Review Article

Metronidazole-induced Metallic Taste: A Systematic Review and Meta-Analysis.

ABSTRACT

Aims: This study aimed to estimate the incidence rate of metallic taste side effects in a patient who received metronidazole versus tinidazole and link it to the safety profile for metronidazole**.**
Study design: Systematic Review and Meta-Analysis.
Place and Duration of Study: This study where written and revised in the pharmaceutical care department at general network for healthcare providers Hospital, Jeddah, Saudi Arabia. between Mar 2021 and Dec 2021.
Methodology: Literature searches were conducted in the following databases: PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. Statistical analysis was performed using Review Manager (RevMan) Version 5.4 software.
Results: Our meta-analysis of randomized controlled trials studies confirm that there is a slight increase in the rate of metallic taste adverse effects, around one-fifth of patients who were treated with tinidazole had developed an incidence rate (5.1%) higher than the patient who treated with metronidazole, our data shows that the incidence rate of metallic taste adverse effects in patients who received metronidazole was 15.5% (58/373) while the incidence rate in patients who received tinidazole was 20.6% (104/505). But the overall rate of metallic taste adverse effects was not statistically significantly different (RR, 1.07; 95% CI, 0.45 to 2.55; P = 0.87). also, there was statistical heterogeneity in the included studies (I2 = 75%).
Conclusion: In our meta-analysis, the incidence rate of metronidazole-associated metallic taste adverse effects was slightly lower than the incidence rate of tinidazole-associated metallic taste adverse effects. It is not statistically significant as the result shows, but still shifting the patient to metronidazole instead of tinidazole may decrease the incidence rate of metallic taste by (5.1%) and give good coverage for the microbial than tinidazole.

Keywords: Metronidazole, Tinidazole, Taste Disorders, Systematic Review, Meta-Analysis.

1. INTRODUCTION

Metronidazole is a type of drug that is widely used in medical practice for the treatment of several types of infectious diseases (1, 2). Metronidazole works by attacking the DNA of bacteria cells and this class of drug is called nitroimidazole (3, 4). Metronidazole is the first nitroimidazole drug that shows useful clinical activity and it is considered as the most widely and used member of the nitroimidazole drug class (5-8). Nitroimidazoles drugs consider as prodrugs and they are activating under a low oxygen environment and this occurs through reduction of the nitro group, leading to the formation of imidazole and cytotoxicity. but, still, the metabolism pathway and cytotoxicity of metronidazole are not definitively characterized (9, 10). Metronidazole is a small uncharged molecule

that is rapidly absorbed by the gastrointestinal tract and absorption doesn't interact or affect by food ingestion (11, 12). Also, metronidazole has a large volume of distribution (Around 80%) (2, 12). Therapeutics level or metronidazole level can be obtained from several sites of the body cavity such as seminal fluid, aqueous humor, secretions of salivary glands, vaginal secretion, meddle ear, pelvic tissues, cerebrospinal fluid, brain abscess, biliary tract, hepatic abscess, breast milk, pleural fluid, and amniotic fluid (2, 12-15). The metabolism of metronidazole occurs mainly in the liver while the elimination occurs mainly in the urine (around 75%) (12, 16). The half-live of metronidazole elimination about 6 hours, the half-life is may prolonged in advanced age or reduced renal function patient, so if the patient has renal failure this means the drug will accumulate and need hemodialysis to wash out the drug from the body (17, 18). The route of administration depends on the severity and indication of disease but mainly the recommended route for most indications in critically ill patients is to start with the intravenous route then shift to oral form once the patient is capable (19, 20). Metronidazole shows a strong antimicrobial effect and very good coverage, which is not only targeted against bacteria, it is also active against a certain type of other organisms such as protozoa and even worms (1, 21, 22). Metronidazole was marketed in 1959 as an effective drug against *Trichomonas vaginalis* (23-26). Metronidazole has very good coverage for gram-positive anaerobic bacteria such as *Peptostreptococci spp*. (27-29). also, it has good coverage for gram-negative anaerobic bacteria such as *Fusobacterium* and *Bacteroides spp*. (30, 31). Metronidazole can attack various types of protozoa such as *Trichomonas vaginalis*, *Entamoeba histolytica*, and *Giardia lamblia* (30, 32-34). Metronidazole remains the first-line treatment for some infections related to inflammatory disorders of the gastrointestinal tract such as *Clostridium difficile* (9, 35, 36). The side effects of metronidazole include nausea, vomiting, diarrhea, abdomen pain, abdominal cramping, headache, dizziness, and weakness (37-41). also, it may lead to neurotoxicity, peripheral neuropathy, encephalopathy, and optic neuropathy in some cases (40, 42-45). In some patients, it may alter the taste to a metallic taste (46, 47). Tinidazole is structurally related to metronidazole but its activity is limited to protozoa such as *Giardiasis and Amebiasis* and also, it covers some bacteria such as *Bacterial vaginosis* organism (48-50). Tinidazole has the similar side effect to metronidazole such as GI upset, Metallic taste, diarrhea, and fatigue (51, 52), but some studies find that tinidazole has a more favorable side effect profile than oral metronidazole notably with better gastrointestinal tolerability, less metallic taste incidence and less severity and the total number of overall side effect (53-56). In this study, we are looking to highlight the incidence rate of metallic taste adverse effect between the metronidazole and the other type of nitroimidazole drugs such as tinidazole, and link it with the safety profile of the metronidazole.

