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Review article

Efficacy and safety of single dose of oral secnidazole 2 g in treatment of bacterial vaginosis: A systematic review and meta-analysis

Shrouk M. Elghazaly[a,b], Khaled M. Hamam[b,c], Marwa M. Badawy[b,c], Nadim Aiman Yakoub Agha[d], Ahmed Samy[e], Ahmed M. Abbas[f,*]

[a] Faculty of Medicine, Assiut University, Assiut, Egypt
[b] Medical Research group of Egypt, Egypt
[c] Faculty of Medicine, 6th October University, Cairo, Egypt
[d] Faculty of Medicine, Cairo University, Cairo, Egypt
[e] Department of Obstetrics and Gynaecology, Faculty of Medicine, Cairo University, Egypt
[f] Department of Obstetrics and Gynaecology, Faculty of Medicine, Assiut University, Egypt

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ABSTRACT

Background: Bacterial vaginosis (BV) is a common disease characterized by vaginal discharge.
Objective: To evaluate the evidence from published randomized clinical trials (RCTs) about the efficacy and safety of single dose of oral secnidazole 2 g in comparison with other drugs.
Search strategy: Electronic databases were searched using the following MeSH terms (bacterial vaginosis OR vaginosis) AND (secnidazole OR secnol OR sabima OR secnidal OR minovage).
Selection criteria: All RCTs assessing effect of secnidazole in treatment of BV were considered for this meta-analysis. Two-hundred thirty two studies were identified of which six studies were deemed eligible for this review.
Data collection and analysis: The extracted data were entered into RevMan software. The relative risk (RR) and 95% confidence interval (CI) were calculated. The extracted outcomes were the clinical cure and adverse effects.
Main results: The pooled estimate showed that ornidazole is superior to a single dose of oral secnidazole in clinical cure at the 4th week after treatment (RR = 0.81; 95% CI [0.73- 0.89], $p < 0.0001$, $I^2 = 0\%$). There were no difference between secnidazole and metronidazole (RR = 0.97; 95% CI [0.90–1.05], $I^2 = 0\%$, $p = 0.5$).
Conclusions: Single oral dose of secnidazole 2 g doesn't differ from metronidazole regimen however, it may be inferior to ornidazole in treatment of BV.

Contents

* Corresponding author at: Department of Obstetrics and Gynaecology, Assiut University, Women Health Hospital, 71511, Assiut, Egypt.
E-mail address: bmr90@hotmail.com (A.M. Abbas).

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Introduction

Bacterial vaginosis (BV) is a common cause of vaginal discharge in women of reproductive age. Increasing concentrations of anaerobic bacteria (eg, Prevotella sp.) cause BV as a result of the decrease in the ordinary H_2O_2 producing Lactobacillus species in the vagina [1]. The main cause for BV is unknown as it comes from complex interactions between bacteria and vaginal tissue. However, it is common in African-American race, women using vaginal douching, women with multiple or new partners, and homosexual women [2]. BV is clinically diagnosed according to Amsel criteria [3]. The treatment includes various antibiotics against anaerobic micro-organisms e.g. secnidazole which is used in Europe and Asia [4].

Secnidazole is one of 5-nitroimidazoles (1-[2-hydroxypropyl]-2-methyl-5-nitromidazole) which are effective in treatment of anaerobic bacteria. 5-nitroimidazoles have shorter half-life except secnidazole whose half-life is longer (17–29 h) [5]. Bohbot et al. compared a single dose of 2 g secnidazole with a standard metronidazole dose for seven days in women with Nugent scores 7 or greater and they found that the cure rate was similar in different groups [6].

Although oral metronidazole, 500 mg twice per day for 7 days, was recommended by the Centers for Disease Control for the treatment of bacterial vaginosis in non-pregnant women, it has side effects like skin rash and some gastrointestinal manifestations so other therapies have been tried [7]. Lamp et al. have reported that secnidazole could be used in a single-dose treatment for patients with BV as it has the same effect in treatment to that of metronidazole administered in multiple doses [5].

