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# Meta-analysis for Searching Efficacy of Tinidazole and Metronidazole

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Background: The 5-nitroimidazole antimicrobial agents are considered as the treatment of choice for managing the amebic, protozoal and anerobic infections since 1969. With the advancement in medical field certain preference of drugs in this group were given. Tinidazole is now considered as a better one as compared to metronidazole because of specific pharmacokinetic & pharmacodynamics properties.

Objectives: To assess the frequency of preferred using tinidazole as compared to metronidazole for managing the amebic, protozoal infections and anerobic infections

Methodology: This is a descriptive study with simple random sampling. Total 32 published studies in 04 decades were included in the study i.e 1978 – 2017. The National and Internationally published data was gathered by using electronic measures and via certain search engines i.e pubmed researches, medscape, Pak medinet.com, google search, Euraopean, Canadian, Australlian, Centre for Disease Control (CDC), and World Health Organization (WHO) published guidelines. The published guidelines, original and review articles were taken for reference. Case reports, editorials & short communications were excluded.

Results: This Meta-analysis review of various published researches showed that out of 69.2%(n=09) out of total 13 studies are in favour of preferring tinidazole. The frequency preference of metronidazole is 23% (n=23). Only one study (7%) showed the efficacy of both drugs is same.

Conclusion: Tinidazole is a better option to manage anaerobic, amebic and protozoal infections.

Keywords: Tinidazole, Metronidazole, Comparative efficacy, Anaerobic, Amebic infection, Protozoal infection

## Introduction

Tinidazole and metronidazole drugs are the 5-nitroimidazole antimicrobial agents. Initially in 1969, it was considered to be of successful use only for unicellular parasites. Tinidazole is structural similarity to metronidazole. These drugs are the approved ones by US Food and Drug Administration and are in common use for more than 2 decades. Both harbor good efficacy against protozoal and anaerobic infection (1,2). Drugs are available in oral, vaginal, topical, intravenous preparation (5).

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A comparative pharmacokinetic studies for Tinidazole upon comparison with metronidazole revealed that tinidazole has higher $C_{max}$ and longer half life in serum concentra-tions (3,4). The half life of tinidazole is 14–14.7 h. The half life of metronidazole is 7.9-8.8 h (14).

Both of these drugs achieve can good tissue levels i.e 70 to 100%. The high steady serum concentration was observed statistically for oral tinidazole as compared to oral metronidazole (4).

Therefore the current study was hypothesized that tinidazole is a better option for managing anaerobic, amebic andprotozoal infection as compared to metronidazole.

## Methodology

The hypothesis of study is that tinidazole is more efficacious to manage anaerobic, amebic and protozoal infection as compared to metronidazole.

### Search method adopted for methodology

Total 32 studies in 04 decades were included in the study i.e 1978 – 2017by simple random sampling technique. All the authentic sources were considered to maintain the quality criteria. The National and Internationally published data was gathered by using electronic measures and via certain search engines i.e pubmed researches, medscape, Pak medinet. com, google search, Euraopean, Canadian, Australlian, Centre for Disease Control (CDC), World Health Organization (WHO) published guidelines.

Inclusion criteria: The published authentic guidelines, original and review articles were included in the study. Exclusion criteria: Case reports, letter to editor, editorials and short communications were excluded.

The Quality criteria for the included data ensured by using the indexed, recognized and authentic medical websites. Data was analyzed by SPSS v19. For statistical justification, frequencies were calculated in terms of percentages.

## Results

Total 32 studies were included in the study. Out of which based upon the inclusion and exclusion criteria,16 studies were selected by simple random sampling techniqueThe results of current study showed that out of 75% (n=12) out of total 16 studies are in favour of preferring tinidazole.

The frequency preference of metronidazole is 18.75% (n=03). Only one study (6.25%) showed the efficacy of both drugs is same. Both these findings are shown in tables I & II.

Regarding the statistics of *Amebiasis,* 05 number (n) of studies are in favour of preferring tinidazole by showing successful outcomes. While 02 (n) studies were against preferring tinidazole over metronidazole. Only one (n=01) study showed same efficacy of both drugs. This is shown in table-I.

Regarding the *Giardiasis and Trichomoniasis*, 05 number (n) of studies are in favour of preferring tinidazole by showing successful outcomes. While 03 (n) studies were against preferring tinidazole over metronidazole. Only one (n=01) study showed same efficacy of both drugs. This is shown in table-I.

