

Prescription of Metronidazole in Paediatric Dentistry-An Evidence Based Approach

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ABSTRACT

Introduction: Metronidazole belongs to the nitroimidazole group of drugs, specifically anti-anaerobic in the nature and has a broad spectrum of activity against protozoa and anaerobic bacteria.

Aim: The purpose of this systematic review was to assess the requisite for metronidazole prescription among children with pulpal infection either during treatment or postoperatively.

Materials and Methods: An electronic literature search was done using databases PubMed, Cochrane Database of Systematic Reviews, OVID and EBSCO Host from January 1991 to December 2015. Hand search were carried out based on cross-references, to find additional citations. Articles that met criteria such as randomised clinical trials, cross-sectional studies, in-vivo human studies were included. Search was confined to

English language. The primary outcome was to evaluate the necessity of metronidazole prescription in children with pulpal pathology. Two independent evaluators were involved in the search and kappa statistics were used to evaluate intra & inter-examiner reliability.

Results: A total of 335 articles were available, among these, only two studies fulfilled established inclusion criteria. These available two studies were cross-sectional studies (Level III). Kappa statistics showed excellent inter and inter-examiner reliability.

Conclusion: Although, metronidazole has antibacterial properties against anaerobic microorganisms, there is no clear evidence regarding its prescription among children with pulpal pathology. Further research is required to support or contradict the use of metronidazole prescription in children during or after pulp therapies.

Keywords: Antibiotics, Drug prescription, Nitromidazole group, Pulpitis

INTRODUCTION

Metronidazole belongs to the nitroimidazole group of drugs, specifically anti-anaerobic in the nature and has a broad spectrum of activity against protozoa and anaerobic bacteria. It is synthesized from a crude extract of streptomycete which is a mixture of two active components enteromycin and azomycin. Further work upon addition and substitution of carbon and nitrogen groups to the azomycin compound resulted in the synthesis of metronidazole [1]. Main therapeutic benefit of metronidazole is removal of pathogenic anaerobes, without disturbing defensive aerobic flora. The drug does not develop resistance among anaerobes as suggested by the consensus of experimental and clinical evidence that is due to decreased uptake of drug, reduced drug efficiency or prevention of entry of the drug or efflux [1-4].

Metronidazole has been proved to be efficacious in treating Acute Ulcerative Gingivitis (AUG), infected socket, osteomyelitis, pericoronitis and certain periapical infections. Metronidazole's antimicrobial activity against anaerobic bacteria is bactericidal and independent of growth rate [2]. It was Shinn who reported that patients receiving metronidazole treatment for trichomoniasis had successful resolution for AUG or trench mouth [3]. Metronidazole has been shown satisfactory results when administered in subjects with acute apical infections and the response was very good in very severe infections [4]. In case of osteomyelitis, administration of metronidazole for five days resulted in complete relief of symptoms with exception of paraesthesia [5]. It has been used as both systemically and topically in the treatment of periodontal disease. It is effective against anaerobic cocci as well as Gram-negative and Gram-positive bacilli [6]. Metronidazole has been used as an intra-canal medicament combined with pulpectomy in infected primary teeth [7].

Metronidazole has got many advantages such as: (i) ready availability; and (ii) oral and intravenous dosage forms; (iii) rapidly bactericidal; (iv) good tissue penetration; (v) cost-effective; (vi) acceptable

pharmacokinetics; and (vii) pharmacodynamics, undiminished antimicrobial activity and apparent inability of susceptible organisms to develop resistance [8]. This drug has been prescribed under the trade name of Flagyl at a dosage of 200 mg (BID) in children and 400 mg in adults.

Many resistant strains of microorganisms have been emerged because of purposeless use of antibiotics and, have become a major concern [9]. This can be attributed to the reasons such as exposure of antibiotics throughout the time, misuse of antibiotics in conditions of no value, excessive use of broad spectrum rather than narrow spectrum antibiotics [10,11]. Superfluous uses of antibiotics are reported in children, mostly for ear and dental infections, which has led to further antibiotic resistance. One of the factors causative for this is the lack of knowledge in prescribing patterns of antibiotics by the dentist [12].