Therefore, the current systematic review and meta-analysis aimed to evaluate the published randomized clinical trials (RCTs) about the efficacy and safety of secnidazole in treatment of BV.

Materials and methods

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [8].

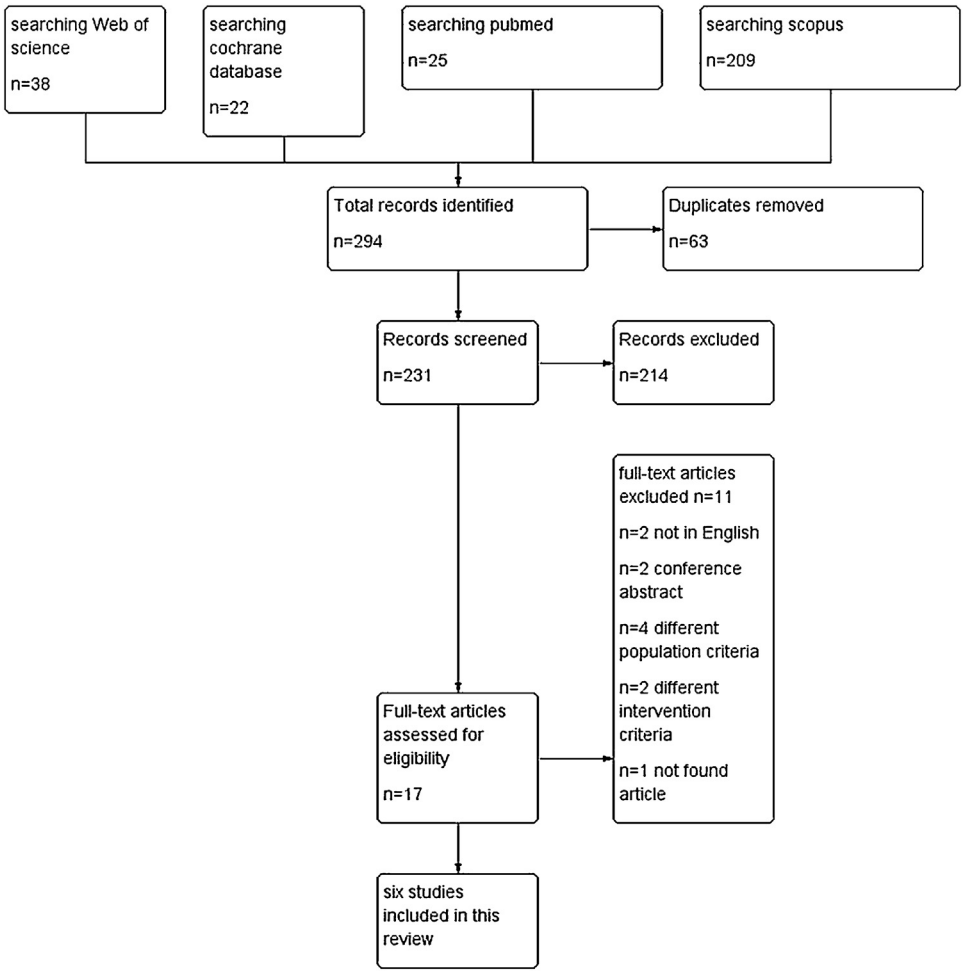


Fig. 1. PRISMA Flow Chart of the study selection process.

Search strategy

A detailed search was conducted using several electronic databases including MEDLINE, EMBASE, ScienceDirect, web of science, Scopus, and the Cochrane Library. Combinations of the following MeSH terms were used: (bacterial vaginosis OR vaginosis) AND (secnidazole OR secnol OR sabima OR secnidal OR minovage). We conducted a manual search of the references of included studies to retrieve studies that were not identified by database searching.

Eligible criteria

We included all published RCTs that compare the efficacy and safety of secnidazole versus placebo or any other active drug in treatment of BV. There was no restriction regarding age, place, ethnicity and publication date.