2. MATERIAL AND METHODS

2.1 SEARCH STRATEGY

To retrieve as much literature as possible on metronidazole and the incidence rate of metallic taste, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines were used in this systematic review and meta-analysis (57). A literature search was conducted using PubMed, EMBASE, and the Cochrane Library. All relevant articles published up to Nov 2021 were considered for our review.
The search strategy was as follows:

PubMed / MEDLINE, National Library of Medicine (Searched until 01 11, 2021) – 73 Results.
#1- Metronidazole.
#2- Tinidazole.
#3- (#1 AND #2) AND ("randomized controlled trial"[Publication Type]).

Embase, Elsevier (Searched until 01 11, 2021) – 136 Results.
#1- 'Metronidazole'.
#2- 'Tinidazole'.
#3- (#1 AND #2) AND [randomized controlled trial]/lim.

Cochrane Library (Searched until 01 11, 2021) – 203 Results.
#1- Metronidazole.
#2- Tinidazole.
#3- (#1 AND #2) in Trials.

We also looked at bibliographies of relevant literature, meta-analyses, and previously published systematic reviews that might be relevant. Literature retrieval was limited to English only and in case of unclear reported data, further communication with the original authors was conducted.

2.2 SELECTION CRITERIA

We performed a comprehensive literature search for studies that compared metronidazole versus tinidazole in the incidence rate of metallic taste adverse events. Inclusion criteria were established a priori to minimize selection bias based on the PICOS (Problem/Patient, Intervention, Comparison, Outcome, Study design) method (58). We restricted our research to original studies published in English. People have metallic taste side effects related to the use of metronidazole or tinidazole. The evaluation indicators of this systematic review and meta-analysis were the incidence rate of metallic taste adverse events related to metronidazole and tinidazole and the risk ratio (RR). All retrieved studies were loaded into the reference management software Note Express 3.2.0.7276.
The inclusion criteria of the study were based on PICOS:

a. population: any patients who were treated with metronidazole or tinidazole and the drug had to follow well-defined protocols regarding drug type, dosage, frequency, and duration of treatment.
b. intervention/comparison: metronidazole / tinidazole.
c. outcomes: incidence rate of metronidazole compared to tinidazole.
d. study design: Randomized Controlled Trials (RCTs).

The exclusion criteria of the study were as follows:

a. Dual therapies were administered.
b. non-English studies.
c. Duplicate studies.
d. case reports.

2.3 DATA EXTRACTION

Three reviewers (R. Alhendi and M. Nouh and Y.Nouh) used standardized data forms to extract the data we needed and then entered it into an Excel table. Any disagreement was resolved by consensus. The quality of individual studies was assessed through the Cochrane Collaboration's tool for assessing the risk of bias (Figure 2). The following data were extracted: author information, study names, study design, funding source, study location, number of patients involved, patient characteristic, a drug used, drug strength, duration of treatment, subject ages, and presenting signs and symptoms.

2.4 STATISTICAL ANALYSIS

For each trial, the risk ratio (RR) was calculated for the incidence rate in patients who receive metronidazole versus tinidazole. The RR was presented with 95% confidence intervals (95% CIs); a $P < .05$ was considered significant. We estimated the degree of heterogeneity among the trial results using the I^2 test (25%, 50%, and 75% represented low,

moderate, and high heterogeneity, respectively). Whenever significant heterogeneity (I^2 > 50%) was achieved, we used a random-effects model to combine the effect sizes of the included studies. funnel plot was performed for publication bias (Figure 3). All these operations were implemented through Review Manager (RevMan) Version 5.4 software (59).

2.5 RISK OF BIAS IN INDIVIDUAL STUDIES

Two authors (Y. Alayafi and B. Alharthy) evaluated the risk of bias in individual studies independently using the Cochrane risk of bias tool (59) (Figure 2). If there was disagreement between the two researchers, the other two researchers (R. Almansour and H. Alshame) were judged again.

3. RESULTS

3.1 Literature review

A flow diagram of this systematic review and meta-analysis is shown in (Figure 1). In summary, 412 studies were identified by our literature search. A total of 389 studies were excluded after an initial screening of titles and abstracts. After reviewing the full text of the remaining studies 7 studies including 876 patients met our inclusion criteria for systematic review and meta-analysis (Table 1).