Metronidazole has been commonly prescribed in children as an adjuvant during pulp therapy or after pulp therapy. According a general dental practitioners survey from United Kingdom reports that 7-10% of antibiotic prescription done by dentists, and 45% of all prescriptions for metronidazole [13,14]. Most of the oro-facial infections in the humans derive from odontogenic infections [13], hence, the prescription of prescribing of antibiotics by general dental practitioners has become an important aspect of dental practice. The resistance of the bacteria to the commonly used antibiotics have become a major universal health care problem and inappropriate use (over- or misuse) of these, contributed to the global predicament of increased microbial resistance [15,16]. Our recent review on clinical uses of metronidazole in paediatric dentistry showed no evidence, to support the use of metronidazole during or after pulp therapy [17]. Hence, the present search was aimed to investigate the necessity of metronidazole prescription among children with pulpal infection either preoperatively or during the treatment based on the existing literature.

MATERIALS AND METHODS

Research question: Is there sufficient evidence to support prescription of metronidazole for pulp therapy in children?

Data extraction: A comprehensive electronic literature search was done using the following databases PubMed, Cochrane Database of Systematic Reviews, OVID and EBSCO Host. The databases were searched with the following MeSH (Medical Subject Heading Terms) terms, in which Boolean operators were used and the asterisk indicates truncation: ("child" OR adolescent* OR "teenagers" OR "teens" OR "youth" OR "early adulthood" OR preschool) and ("Metronidazole" OR "2- Methyl 5- Nitroimidazole 1- ethanol" OR "Metrogel" OR "Flagyl" OR "Metronidazole hydrochloride" OR "Metronidazole monohydrochloride" OR "Metronidazole phosphate") AND ("Oral drug administration" or "Oral administration" OR "Teeth" OR "Baby teeth" OR "Milk teeth" OR "Primary dentition" OR "Deciduous teeth" OR "Permanent teeth" OR "Dental pulp autolysis" OR "Dental pulp gangrene" OR "Pulp mummification" OR "Periapical abscess" OR "Dental pulp necrosis") AND ("Oral health" OR "Dental health" OR Prognosis).

Research protocol: The search period was January 1991 to December 2015 and the search was confined to English language. Hand search was conducted to retrieve additional data on the use of metronidazole in children during or after pulp therapy. Articles in the potentially entitled list were searched manually, and titles and abstracts were screened. Only articles published in English during search period, studies included done on children, pulp therapies in primary teeth were included. Clinical studies regarding prescription of metronidazole in conditions other than pulpal diseases, non-human in-vitro studies, all grey literature, articles other than English language and irrelevant studies were excluded. Full texts of the remaining articles were retrieved and included for further screening. In addition, hand search was carried out based on cross references,

citations and bibliographies of these articles to ascertain relevant and additional data. Finally, articles that met the criteria such as clinical trials on children with prescription of metronidazole in pulpal diseases were included in the analysis of the systematic review. Two independent examiners (SA and MSK) were involved in the study for evaluation and kappa statistics used to check inter- and intra- examiner reliability to avoid the bias. Search MeSH terms and alternate terms enclosed in search strategy used in the present study was mentioned in [Table/Fig-1]. The quality of the studies was assessed based checklist suggested by Shekelle PG et al., shown in [Table/Fig-2] [18].

RESULTS

The initial search identified a total of (n=342) articles from both electronic and manual searches {PubMed (166), Cochrane (6), EBSCO (5) and Ovid (158) and through other sources (7)}. Among them duplicate studies were excluded (n=8). During second stage screening (n=305) articles were excluded based on the evaluation of titles and abstracts. Twenty nine publications were thoroughly screened and (n=8) full text articles assessed for eligibility. A total of (n=21) articles were excluded with reason. At third stage of screening six articles were excluded because most of the studies discussed about the usage of metronidazole as an intra-canal medicament in triple antibiotic paste along with ciprofloxacin, minocycline and enduring were review articles. Only two articles (N = 2) which met the inclusion criteria like antibiotic prescription among children were included and evaluated thoroughly [Table/Fig-3]. Excellent intra-examiner reliability (K=0.9) and good inter examiner (K=0.7) was evident. In the present systematic review a total of eight studies have been included after comprehensive screening. Among them, only two were eligible for final analysis. Remaining six were excluded because of the age criteria of the participants and rest of them were review studies. Among the two included studies [19,20], one