The study population included non-lactating, non-pregnant adult women with BV only. The diagnosis was defined by Amsel criteria (20% clue cells or greater, abnormal vaginal discharge, pH 4.7 or Greater, positive whiff test). Patients were over 18 years and had no additional vaginal pathology.

We excluded studies for the following reasons: 1) non-English, 2) conferences, books, review articles, posters, thesis, editorial, notes, letters, case series, case reports, 3) unreliable extracted data, overlapped data sets and only abstract available, 4) animal studies.

The reported primary outcome was the clinical cure rate after 4 weeks defined as: normal vaginal discharge, negative Whiff test, clue cells <20%. Secondary outcomes were the adverse events (total adverse events and drug-related adverse events).

Study selection

Title and abstract of all identified articles were screened independently by three reviewers (SMA, KMH and AS) to assess their relevance to the meta-analysis. In case of disagreement, the full text was retrieved and reviewed independently by a senior author (AMA) for a final decision.

All identified articles were evaluated according to a standardized format including study design, methods, participant characteristics, intervention, and results. Two investigators (MMB and NAYA) scored the studies and collected the information independently. In case of discrepancies in scoring, a consensus was reached after discussion.

Data extraction and analysis

The extracted data from the selected studies included the baseline characteristics of the study participants. The extracted outcomes were the clinical cure rate and adverse effects. After that, all data were entered into RevMan software (Review Manager, version 5.1, The Cochrane Collaboration, 2011; The Nordic Cochrane Centre, Copenhagen, Denmark) for meta-analysis. The relative risk (RR) and 95% confidence interval (CI) were calculated. Statistical heterogeneity between studies was assessed by I-squared (I^2) statistics [9] and values of $\geq$50% were indicative of high heterogeneity. We used fixed effect model in analysis as our results are all homogeneous according to chi-square test and I^2 value.

Pooled analyses of data from all studies were performed for primary and secondary outcomes. We conducted subgroup analysis for different forms of controls in all outcomes. We used

Table 1
Summary of included studies.

Study	Design	Intervention	population	Results
Saraçolu et al, 1998 [23]	Open, randomized, prospective clinical trial	Oral ornidazole 2*500 mg/day for 5 days Vs vaginal ornidazole 500 mg/day for 5 days Vs oral and vaginal ornidazole for 5 days Vs oral secnidazole 2 g in a single dose Vs oral secnidazole 2 g in a single dose and vaginal ornidazole 500 mg/day for 5 days Vs oral secnidazole 2 g in a single dose and vaginal metronidazole 2*500 mg/day for 7 days Vs oral ornidazole 2*500 mg/day for 5 days and vaginal metronidazole 2*500 mg/day for 7 days Vs vaginal metronidazole 2*500 mg/day for 7 days.	Non-pregnant women with bacterial vaginosis according to Amsel's criteria.	Vaginal treatments including ornidazole and metronidazole are not as effective as both oral and vaginal drug combinations.
Núñez et al, 2005 [24]	Randomized, double-blind and comparative clinical trial.	Single 1 g single oral dose of secnidazole Vs single 2 g single oral dose of secnidazole.	Non-lactating non-pregnant women with bacterial vaginosis according to Amsel's criteria.	a single 1-g oral dose of secnidazole is effective to cure bacterial vaginosis associated with G. vaginalis.
Bohbot et al, 2010 [6]	Multicenter, Double-Blind, Double-Dummy Randomized Phase III non-inferiority Study.	Metronidazole 500 mg, 2 doses/day for seven days Vs secnidazole 2 g single oral dose secnidazole	Nonpregnant women with clinical signs of bacterial vaginosis who met Amsel's criteria: abnormal vaginal discharge, +Ve whiff ; test results, and a vaginal pH > 4.5, a Nugent score > seven	The secnidazole regimen studied represents an eff ;ective treatment.
Thulkar et al, 2012 [25]	Parallel, randomized clinical trial	Oral single dose of metronidazole 2 g Vs tinidazole 2 g Vs secnidazole 2 g Vsornidazole 1.5 g	Non-pregnant women with bacterial vaginosis who met all Amsel criteria: abnormal discharge, PH > 4.5 and clue cells more than 20%	Tinidazole and ornidazole have a better cure rate as compared to metronidazole in cases of bacterial vaginosis
Hillier et al, 2017 [26]	Parallel, randomized, double-blind, dose-ranging, placebo-controlled clinical trial	1 or 2 g secnidazole vs placebo	Nonpregnant women were in general good health and met the four Amsel criteria for bacterial vaginosis.	Oral granules containing 1 and 2 g secnidazole were superior to placebo in bacterial vaginosis treatment.
Tariq et al, 2017 [27]	Double-blinded randomized controlled trial.	Active 2% clindamycin and placebo oral preparation Vs single oral dose 2-gm secnidazole with placebo vaginal cream.	Non-pregnant women with bacterial vaginosis who have an abnormal discharge, vaginal pH > 4.5, positive "whiff" test, and clue cells on microscopy	Multiple doses of vaginal clindamycin are superior to a single dose of oral secnidazole for the treatment of bacterial vaginosis.