3.2 Study characteristics

Among the 7 studies, 5 studies did not provide baseline diseases (55, 60-63) (Table 2). The total daily dose for most studies was 2000 mg for metronidazole and tinidazole (54, 55, 60, 62, 63), except 2 studies were the first study the dose was divided into two groups, the first group was given orally in a twice-daily dose of 500mg, and the other group receives 1gram twice daily 400 mg (61), the second study the patient start on intravenous (2–2.5 g/day) then shifted to oral (2–2.4 g/day) for the metronidazole group and the other group they receive (1.6 g/day) intravenous then shifted to oral (2 g/day) (64). The duration of treatment for most studies was 7 days for metronidazole and 4 days for tinidazole (54, 60, 63), except 4 studies were the first study the duration was 14 days for metronidazole and 5 days for tinidazole (64), and for the rest of the three studies, the duration was 7 days for metronidazole and tinidazole (55, 61, 62). All the studies included were randomized controlled trials (54, 55, 60-64), and two of them were designed to be double-blind (61, 62). Funding statements were not mentioned for all the studies included (54, 55, 60-64). Four of the studies were included were conducted in India (54, 55, 63, 64), except three studies were conducted in other countries, the first one was conducted in Bangladesh (60), and the other one was conducted in England (61), and the last one was conducting in Thailand (62). The previous information related to study characteristics will be included in (Table 1).

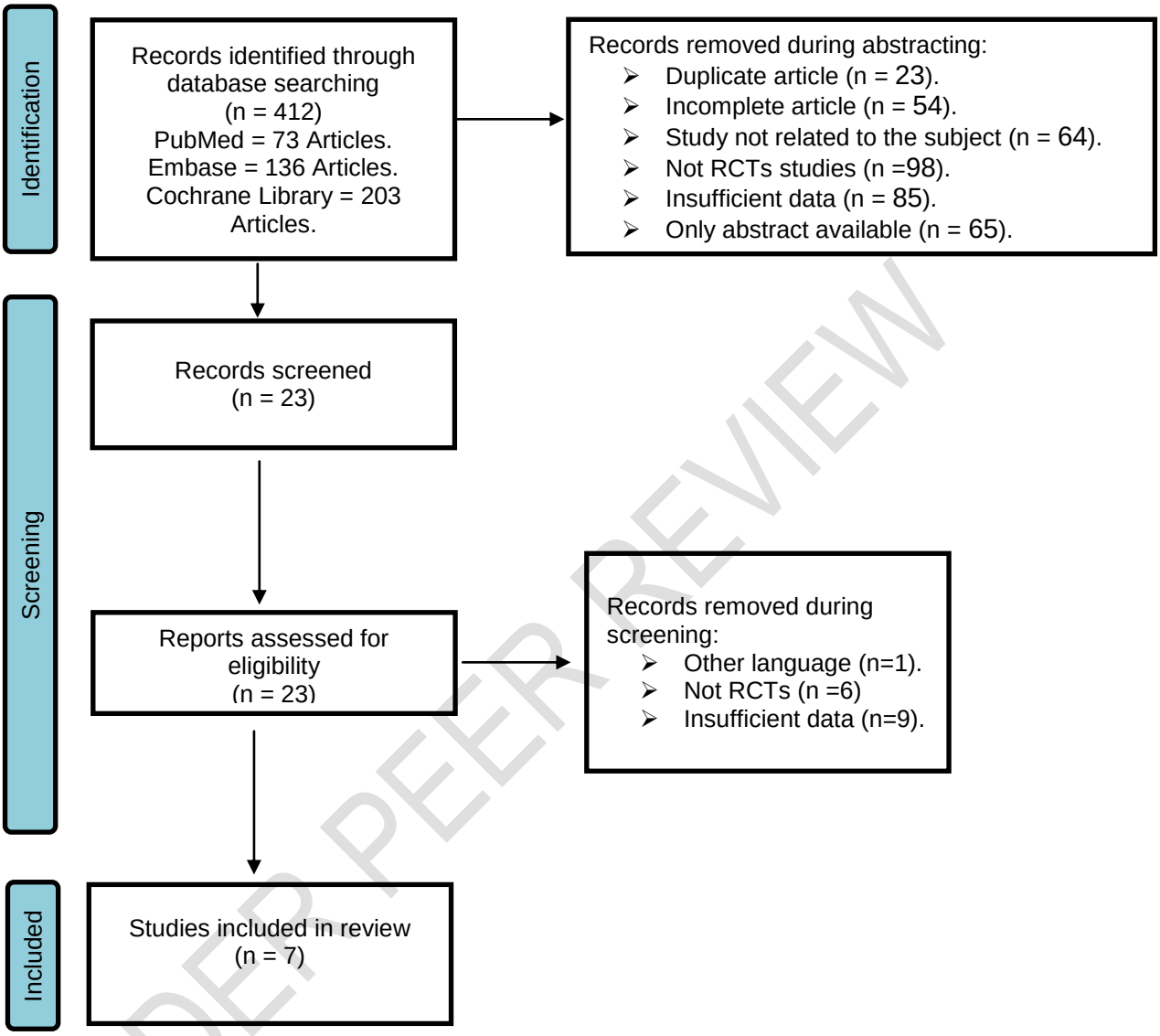


Figure 1. PRISMA flow diagram of the studies included in this systematic review and meta-analysis.