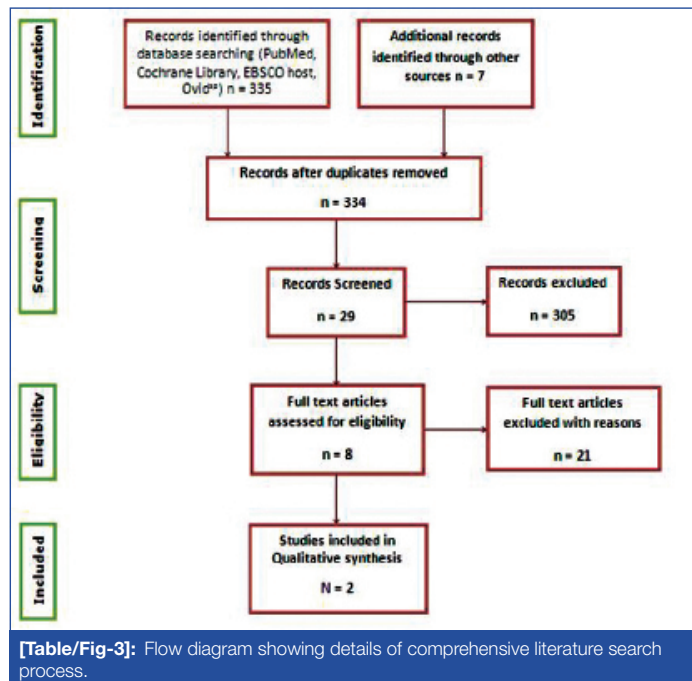
PICO	Population	Intervention	Comparison	Outcome
Characteristics considered	Children	Metronidazole in dental infection	Irrigant and Medicament, Necrotic pulp and Periradicular lesion, Primary teeth and young permanent teeth	Dental health, Oral health.
MeSH terms	Child, Adolescent	Metronidazole	Root canal Irrigants, Dental pulp Necrosis, Periapical abscess; Deciduous teeth, permanent teeth	Oral health
Alternative terms	Teenagers, Teens, Youth, Early adulthood, Preschool	2-Methyl-5-nitroimidazole-1-ethanol, Flagyl, MetroGel, Metronidazole Hydrochloride, Metronidazole Monohydrochloride, Metronidazole Phosphate,	Canal irrigants, Root canal medicaments; Dental pulp necrosis, Dental pulp gangrene; Pulp mummification, Dental pulp autolysis, deciduous tooth, Primary dentition, Milk tooth, Baby teeth, Teeth	Health, Oral

[Table/Fig-1]: Medical Subject Heading terms and alternate terms enclosed in search strategy.

Classification schemes
Category of evidence:
Ia: Evidence for meta-analysis of randomised controlled trials
Ib: Evidence from at least one randomised controlled trial
IIa: Evidence from at least one controlled study without randomisation
IIb: Evidence from at least one other type of quasi-experimental study
III: Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV: Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
Strength of recommendation:
A: Directly based on category I evidence
B: Directly based on category II evidence or extrapolated recommendation from category I evidence
C: Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D: Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

[Table/Fig-2]: Level of evidence based Shekelle PG et al., [18].

study which was a cross-sectional study conducted in Pakistan, examined the patterns of prescribing antibiotics and painkillers as per diagnosis by the dentists and other being a questionnaire study, conducted in India, assessed the therapeutic prescription of antibiotics in the dental office. Considering the level of evidence the available two studies belongs to LEVEL III, which are observation studies without controls based on quality assessment criteria suggested by Shekelle PG et al., [18].



DISCUSSION

Metronidazole is extremely effective against gram-negative anaerobic pathogens responsible for acute oro-facial infections and chronic periodontitis. Metronidazole has been commonly prescribed as an adjuvant during pulp therapy or after pulp therapy in paediatric dentistry. Combination of metronidazole with a β -lactam antibiotic for oral infections may be indicated for the management of aggressive periodontitis and serious acute oro-facial infections [19]. Metronidazole is a concentration-dependent, not time-dependent, antibiotic. The promiscuous use of metronidazole for classic chronic periodontitis is a misuse of the drug and may contribute to the increasing resistance of metronidazole seen with parasites, *H. pylori*, and other microorganisms [20].

Many resistant bacterial strains have emerged due to inappropriate use (over- or misuse) of these antibiotics, which has become a major universal health care problem and, contributed to the global predicament of increased microbial resistance. From the present search, authors only found two relevant studies on prescription metronidazole for children after pulp therapy. A cross-sectional study [21] from Pakistan investigated the pattern of antibiotic and analgesics prescriptions per diagnosis among the oral health providers of Dow University of Health Sciences (DUHS), Karachi. During a two week period, all the outpatient forms along with the number of prescriptions and defined daily doses filled by the oral health providers were gathered. A sum of 709 patient prescription forms were screened and included in the data analysis, among them 17% of the dentists prescribed antibiotics and 64% of the prescriptions showed that antibiotics were commonly prescribed for the diagnosis of dental caries with pulpitis. Amoxicillin and metronidazole were the most commonly prescribed antibiotics for children with pulpal disease. Hence, the authors suggested that there is a clear need to emphasise correct diagnostic methods to develop contextualised prescription guidelines, and authors concluded

that the optimum effect of antibiotics and analgesics will be achieved without compromising patient's health [21].