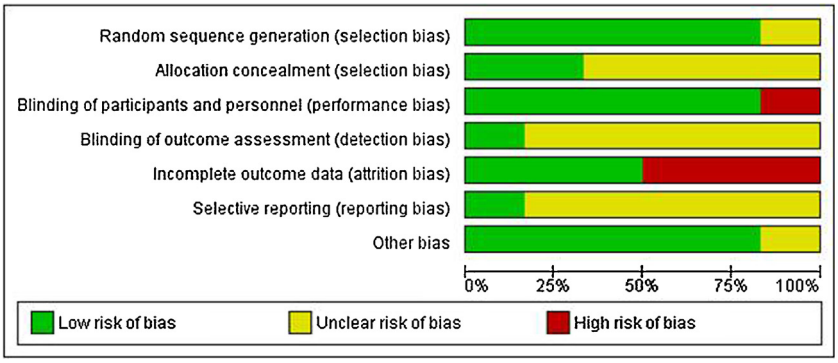


Fig. 2. Diagram of quality of included studies.

subgrouping in clinical cure at the 4th week according to forms of ornidazole (single oral dose 1.5 g and two oral doses 500 mg/day for five days) and metronidazole (single oral dose 2 g, two vaginal doses 500 mg and two oral doses 500 mg). The same occurred with adverse effects according to different controls (two oral doses of metronidazole 500 mg, single oral dose secnidazole 1 g).

Quality of included studies and risk of bias assessment

The risk of bias was assessed according to Cochrane risk of bias tool, which described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [10]. The Cochrane Collaboration risk of bias tool includes six domains, namely "Random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias" [10]. The reviewers rated the quality of the included studies as low risk, high risk or unclear risk of bias.

Publication bias

The number of included studies in the analysis was less than 10 studies, so we cannot assess the publication bias using Egger test [11].

Results

Search results characteristics of included studies

The searching process returned a total of 294 records. We removed the duplicates using Endnote software; of the remaining 231 records screened by title/abstract 17 records seemed to be eligible. After reading the Full-text of the 17 studies we excluded 11 studies which were ineligible according to the criteria (Fig. 1). Two studies are non-English [12,13], two studies are conference abstracts [14,15], four studies have different population criteria [16–19], two studies have different intervention criteria [20,21] and lastly one citation was not found [22]. Six RCTs were finally included and their characteristics are shown in Table 1.

Risk of bias assessment

We used the Cochrane Collaboration's tool for assessing risk of bias to assess the risk of bias as mentioned above. Quality of included studies was from high to moderate quality. Summary of risk of bias assessment is shown in Figs. 2 and 3.

Outcomes

Primary outcome

Clinical cure at 4th week

Single oral dose of secnidazole 2 g vs ornidazole. The overall effect size favoured ornidazole over a single oral dose of secnidazole 2 g [RR = 0.81, 95%CI (0.73–0.89), P < 0.0001] (Fig. 4). The pooled studies were homogenous (P = 0.62; I^2 = 0%).