3.3 Metallic taste incidence rate

Regarding the 7 studies were included for this study, the incidence rate of metallic taste adverse effects in patients who received metronidazole was 15.5% (58/373) while the incidence rate in patients who received tinidazole was 20.6% (104/505). The rate of metallic taste adverse effects was not statistically significantly different but the incidence rate was slightly higher with the patient who receive tinidazole instead of metronidazole (RR, 1.07; 95% CI, 0.45 to 2.55; P = 0.87). also, there was statistical heterogeneity in the included studies (I^2 = 75%). The metallic taste incidence rates for the different studies were shown in (Figure 2).

Table 1. Characteristics of Included Studies.

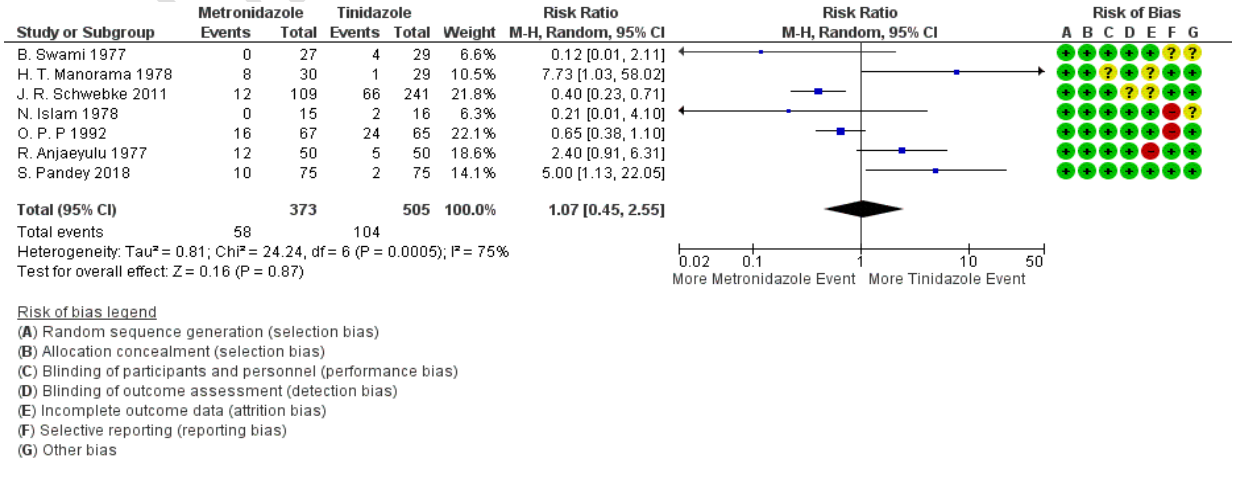
Study Design	Funding Source	Location	Number of Patient (METRO VS TINI)	Patient Characteristics	Metronidazole vs Comparator	Duration (METRO VS TINI)
Randomized Controlled Trials.	Not mention.	India.	50 vs 50	patient was screened for the presence of *Trichomonas vaginalis.*	Both drugs were given orally in a single daily dose of 2g	7 Days vs 4 Days.
Randomized Controlled Trials.	Not mention.	India.	27 vs 29	Patients symptomatic intestinal A*moebiasis* with trophozoites or cysts present in the stools were included.	Both drugs were given orally in a single daily dose of 2g	7 Days vs 4 Days.
Randomized Controlled Trials.	Not mention.	India.	30 vs 27	Any out-patient patient with symptoms and signs suggestive *Trichomonas vaginitis.*	Both drugs were given orally in a single daily dose of 2g	7 Days vs 7 Days.
Randomized Controlled Trials.	Not mention.	Bangladesh.	15 vs 16	Patients with unequivocal clinical, radiological, and laboratory evidence of hepatic Amoebiasis were included.	Both drugs were given orally in a single daily dose of 2g	7 Days vs 4 Days.
Randomized Controlled Trials, Double-blind.	Not mention.	Thailand.	67 vs 65	Nonpregnant woman *Trichomoniasis.*	Both drugs were given orally in a single daily dose of 2g	7 Days vs 7 Days.
Randomized Controlled Trials, Double-blind.	Not mention.	England	109 vs 241	Heterosexual women who presented with a symptom of bacterial *Vaginosis.*	Both drugs were given orally in a twice-daily dose of 500mg, and one group receive 1gram twice daily	7 Days vs 7 Days.
Randomized Controlled Trials.	Not mention.	India.	75 VS 75	Patients with clinical features and radiological evidence of liver abscess and positive *Amebic* serology.	Start on IV 2–2.5 g/day then oral 2–2.4 g/day VS 1.6 g/day IV then oral (2 g/day).	14 Days vs 5 Days.

ABBREVIATION: METRO: Metronidazole; TINI: Tinidazole.