Regarding the *bacterial infections i.e anaerobes*, 08 number (n) of studies are in favour of preferring tinidazole by showing successful outcomes. While 03 (n) studies were against preferring tinidazole over metronidazole. Only one (n=01) study showed same efficacy of both drugs. This is shown in table I.

The overall distribution for frequencies in terms of percentages is tabulated in table-II.

**Table-I:** Data of 4 (four decades) for the use of Tinidazole & Metronidazole in various clinical conditions (1/2)

| Sr. No. | Studies | Drugs Efficacy | Efficacy Against Various Clinical Conditions (Amebic, Protozoal & Anaerobic Infection) | | | | |
|---|---|---|---|---|---|---|---|
| | | | Amebic | Protozoal | | Bacteria (Anaerobes) | |
| | | | Amebi-asis | Giardi-asis | Tricho-moniasis | Bcterial vaginosis | Oral Infections |
| 1. | *Bakshi, JS(1978)* [15] | Tinidazole | 96% | 88.3% | - | - | - |
| | | Metronidazole | 75.5% | 46.7% | - | - | - |
| 2. | Armstrong NR(2011) [4] | Tinidazole | >90% | >90% | >90% | >90% | - |
| | | Metronidazole | <90% | <90% | <90% | <90% | - |
| 3. | *Marceo J (2013),*[7] | Tinidazole | Same efficacy | Same efficacy | Same efficacy | Same efficacy | - |
| | | Metronidazole | Same efficacy | Same efficacy | Same efficacy | Same efficacy | - |
| 4. | CDC guidelines – 2017 [19] | Tinidazole | Not preferred | Not preferred | Not preferred | Not preferred | - |
| | | Metronidazole | Preferred | Preferred | Preferred | Preferred | - |
| 5. | Canadian Guidelines – 2016 Ottawa ON (2008) [20] | Tinidazole | - | - | Not preferred | Not preferred | - |
| | | Metronidazole | - | - | Preferred | Preferred | - |
| 6. | Menard JP. (2009) (longer duration of treatment) [5] | Tinidazole | 27% | 27% | - | 27% | - |
| | | Metronidazole | 18% | 18% | - | 18% | - |
| 7. | Raja IM (2016) short term duration [6] | Tinidazole | Not preferred | Not preferred | Not preferred | Not preferred | - |
| | | Metronidazole | Preferred | Preferred | Preferred | Preferred | - |
| 8. | Löfmark S (2010) [2] | Tinidazole | Preferred | Preferred | Preferred | Preferred | - |
| | | Metronidazole | Not preferred | Not preferred | Not preferred | Not preferred | - |
| 9. | *Brandt M (2008)* [10] | Tinidazole | Preferred | - | - | - | - |
| | | Metronidazole | Not preferred | - | - | - | - |
| 10. | Hanson JM (2000) [11] | Tinidazole | Preferred | - | - | - | - |
| | | Metronidazole | Not preferred | - | - | - | - |
| 11. | Clinical guidelines of Australasian College of Sexual Health Physicians in 2004 [17] | Tinidazole | - | - | Preferred | Preferred | - |
| | | Metronidazole | - | - | Not preferred | Not preferred | - |
| 12. | UK National guidelines for the year 2006 [18] | Tinidazole | Preferred drug | - | - | - | - |
| | | Metronidazole | Not preferred | - | - | - | - |
| 13. | US Food and Drug Administration (FDA), Europe, Asia and Latin Ammerica [21] | Tinidazole | - | - | - | Preferred drug | - |
| | | Metronidazole | - | - | - | Not preferred | - |
| 14. | Rasteriene R (2015) [25] | Tinidazole | - | - | - | - | 27.9% |
| | | Metronidazole | - | - | - | - | - |
| 15. | Barak O (2013)[30] | Tinidazole | - | - | - | - | Preferred |
| | | Metronidazole | - | - | - | - | Not preferred |
| 16. | Manso F(2008) [31] | - | - | - | - | - | Preferred drug |
| | | - | - | - | - | - | Not preferred |