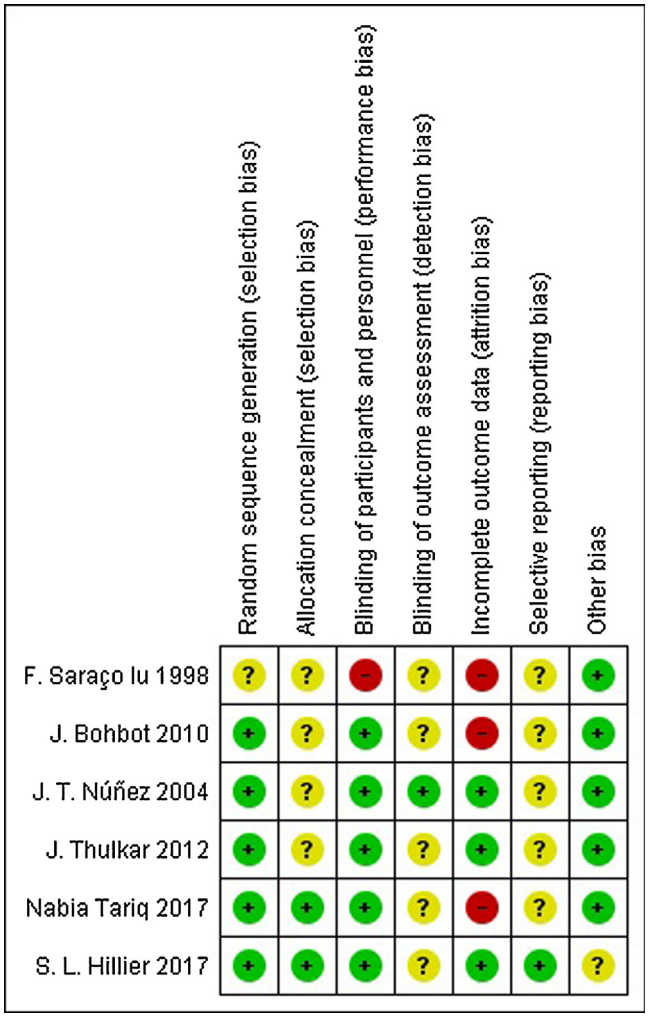


Fig. 3. Risk of bias summary graph.

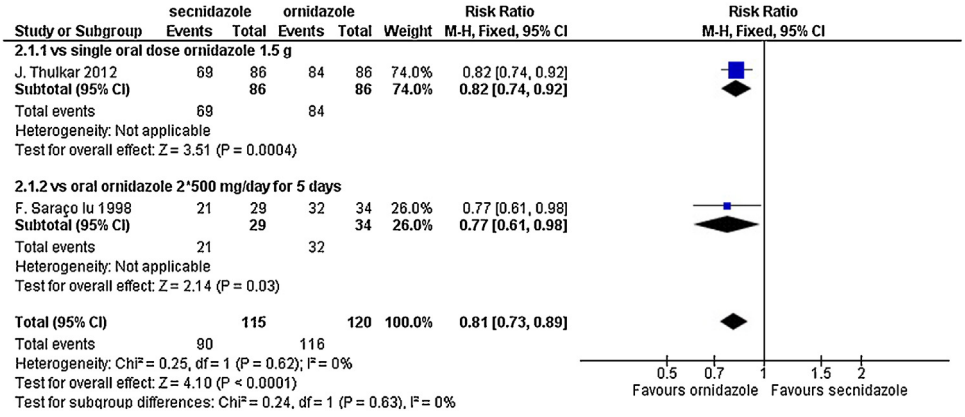


Fig. 4. Forest plot for the clinical cure at 4th week after treatment comparing single oral dose Secnidazole 2 g vs ornidazole.