Study	*R. Anjaneyulu 1977 (63).*		*B. Swami 1977 (54).*		*H. T. Manorama 1978 (55).*		*N. Islam 1978 (60).*		*O. P. P 1992 (62).*		*J. R. Schwebke 2011 (61).*		*S. Pandey 2018 (64).*	
	METRO	**TINI**	**METRO**	**TINI**	**METRO**	**TINI**	**METRO**	**TINI**	**METRO**	**TINI**	**METRO**	**TINI**	**METRO**	**TINI**
No. of patient	27	29	50	50	15	16	30	29	67	65	109	241	75	75
Age (year, mean)	30 ± 2	31 ± 2	26.5	26.8	30 ± 20	35 ± 25	25 ± 1	27 ± 1	37 ± 10	36 ± 10	28 ± 6	28 ± 7	38 ± 13	39 ± 13
Presenting signs and symptoms														
Abdomen pain	24	21	-	-	-	-	-	-	-	-	-	-	96	70
Dysentery	22	20	-	-	-	-	-	-	-	-	-	-	8	7
Tender hepatomegaly	4	1	-	-	-	-	-	-	-	-	-	-	65	67
Fever	3	1	-	-	-	-	-	-	-	-	-	-	65	63

Table 2. Patient demographics and baseline characteristics.

Abbreviation: METRO: Metronidazole; TINI: Tinidazole



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 2. Forest plot showing the risk ratios of the incidence rate of metallic taste adverse effects using random-effects models in patients who receive metronidazole versus tinidazole. A vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios. CI, confidence interval; MH, Mantel-Haenszel. also, a Quality assessment graph for included studies was included in this chart**.**

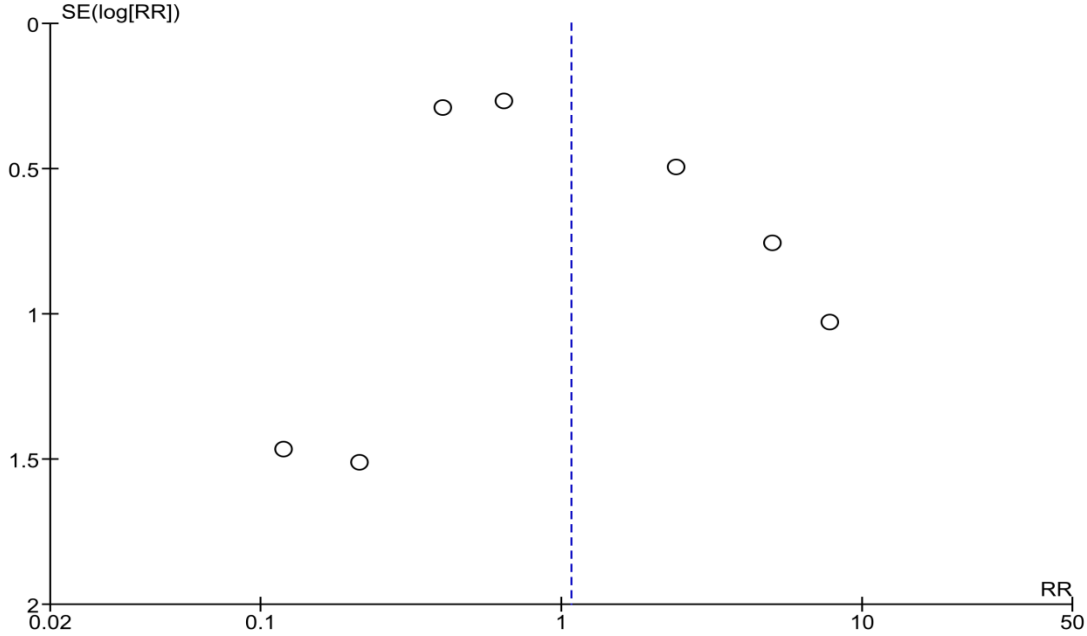


Figure 3. Funnel plots show publication bias of studies related to the incidence rate of metallic taste after using metronidazole or tinidazole drugs**.**

4. DISCUSSION

A metallic taste side effect is a risk factor for patients incompliant and discontinues the treatment course. The incidence rate of metallic taste adverse effects in patients who received metronidazole was 15.5% (58/373) while the incidence rate in patients who received tinidazole was 20.6% (104/505) (Figure 2). Metronidazole was used as first-line therapy for decades; however, still, microbial coverage for eradication of microbes is higher with the metronidazole than tinidazole (5-8). Our meta-analysis of randomized controlled trials confirms that there is a slight increase in the rate of metallic taste adverse effects, occurring in approximately one-fifth of treated patients with an incidence rate (5.1%) higher in patients treated with tinidazole regimens instead of metronidazole. However, individual studies have described the incidences rate which is ranging from (3% up to 37%). This variability in incidence rate is due to heterogeneous patient populations, ranges of doses used, and the severity of illness differences. In contrast, our analysis mainly identified studies for a patient treated with metronidazole or tinidazole and the drug had to follow well-defined protocols regarding drug type, dosage, frequency, and duration of treatment. In addition, we analyzed only studies that were randomized controlled studies. There are several risk factors related to metronidazole and tinidazole-associated metallic taste adverse effects that are described in the literature. Those that are consistently reported include age, presence with previous signs and symptoms such as fever, dysentery, abdomen pain, and tender hepatomegaly (Table 2) (54, 64). In our analysis, the mean/median age of patients in most included studies was above 31 years of age. Other patient-specific data was not uniformly reported across the included studies. The risk for have metallic taste adverse effects may also be associated with the duration of metronidazole or tinidazole therapy. There are several strengths to our analysis, We only included randomized controlled studies in our article. In addition, metronidazole dosing in most of the