Table-I: Data of 4 (four decades) for the use of Tinidazole & Metronidazole in various clinical conditions (2/2)

| Sr. No | Studies | Drugs Efficacy | Efficacy Against Various Clinical Conditions (Amebic, Protozoal & Anaerobic Infection) | | | | |
|---|---|---|---|---|---|---|---|
| | | | Amebic | Protozoal | | Bacteria (Anaerobes) | |
| | | | Amebi-asis | Giardi-asis | Tricho-moniasis | Bcterial vaginosis | Oral Infections |
| 17. | *Bakshi, JS(1978)* [15] | Tinidazole | 96% | 88.3% | - | - | - |
| | | Metronidazole | 75.5% | 46.7% | - | - | - |
| 18. | Armstrong NR(2011) [4] | Tinidazole | >90% | >90% | >90% | >90% | - |
| | | Metronidazole | <90% | <90% | <90% | <90% | - |
| 19. | *Marceo J (2013),*[7] | Tinidazole | Same efficacy | Same efficacy | Same efficacy | Same efficacy | - |
| | | Metronidazole | Same efficacy | Same efficacy | Same efficacy | Same efficacy | - |
| 20. | CDC guidelines – 2017 [19] | Tinidazole | Not preferred | Not preferred | Not preferred | Not preferred | - |
| | | Metronidazole | Preferred | Preferred | Preferred | Preferred | - |
| 21. | Canadian Guidelines – 2016 Ottawa ON (2008) [20] | Tinidazole | - | - | Not preferred | Not preferred | - |
| | | Metronidazole | - | - | Preferred | Preferred | - |
| 22. | Menard JP. (2009) (longer duration of treatment) [5] | Tinidazole | 27% | 27% | - | 27% | - |
| | | Metronidazole | 18% | 18% | - | 18% | - |
| 23. | Raja IM (2016) short term duration [6] | Tinidazole | Not preferred | Not preferred | Not preferred | Not preferred | - |
| | | Metronidazole | Preferred | Preferred | Preferred | Preferred | - |
| 24. | Löfmark S (2010) [2] | Tinidazole | Preferred | Preferred | Preferred | Preferred | - |
| | | Metronidazole | Not preferred | Not preferred | Not preferred | Not preferred | - |
| 25. | *Brandt M (2008)* [10] | Tinidazole | Preferred | - | - | - | - |
| | | Metronidazole | Not preferred | - | - | - | - |
| 26. | Hanson JM (2000) [11] | Tinidazole | Preferred | - | - | - | - |
| | | Metronidazole | Not preferred | - | - | - | - |
| 27. | Clinical guidelines of Australasian College of Sexual Health Physicians in 2004 [17] | Tinidazole | - | - | Preferred | Preferred | - |
| | | Metronidazole | - | - | Not preferred | Not preferred | - |
| 28. | UK National guidelines for the year 2006 [18] | Tinidazole | Preferred drug | - | - | - | - |
| | | Metronidazole | Not preferred | - | - | - | - |
| 29. | US Food and Drug Adm.(FDA), Europe, Asia, LatinAmmerica [21] | Tinidazole | - | - | - | Preferred drug | - |
| | | Metronidazole | - | - | - | Not preferred | - |
| 30. | Rasteriene R (2015) [25] | Tinidazole | - | - | - | - | 27.9% |
| | | Metronidazole | - | - | - | - | - |
| 31. | Barak O (2013)[30] | Tinidazole | - | - | - | - | Preferred |
| | | Metronidazole | - | - | - | - | Not preferred |
| 32. | Manso F(2008) [31] | - | - | - | - | - | Preferred drug |
| | | - | - | - | - | - | Not preferred |

## Discussion

The results of current study shows that tinidazole is a better drug for managing amebic, protozoal and anaerobic infections. This findings are supported by many published studies by justifying the preference for using tinidazole. Menard JP (2009); showed that the treatment failure rate was less for tinidazole i.e 27% when compared to metronidazole i.e 18% for longer duration of treatment (5). Raja IM (2016); also described that the relapse rate of infections for short term duration has no significant difference (6). Marceo J (2013); concluded that the efficacy for the treatment of tinidazole and metronidazole are similar for treating bacterial vaginosis. Tinidazole was considered ineffective for the treatment of plasmodium infection (3,7).

