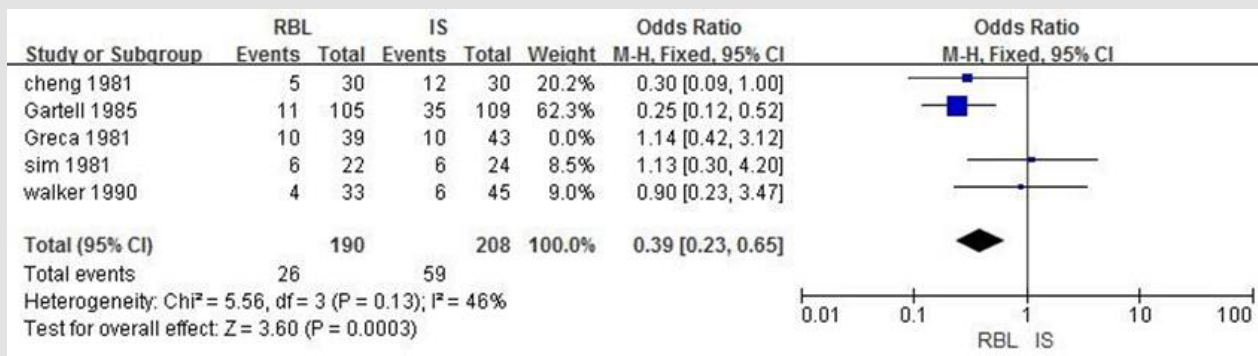
Figure 4: RBL vs IS effective rate.

c. IS vs IRC: A total of 267 patients are included in 2 literatures. Heterogeneity analysis shows that there is no heterogeneity (P = 0.77, I^2 = 0%). Fixed effect model analysis is carried out. The results shows that there is no significant difference in the effective rate between IS group and IRC group (OR = 0.66, 95% CI: 0.37-1.19, P = 0.17), indicating that the treatment effect of the two groups is similar, as shown in Figure 5.

Figure 5: IS vs IRC effective rate.

The Recurrence Rate

a. RBL vs IRC: A total of 612 patients are included in 4 literatures. Fixed effect model analysis is used and the heterogeneity analysis indicates that there is heterogeneity (P=0.004, I^2=77%). By eliminating literatures one by one, it is found that the heterogeneity decreases after eliminating literatures Walker.1990, with statistical difference.(OR=0.40, 95%CI:0.24-0.67, I^2=44%, P=0.0003), suggesting that the recurrence rate of the RBL group is lower than that of the IRC group, as shown in Figure 6.
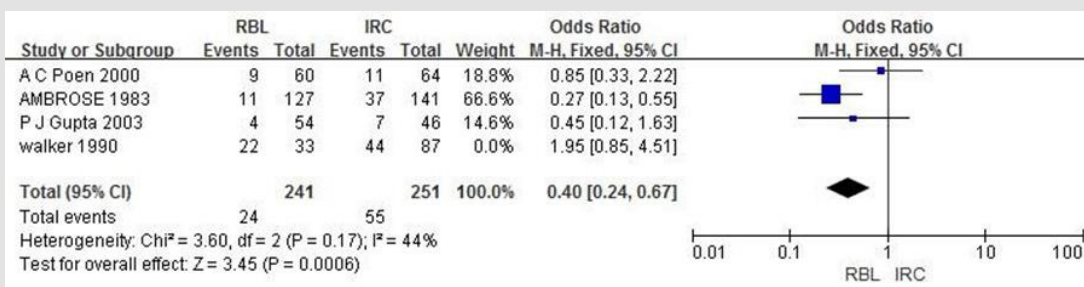

Figure 6: RBL vs IRC recurrence rate.

b. RBL vs IS: A total of 480 patients are included in 5 literatures. Fixed effect model analysis is used and the heterogeneity analysis indicates that there is heterogeneity (P=0.02, I^2=67%). By eliminating literatures one by one, it is found that the heterogeneity decreases after eliminating literatures Walker.1990, with statistical difference (OR=0.34, 95%CI:0.19-0.61, I^2=264%, P=0.0003), suggesting that the recurrence rate of the RBL group is lower than that of the IS group, as shown in Figure 7.
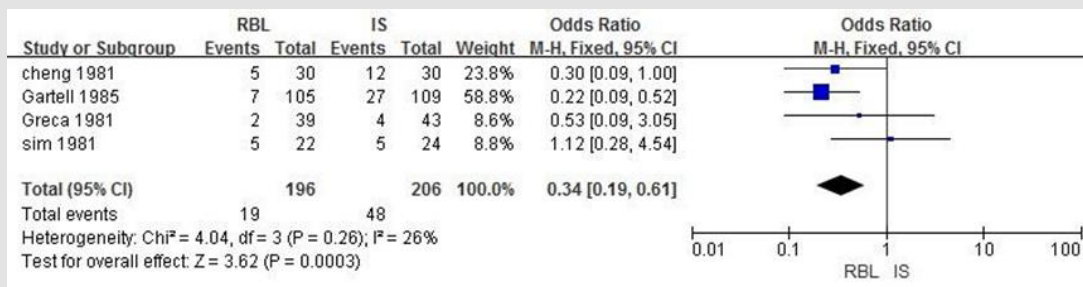
Figure 7: RBL vs IS recurrence rate.