included studies was (2000mg Once Daily) and tinidazole dose was (2000mg Once Daily) (54, 55, 60, 62, 63), except two studies were the first study the dose divided into two groups, the first group was given orally in a twice-daily dose of 500mg, and the other group receives 1gram twice daily 400 mg (61), the second study the patient start on intravenous (2–2.5 g/day) then shifted to oral (2–2.4 g/day) for the metronidazole group and the other group they receive (1.6 g/day) intravenous then shifted to oral (2 g/day) (64). This dosing is expected to produce concentrations associated with the maximal tolerability threshold. Also, all randomized controlled trials were not funded by any industry or other institution, or society and the population was representative of patients from more than 4 continents. Some limitations may affect the validity and limit the generalizability related to this analysis and it is worth to considerate it. First, the studies in this analysis used variable duration for treatment, which can make clinical application challenging. Second, the overall number of patients in our analysis were relatively small. Finally, there was insufficient detail to examine the progression and resolution of metallic taste adverse effects along a continuum among the individual studies.

5. CONCLUSION

In our meta-analysis, the incidence rate of metronidazole-associated metallic taste adverse effects was slightly lower than the incidence rate of tinidazole-associated metallic taste adverse effects. It is not statistically significant as the result shows, but still shifting the patient to metronidazole instead of tinidazole may decrease the incidence rate of metallic taste by (5.1%) and give good coverage for the microbial than tinidazole.

SUPPLEMENTARY DATA

Search Strategies, Tables, and Figures were uploaded externally for further information.

CONSENT

A consent statement is not applicable, because there is no animal or human experimental in this study.

ETHICAL APPROVAL

An ethical approval statement is not applicable, because this study is based exclusively on published literature

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCES

1. Hof H. [Antimicrobial therapy with nitroheterocyclic compounds, for example, metronidazole and nitrofurantoin]. Immun Infekt. 1988;16(6):220-5.

2. Lamp KC, Freeman CD, Klutman NE, Lacy MK. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. Clin Pharmacokinet. 1999;36(5):353-73.
3. Edwards DI. Nitroimidazole drugs--action and resistance mechanisms. I. Mechanisms of action. J Antimicrob Chemother. 1993;31(1):9-20.
4. Kedderis GL, Argenbright LS, Miwa GT. Covalent interaction of 5-nitroimidazoles with DNA and protein in vitro: mechanism of reductive activation. Chem Res Toxicol. 1989;2(3):146-9.
5. Sobel R, Sobel JD. Metronidazole for the treatment of vaginal infections. Expert Opin Pharmacother. 2015;16(7):1109-15.
6. Okumura H, Fukushima A, Taieb V, Shoji S, English M. Fidaxomicin compared with vancomycin and metronidazole for the treatment of Clostridioides (Clostridium) difficile infection: A network meta-analysis. J Infect Chemother. 2020;26(1):43-50.
7. Kissinger P, Muzny CA, Mena LA, Lillis RA, Schwebke JR, Beauchamps L, et al. Single-dose versus 7-day-dose metronidazole for the treatment of trichomoniasis in women: an open-label, randomised controlled trial. Lancet Infect Dis. 2018;18(11):1251-9.
8. Batista L, Pérez Jove J, Rosinach M, Gonzalo V, Sainz E, Loras C, et al. Low efficacy of metronidazole in the eradication of Blastocystis hominis in symptomatic patients: Case series and systematic literature review. Gastroenterol Hepatol. 2017;40(6):381-7.
9. Dingsdag SA, Hunter N. Metronidazole: an update on metabolism, structure-cytotoxicity and resistance mechanisms. J Antimicrob Chemother. 2018;73(2):265-79.
10. Fang H, Edlund C, Hedberg M, Nord CE. New findings in beta-lactam and metronidazole resistant Bacteroides fragilis group. Int J Antimicrob Agents. 2002;19(5):361-70.
11. Alestig K, Freij L, Arnold E. Absorption and excretion of metronidazole after administration of metronidazole benzoate mixture. Scand J Infect Dis. 1980;12(2):149-52.
12. Eggleston M. Metronidazole. Infect Control. 1986;7(10):514-8.
13. Siegler D, Kaye CM, Reilly S, Willis AT, Sankey MG. Serum, saliva, and sputum levels of metronidazole in acute exacerbations of chronic bronchitis. Thorax. 1981;36(10):781-3.
14. Mustofa, Suryawati S, Santoso B. Pharmacokinetics of metronidazole in saliva. Int J Clin Pharmacol Ther Toxicol. 1991;29(12):474-8.
15. Specht TE, Brown MP, Gronwall RR, Rib WJ, Houston AE. Pharmacokinetics of metronidazole and its concentration in body fluids and endometrial tissues of mares. Am J Vet Res. 1992;53(10):1807-12.
16. Bergan T, Leinebo O, Blom-Hagen T, Salvesen B. Pharmacokinetics and bioavailability of metronidazole after tablets, suppositories and intravenous administration. Scand J Gastroenterol Suppl. 1984;91:45-60.
17. Ellison MJ. Vancomycin, metronidazole, and tetracyclines. Clin Podiatr Med Surg. 1992;9(2):425-42.
18. Roux AF, Moirot E, Delhotal B, Leroy JA, Bonmarchand GP, Humbert G, et al. Metronidazole kinetics in patients with acute renal failure on dialysis: a cumulative study. Clin Pharmacol Ther. 1984;36(3):363-8.
19. Loft S, Døssing M, Poulsen HE, Sonne J, Olesen KL, Simonsen K, et al. Influence of dose and route of administration on disposition of metronidazole and its major metabolites. Eur J Clin Pharmacol. 1986;30(4):467-73.
20. Houghton GW, Thorne PS, Smith J, Templeton R, Collier J. Comparison of the pharmacokinetics of metronidazole in healthy female volunteers following either a single oral or intravenous dose. Br J Clin Pharmacol. 1979;8(4):337-41.
21. Falagas ME, Gorbach SL. Clindamycin and metronidazole. Med Clin North Am. 1995;79(4):845-67.
22. Jenks PJ, Edwards DI. Metronidazole resistance in Helicobacter pylori. Int J Antimicrob Agents. 2002;19(1):1-7.
23. van der Wouden EJ, Thijs JC, Kusters JG, van Zwet AA, Kleibeuker JH. Mechanism and clinical significance of metronidazole resistance in Helicobacter pylori. Scand J Gastroenterol Suppl. 2001(234):10-4.