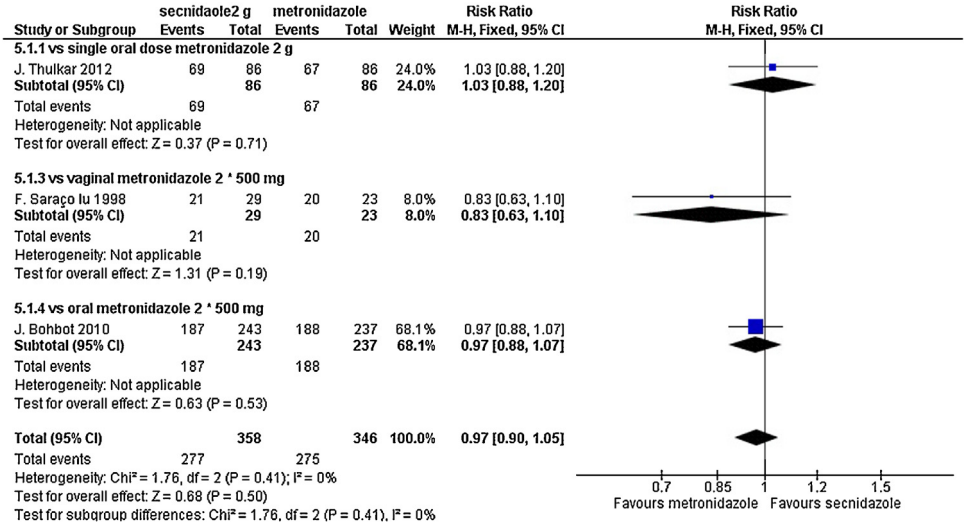


Fig. 5. Forest plot for the clinical cure at 4th week after treatment comparing single oral dose Secnidazole 2 g vs metronidazole.

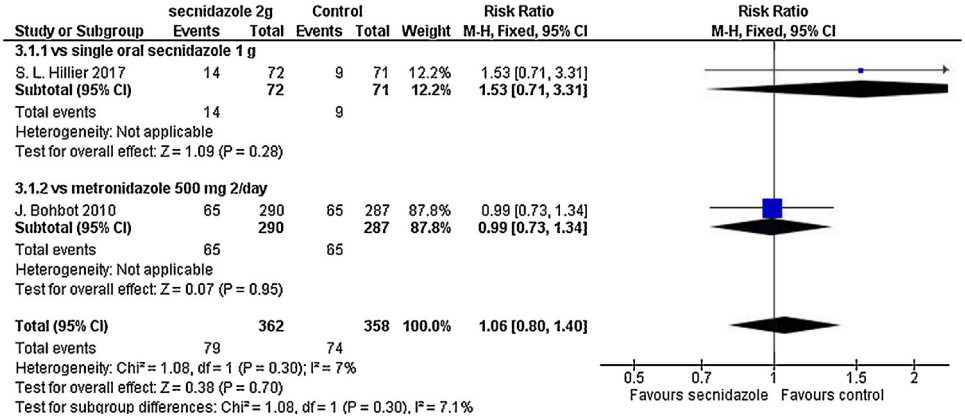
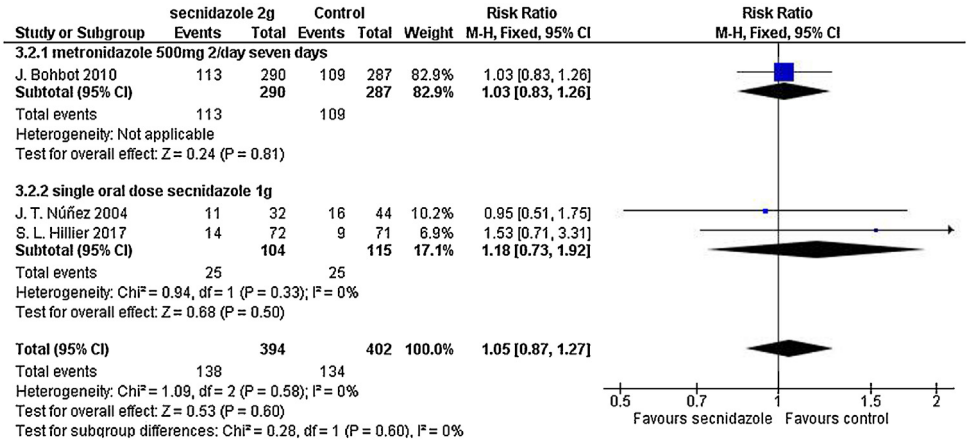


Fig. 6. Forest plot for treatment-emergent adverse effects.