**Table-II:** Data of 04 (Four Decades); %

| Drugs | Researches in favour | | Researches not in favour | | Same efficacy of both drugs | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Tinidazole | 12 | 75 | 03 | 18.75 | 01 | 6.25 |
| Metronidazole | 03 | 18.75 | 12 | 75 | | |

The commonly encountered adverse reactions for both the drugs are same i.e yeast infections, nausea, vomiting, and bad or metallic taste in mouth (8). Oduyebo OO (2009); detected that the candidiasis is not a side effect of topical metronidazole (9). Brandt M (2008); described that the side effects of metronidazole are severe and commonly seen even on single oral or topical administration of metronidazole (10). Thus, upon comparison with tinidazole, longer duration of treatment with metronidazole is difficult because of early occurrence of side effects. The resultant outcome is the incomplete treatment and higher relapse rates with metronidazole therapy. [11] No renal or haematological side effect was reported from either of these drugs (15).

Therefore because of less side effects and cost effective as well, tinidazole should be preferred on metronidazole (5). Sanz et al (1985); concluded that a single 2gm dose of tinidazole was more effective i.e in 92% cases as compared to single 2 mg dose of metronidazole (12). Buranawarodmkul etal (1990); and Thulkar J (2012); supplemented the findings of Sanz et al (13,14).

Cure rates of tinidazole is >90% for the treatment of giardiasis, amebiasis, trichomoniasis, bacterial vaginosis and amebic liver abscess (1,3). The study findings by Bakshi, JS (1978); showed that the dose of tinidazole and metronidazole for the management of amebic liver abscess is same i.e 2 gm once daily dose used for 2 days. Upon comparison of both groups the cure rate for patients using tinidazole was 96% while for metronidazole it was 75.5%. For giardiasis the calculated dose of 50mg/kg body weight was used for two groups each i.e treated by tinidazole and metronidazole respectively. The results revealed 88.3 % cure rate for tinidazole. While it was 46.7% for the group managed by metronidazole (15).

Bacterial vaginosis is a very commonly encountered lower reproductive tract infection in females. The responsible microbes are mostly anaerobes like Mobillincus species, Prevotella species, Mycoplasma hominis and Gardnerella vaginalis. While trichomoniasis is a protozoal casue of vaginosis. It is caused by Trichomonas vaginalis i.e flagellated protozoa (16). The reported Clinical Guidelines of Australasian

College of Sexual Health Physicians in 2004, tinidazole was considered as a drug of choice for managing bacterial vaginosis by 2gm single dose (17). The published UK National guidelines for the year 2006 recommended tinidazole a first line management option for bacterial vagionsis in a single 2gm dose (18). Many studies conducted in the years 2006 & 2008 didn't preferred tinidazole to manage bacterial vaginosis (19,20). In the year 2011, US Food and Drug Administration (FDA), Europe, Asia and Latin Ammerica also approved Tinidazole as the drug of choice for treating bacterial vaginosis because of its good efficacy and the significant results of Livengood etal (2007) study (8,21).

In 2016, tinidazole was considered as a better management option for Helicobacter pylori gastric infection as part of its triple therapy management (22). The cure rate of patients having trichomoniasis, giardiasis and amebiasis is significantly more than the ones treated with metronidazole (23).

A reported data for the year 2016 revealed that because of good penetration in blood brain barrier, efficacy of metronidazole to treat central nervous system, bone and teeth infections is more as compared to tinidazole (24).

The common anerobes involved in oral infections include Prevotella intermedia/nigrescens, Streptococcus constellatus, and Aggregatibacter actinomycetemcomitans (25).

Odeh NSR (2010) and Patait M (2015) narrated that the commonly prescribing antibiotics for dental procedures include metronidazole,macrolides, betalactams, tetracyclines and clindamycin (26-29). The study report by Rasteriene R (2015) showed 27.9% susceptinility to metronidazole (30). Rams TE (2014) showed that metronidazole is resistant to all these anaerobes (25). Barak O (2013) supplemented that the efficacy of metronidazole is less for anaerobes (31). Manso F(2008) concluded by his study that tinidazole because of having good bactericidal activityharbours excellent susceptibility against anaerobes. He justified that because of its pharmacokinetic andpharmacodynamic properties it results in successful outcome for managing anaerobic odontogenic infections (32).

## Conclusion

Tinidazole because of specific pharmacokinetic and pharmacodynamics properties, is a better option to manage amebic, protozoal and anaerobic infections.

## Recommendation

Tinidazole should be amongst the first line drugs to manage amebic, protozoal and anaerobic infections

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