24. Leitsch D. A review on metronidazole: an old warhorse in antimicrobial chemotherapy. Parasitology. 2019;146(9):1167-78.
25. Moya IA, Su Z, Honek JF. Current and future perspectives on the chemotherapy of the parasitic protozoa Trichomonas vaginalis and Entamoeba histolytica. Future Med Chem. 2009;1(4):619-43.
26. Marrero-Ponce Y, Meneses-Marcel A, Rivera-Borroto OM, García-Domenech R, De Julián-Ortiz JV, Montero A, et al. Bond-based linear indices in QSAR: computational discovery of novel anti-trichomonal compounds. J Comput Aided Mol Des. 2008;22(8):523-40.
27. Jokipii AM, Jokipii L. Comparative activity of metronidazole and tinidazole against Clostridium difficile and Peptostreptococcus anaerobius. Antimicrob Agents Chemother. 1987;31(2):183-6.
28. Roche Y, Yoshimori RN. In-vitro activity of spiramycin and metronidazole alone or in combination against clinical isolates from odontogenic abscesses. J Antimicrob Chemother. 1997;40(3):353-7.
29. Shroĭt IG, Anisimova LA, Khodyreva GD, Kozliuk AS, Bukova VE. [Effect of metronidazole on the course of experimental anaerobic streptococcal pneumonia]. Zh Mikrobiol Epidemiol Immunobiol. 1986(8):21-4.
30. Freeman CD, Klutman NE, Lamp KC. Metronidazole. A therapeutic review and update. Drugs. 1997;54(5):679-708.
31. Mouton C, Dextraze L, Mayrand D. [Susceptibility of potential periodontopathic bacteria to metronidazole, spiramycin and their combination]. J Biol Buccale. 1984;12(1):17-26.
32. Lin HC, Chu LJ, Huang PJ, Cheng WH, Zheng YH, Huang CY, et al. Proteomic signatures of metronidazole-resistant Trichomonas vaginalis reveal novel proteins associated with drug resistance. Parasit Vectors. 2020;13(1):274.
33. Pal D, Banerjee S, Cui J, Schwartz A, Ghosh SK, Samuelson J. Giardia, Entamoeba, and Trichomonas enzymes activate metronidazole (nitroreductases) and inactivate metronidazole (nitroimidazole reductases). Antimicrob Agents Chemother. 2009;53(2):458-64.
34. Hager WD, Rapp RP. Metronidazole. Obstet Gynecol Clin North Am. 1992;19(3):497-510.
35. Oksi J, Anttila VJ, Mattila E. Treatment of Clostridioides (Clostridium) difficile infection. Ann Med. 2020;52(1-2):12-20.
36. Stein BE, Greenough WB, 3rd, Mears SC. Management and prevention of recurrent clostridium difficile infection in patients after total joint arthroplasty: a review. Geriatr Orthop Surg Rehabil. 2012;3(4):157-63.
37. Cañete R, Rodríguez P, Mesa L, Brito K, Prior A, Guilhem D, et al. Albendazole versus metronidazole in the treatment of adult giardiasis: a randomized, double-blind, clinical trial. Curr Med Res Opin. 2012;28(1):149-54.
38. Kim JY, Lee SY, Kim JH, Sung IK, Park HS. Efficacy and safety of twice a day, bismuth-containing quadruple therapy using high-dose tetracycline and metronidazole for second-line Helicobacter pylori eradication. Helicobacter. 2020;25(2):e12683.
39. Puri P, Parnami P, Chitkara A, Athwal PSS, Khetrapal S. Antibiomania: A Rare Case of Metronidazole-Induced Mania. Cureus. 2021;13(1):e12414.
40. Hernández Ceruelos A, Romero-Quezada LC, Ruvalcaba Ledezma JC, López Contreras L. Therapeutic uses of metronidazole and its side effects: an update. Eur Rev Med Pharmacol Sci. 2019;23(1):397-401.
41. AlDhaleei W, AlMarzooqi A, Gaber N. Reversible metronidazole-induced neurotoxicity after 10 weeks of therapy. BMJ Case Rep. 2018;2018.
42. Sørensen CG, Karlsson WK, Amin FM, Lindelof M. Metronidazole-induced encephalopathy: a systematic review. J Neurol. 2020;267(1):1-13.
43. Tauro A, Beltran E, Cherubini GB, Coelho AT, Wessmann A, Driver CJ, et al. Metronidazole-induced neurotoxicity in 26 dogs. Aust Vet J. 2018;96(12):495-501.
44. Vitturi BK, da Silva Júnior RG, da Rocha AJ, Narimatsu K. Metronidazole-induced encephalopathy. Rev Neurol (Paris). 2018;174(5):342-3.