A questionnaire study [22] was conducted in India to assess the therapeutic prescription of antibiotics in the dental office. A questionnaire was sent to the dentists to collect data pertaining to the conditions in which antibiotics were prescribed and the most commonly prescribed antibiotic. Forty two faculty members from two dental colleges in the same vicinity were included, of which 41 questionnaires responded completely. Authors reported that amoxicillin was the most commonly prescribed antibiotic followed by amoxicillin combinations; whereas metronidazole was most widely prescribed antibiotic for the anaerobic infections. The study concluded that limiting the prophylactic antibiotic prescription in the healthy individual with no underlying systemic diseases or immune-compromised conditions is recommended [23]. However, the study population is very low in this study and hence results can not be generalised to the entire dentists' community in India.

Antibiotics are commonly used in dentistry for prophylactic as well as therapeutic purposes [12]. Two main reasons for its use in paediatric dentistry are control of oral infection and prevention of the Sub-Acute Bacterial Endocarditis (SABE) [24]. Amoxicillin and Metronidazole are most commonly prescribed antibiotics for the management of pulpitis and caries [21]. Metronidazole is most widely prescribed for anaerobic infections [24]. Many of the oral diseases usually seen by dentist are inflammatory in origin and associated with pain. Most of them originate from acute and chronic inflammation of the pulpal tissue which requires operative intervention rather than the antibiotics [24]. Nevertheless, many dentists prescribe antibiotics for pulpitis, to relieve pain and infection. If periapical tissues have been involved and an abscess is formed, drainage either by endodontic therapy or by extraction of affected tooth is considered for the management. In these cases, antibiotics are given as an adjunct to the treatment to avoid the swelling and also to prevent metastasis of the infection to the vital tissues [22].

A group from Germany studied the activity of various antibiotics on 164 isolates from subgingival plaque of 66 patients (progressive periodontitis) and 192 bacterial strains from pus of 74 patients with dental abscesses [25]. Author found that the majority of microbes isolated from pus from odontogenic abscesses were Gram negative anaerobes and were highly susceptible to clindamycin and metronidazole than other antibiotics but that 22% of isolated bacteria were resistant to penicillin by producing beta-lactamases. More emphasis should be made, regarding the need for educational initiatives to rationalise the use of antibiotics in dental practice as well as prescription of these at correct dosages without development of resistant bacteria [26]. Similarly, dental practitioners in Eastern Mediterranean region have shown a tendency to prescribe on a patient's demand or socially, especially when short of time [26,27]. Localized oral lesions include periodontal abscess, acute necrotizing ulcerative gingivitis, and pericoronitis are usually in dental practice are indicated for use of antibiotics [28]. It has been told that in some situations non-clinical factors such as patient's expectation of an antibiotic prescription, convenience, and necessitated by the background of the patients are considered unscientific reasons for antibiotic prescription. Hence, this systematic review was planned to rule out the need for prescription of metronidazole in children during and after pulp therapies. Surprisingly, there are no clinical trials to contradict or to support the therapeutic use of metronidazole during or after pulp therapy. There are no randomised clinical trials rather clinical studies to support or contradict the prescription of the metronidazole in children undergoing with pulp therapy. Ingham HR et al., reported that metronidazole was as beneficial as penicillin [4]. Further research is recommended regarding the necessity of metronidazole prescription in children, because

misuse of these drugs had led to emergence of drug resistant microbial species. Prolonged period of prescription of drug regimen might be one of the reasons for the drug resistance.

CONCLUSION

To conclude it appears that prescription of metronidazole in children for pulpal infection may not be reliable, as pulpitis is an inflammatory condition which can be relieved by endodontic treatment. Due to insufficient availability of information to provide a dogmatic regimen for clinical use of metronidazole, clinical trials are recommended to support the use metronidazole. Nevertheless, further research is necessary to confirm the necessity of metronidazole prescription in children, based on the level of available evidence.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jun 14, 2018**
Date of Peer Review: **Jul 13, 2018**
Date of Acceptance: **Aug 31, 2018**
Date of Publishing: **Dec 01, 2018**