c. **IS vs IRC:** A total of 267 patients are included in 2 literatures, and the heterogeneity analysis indicates that there is heterogeneity (P=0.04, I^2=76%). Since there are only 2 literatures, random effect model analysis is carried out, and the results showed that there is no significant statistical difference in the recurrence rate between IS group and IRC group(OR=0.59,95%CI:0.14-2.39,P=0.46), suggesting that the recurrence rate of IS group and IRC group is similar, as shown in Figure 8.
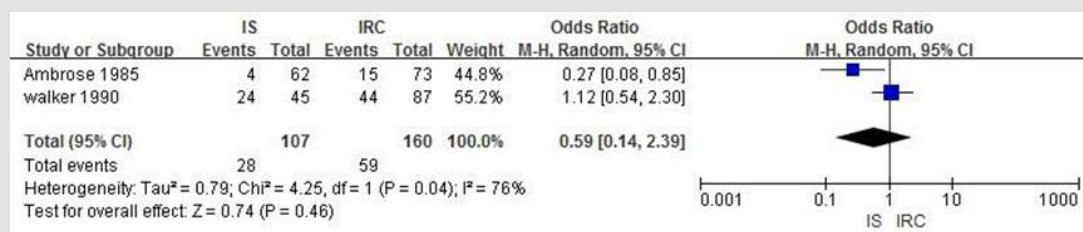

Figure 8: IS vs IRC recurrence.

Incidence of Complications

a. **RBL vs IRC:** A total of 782 patients are included in 6 literatures. Fixed-effects model is used and the heterogeneity analysis indicates that there is heterogeneity (P=0.03, I^2=59%). By eliminating literatures one by one, it is found that the heterogeneity decreases after eliminating literatures Walker.1990, with statistical difference (OR=1.91, 95%CI: 1.15~3.16, I^2=19%, P=0.01), suggesting that the incidence of complications in the RBL group is lower than that in the IRC group, as shown in Figure 9.
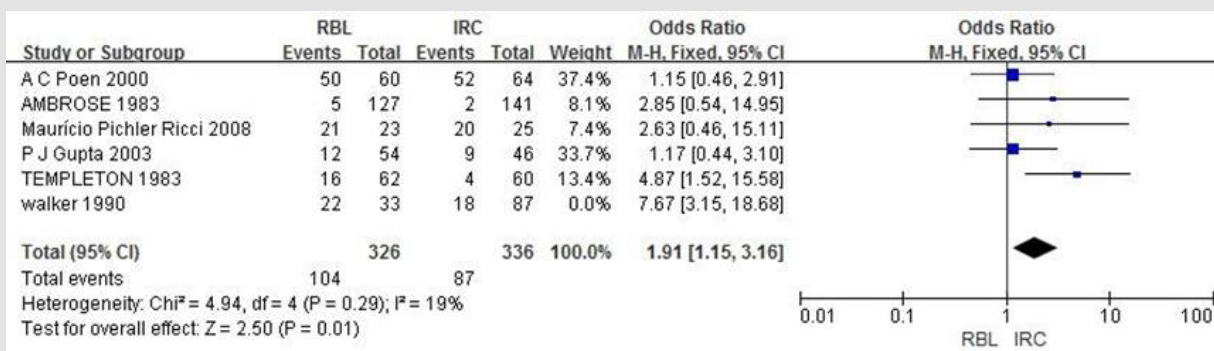

Figure 9: RBL vs IRC complication rate.

b. **RBL vs IS:** A total of 554 patients are included in 6 articles and heterogeneity analysis indicates no heterogeneity (P=0.49, I^2=0%). The fixed-effect model analysis is carried, and the results shows that there is no significant difference in the incidence of complications between the RBL group and the IS group (OR =0.02, 95%CI: -0.03~0.07, P=0.42), as shown in Figure 10.
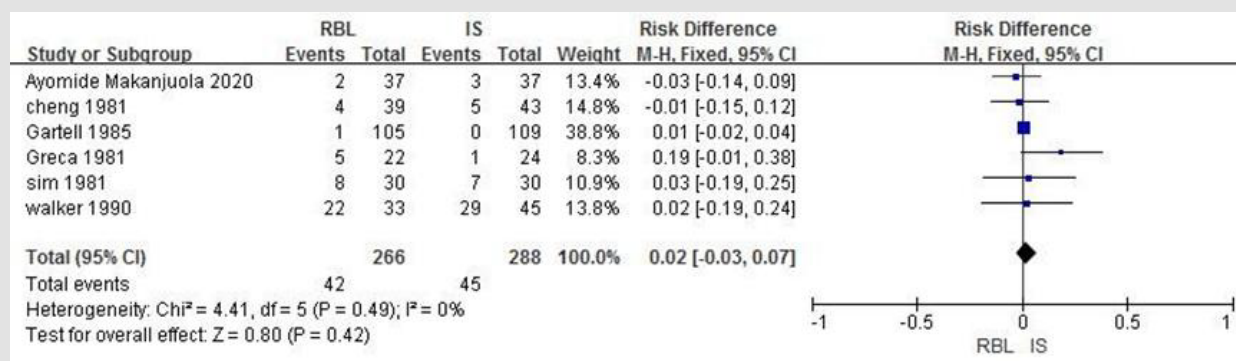
Figure 10: RBL vs IS complication rate.