45. Kuriyama A, Jackson JL. Defining metronidazole-induced encephalopathy. J Neurol. 2019;266(5):1272-3.
46. Mansour-Ghanaei F, Shafaghi A, Fallah M. The effect of metronidazole in treating human fascioliasis. Med Sci Monit. 2003;9(10):Pi127-30.
47. Sadjjadi SM, Alborzi AW, Mostovfi H. Comparative clinical trial of mebendazole and metronidazole in giardiasis of children. J Trop Pediatr. 2001;47(3):176-8.
48. Nailor MD, Sobel JD. Tinidazole for bacterial vaginosis. Expert Rev Anti Infect Ther. 2007;5(3):343-8.
49. Nailor MD, Sobel JD. Tinidazole for the treatment of vaginal infections. Expert Opin Investig Drugs. 2007;16(5):743-51.
50. Gookin JL, Stauffer SH, Coccaro MR, Poore MF, Levy MG, Papich MG. Efficacy of tinidazole for treatment of cats experimentally infected with Tritrichomonas foetus. Am J Vet Res. 2007;68(10):1085-8.
51. Carmine AA, Brogden RN, Heel RC, Speight TM, Avery GS. Tinidazole in anaerobic infections: a review of its antibacterial activity, pharmacological properties and therapeutic efficacy. Drugs. 1982;24(2):85-117.
52. Cimerman B, Camilo Coura L, JM CS, Gurvitz R, Rocha RS, Bandeira S, et al. Evaluation of Secnidazole Gel and Tinidazole Suspension in the Treatment of Giardiasis in Children. Braz J Infect Dis. 1997;1(5):241-7.
53. Armstrong NR, Wilson JD. Tinidazole in the treatment of bacterial vaginosis. Int J Womens Health. 2010;1:59-65.
54. Swami B, Lavakusulu D, Devi CS. Tinidazole and metronidazole in the treatment of intestinal amoebiasis. Curr Med Res Opin. 1977;5(2):152-6.
55. Manorama HT, Shenoy DR. Single-dose oral treatment of vaginal trichomoniasis with tinidazole and metronidazole. J Int Med Res. 1978;6(1):46-9.
56. Levi GC, de Avila CA, Amato Neto V. Efficacy of various drugs for treatment of giardiasis. A comparative study. Am J Trop Med Hyg. 1977;26(3):564-5.
57. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777-84.
58. Major MP, Major PW, Flores-Mir C. Benchmarking of reported search and selection methods of systematic reviews by dental speciality. Evidence-Based Dentistry. 2007;8(3):66-70.
59. Van der Mierden S, Tsaioun K, Bleich A, Leenaars CHC. Software tools for literature screening in systematic reviews in biomedical research. Altex. 2019;36(3):508-17.
60. Islam N, Hasan K. Tinidazole and metronidazole in hepatic amoebiasis. Drugs. 1978;15 Suppl 1:26-9.
61. Schwebke JR, Desmond RA. Tinidazole vs metronidazole for the treatment of bacterial vaginosis. Am J Obstet Gynecol. 2011;204(3):211.e1-6
62. P OP, Jetsawangsri T. Split-dose metronidazole or single-dose tinidazole for the treatment of vaginal trichomoniasis. Sex Transm Dis. 1992;19(5):295-7.
63. Anjaeyulu R, Gupte SA, Desai DB. Single-dose treatment of trichomonal vaginitis: a comparison of tinidazole and metronidazole. J Int Med Res. 1977;5(6):438-41.
64. Pandey S, Gupta GK, Wanjari SJ, Nijhawan S. Comparative study of tinidazole versus metronidazole in treatment of amebic liver abscess: A randomized control trial. Indian Journal of Gastroenterology. 2018;37(3):196-201.

DEFINITIONS, ACRONYMS, ABBREVIATIONS

MH: Mantel-Haenszel.
CI: Confidence interval.
RR: Risk ratio.

METRO: Metronidazole.
TINI: Tinidazole.
VS: versus.

APPENDIX

I want to highlight that two authors want to add their accounts in ORCID ID to this study, so please involve their information in this study before publication.
This is their information (name and ORCID ID):

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