Single oral dose of secnidazole 2 g vs Metronidazole. The overall effect size didn't show any difference between single oral dose secnidazole and metronidazole in terms of efficacy [RR-0.97, 95%CI (0.90–1.05), P = 0.5]. (Fig. 5). The pooled studies were homogenous (P = 0.41; I^2 = 0%).

Secondary outcomes

Adverse effects

Treatment-emergent adverse effects. The overall effect size between a single oral dose of secnidazole 2 g and control didn't show any difference between the two groups in terms of risk ratio of treatment-emergent adverse effects (RR = 1.06, 95% CI (0.80–1.04), P = 0.7] (Fig. 6). The pooled studies were homogeneous (P = 0.30; I^2 = 7%).

Patient complaint due to overall adverse effects. The overall effect size between a single oral dose of secnidazole 2 g and control didn't show any difference between the two groups in terms of risk ratio of overall adverse effects (RR = 1.05, 95% CI (0.87–1.27), P = 0.6] (Fig. 7). The pooled studies were homogeneous (P = 0.60; I^2 = 0%).

Comment

To the best of our knowledge, this is the first systematic review and meta-analysis to investigate the efficacy and safety of secnidazole in treatment of bacterial vaginosis.

We found that the single oral dose of secnidazole 2 g results in the same clinical cure as metronidazole with its different doses: oral 2 g, 1 g or vaginal 1 g as there isn't a significant statistical difference between them.

When we compared single oral dose of secnidazole 2 g and oral ornidazole, we found that ornidazole is better than secnidazole in the treatment of BV according to the clinical cure rate after 4 weeks of treatment. Secnidazole 2 g adverse effects did not differ from those of secnidazole 1 g or metronidazole. These results are applicable to non-pregnant women aged more than 18 years old.

Donders et al. reported that all 5-nitroimidazoles (metronidazole, secnidazole, tinidazole and ornidazole) have similar efficacy in treatment of BV [28]. However, our results showed that ornidazole is superior to secnidazole. Another study showed that rifaximin 25 mg/day for five days is a good regimen for treating BV when compared with placebo with a cure rate 48%, however the small sample size (n = 114) limits the result [29].

Saraçolu et al. showed that oral single dose secnidazole 2 g has a 28% recurrence rate which is higher than the 6% with oral ornidazole 2 × 500 mg/day for five days with evaluation between 30–40 days after treatment [23]. This agrees with our results that ornidazole is better than secnidazole regimen. Recurrence after using antibiotics occurs because Gardnerella vaginalis activates some genes to repair DNA damage caused by antibiotics [30]. More research is needed to improve new treatments to stop DNA repair enzymes to decrease the resistance to antibiotics

The main strength of our meta-analysis is its high quality as it is based on RCTs. Search methods and eligibility criteria are well defined. We followed PRISMA checklist to prepare this study. Finally, we prepared this study in steps according to Cochrane handbook of systematic review for interventions.

Our main limitations in this review are the small number of included studies and small sample size of some studies. Additionally, discrete comparisons found in these studies limited our findings as they prevented us from showing all the findings in one meta-analysis. Another limitation was that we measured the efficacy only according to the clinical cure 4 weeks after treatment; therefore more research is needed here. Finally, the variations in the routes of administrations and dosages of the treatment given.

Conclusion

This systematic review and meta-analysis suggests that single oral dose secnidazole 2 g is similar clinically to metronidazole; however it may be inferior to ornidazole in treatment of BV.

Conflict of interest

The authors declare that they have no conflict of interest.

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