Discussion

Hemorrhoid is a soft venous mass produced by the dilation and flexion of the submucosal and cutaneous inferior venous plexus at the end of the rectum, which contains normal spongy tissue structures such as minute arteriovenous anastomosis, connective tissue, and nerve tissue, thus playing an important role in assisting and controlling defecation. Hemorrhoids are the most common anorectal diseases in adults, accounting for 89.25% of all anorectal diseases, and treatment needs are huge. The main clinical manifestations of internal hemorrhoids include bleeding, prolapse, pain and perianal itching, and in several cases, it can be complicated with thrombosis, incarceration, strangulation and difficulty in defecation, which significantly affects the patient's quality of life. The treatment of internal hemorrhoids focuses on the elimination of symptoms caused by internal hemorrhoids. The commonly used treatment methods for internal hemorrhoids include non-surgical treatment and surgical treatment, among which non-surgical treatment includes RBL, IS, and IRC. The national guidelines of the United States, Japan, France, and China countries recommend that the above methods are mainly used for the treatment of I-III degree internal hemorrhoids [1,5,6], but the efficacy and safety of various methods are still controversial. In this article, the efficacy, recurrence rate and complication rate of the above three methods for the treatment of internal hemorrhoids are analyzed and compared in order to comprehensively and objectively evaluate the efficacy and safety of RBL, IS and IRC in the treatment of internal hemorrhoids. The results of this study show that the efficiency of RBL group is better than that of IS group, which is consistent with the research results of Jacobs, D et al. it is mentioned in the research report that the long-term effective rate of RBL group is about 90% among patients with internal hemorrhoids of grade I-III, while the long-term remission rate of only one-third of the patients treated with IS, indicating that the long-term effective rate of RBL is superior to that of the IS group [7]. Similarly, the research results of MacRae HM et al. also show that for I-III degree internal hemorrhoids, it is recommended to use RBL as the first-line treatment, and its curative effect is better than IS. Compared with patients receiving IS or IRC treatment, the need for retreatment in RBL group is obviously reduced [8]. This study has shown that the efficacy of the RBL group was comparable to that of the IRC group. The research by Ricci MP et al. also reported that the success rate of 4 weeks after RBL was not different from that of IRC, that is, the short-term clinical efficacy of RBL was comparable to that of IRC [9].

This study shows that the efficiency of IS group is equivalent to that of IRC group, which is similar to the research results of MacRae, MD et al. . It is mentioned in the research report that there is no difference in any outcome index between IS group and IRC group [10]. IS is the most effective for I-II degree internal hemorrhoids, and postoperative bleeding is rare. For patients with high risk of bleeding, such as patients receiving anticoagulant therapy, this method should be considered [7]. This study suggests that the incidence of complications in RBL group is lower than that in IRC group. However, the research of Johanson JF et al. Showed that RBL has better long-term efficiency, but the incidence of pain after treatment is higher. In contrast, the complications of IRC are few and not serious [11]. The reason for the analysis may be that the current guidelines classify pain as a type of complication. This article does not analyze pain alone, but classifies it as a complication for analysis. This study shows that the recurrence rate of RBL group is lower than that of IS group and IRC group. A C Poen et al. reported that 18% of the patients receiving RBL treatment had symptomatic recurrence, while 20% of the patients receiving IRC treatment had symptomatic recurrence to the level before treatment [12], and the longer the follow-up time was, the higher the symptom recurrence rate was [13]. Meta-analysis of non-surgical treatment showed that the recurrence rate of I-II internal hemorrhoids patients after IS was relatively high, while the discomfort caused by RBL was relatively high [14-24].

The Limitations of this Study

1) Although the research documents included in the systematic review are all RCTs, the follow-up time varies, and there is a lack of multi-center, large-scale, long-term follow-up RCT research results.

2) Some studies have a small sample size, and some evaluation indicators only have 2-3 literatures for effect combination, and the outcome indicators of the analysis are not fully mentioned, such as: surgical recovery time, cost-benefit ratio, patient satisfaction, etc. To systematically evaluate the three methods, there is still a lack of high-quality RCTs research.

3) The cases of internal hemorrhoids in some literatures are not classified.

In conclusion, for the treatment of grade I - III internal hemorrhoids, the safety of RBL group is better than IS group and IRC group, and the efficacy is better than IS group or equivalent to IRC group. Therefore, RBL can be the first choice among the three treatment methods, but it still needs to be verified by multi-center, large-sample and high-quality RCTs.

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