Infection, Alveolar Osteitis, and Adverse Effects Using Metronidazole in Healthy Patients Undergoing Third Molar Surgery: A Meta-analysis

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Abstract

Purpose The aim of this systematic review and meta-analysis was to evaluate the risk of surgical infection, alveolar osteitis, and adverse effects using systemic metronidazole in comparison with placebo in healthy patients undergoing third molar surgery.

Materials and Methods The eligible reports were identified from diverse science sources. Clinical trials meeting the inclusion and exclusion criteria and an acceptable Oxford Quality Score were included in this study. The evaluation of risk was done using the Risk Reduction Calculator and Review Manager 5.3., from the Cochrane Library. A significant risk reduction was assumed when the upper limit of the 95% confidence intervals was <1 and the lower limit did not cross zero (negative number) alongside

a *p* value of <0.05 for the overall test. Data of 667 patients from five clinical trials were used for the assessment of risk.

Results Our analysis showed no reduction of the risk of infection or dry socket in patients receiving metronidazole compared to whom took placebo. Meanwhile, the adverse effects did not exhibit a difference between the studied groups.

Conclusion The routine use of systemic metronidazole to prevent surgical site infection and/or dry socket in healthy patients undergoing third molar surgery is not recommended.

Keywords Metronidazole · Third molar surgery · Surgical infection · Alveolar osteitis · Adverse effects

Introduction

Systemic metronidazole has been used for preventing surgical site infection [1–5] and alveolar osteitis [2, 4–11] in third molar surgery. It has been employed in single- [2, 4–7] or multiple-dose [1–4, 8, 9] before and/or after this kind of surgical procedure. However, its clinical effectiveness never has been demonstrated in the prevention of wound infection and dry socket in third molar removal. Several systematic reviews [12] and meta-analyses [13–16] have showed contradictory results about the success of the systemic antibiotics in the prophylaxis of surgical site infection in third molar removal. With the purpose of justifying the systemic administration of metronidazole, our clinical research group performed this systematic review and meta-analysis to evaluate the risk of wound infection, alveolar osteitis, and adverse effects in healthy patients undergoing third molar surgery.

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Material and Methods

Search Strategies

Clinical studies employing metronidazole in comparison with a placebo group were sought from PubMed, Cochrane Library, Imbiomed, LILACS, and Google Scholar. The words utilized in the search were: “Metronidazole,” “wound infection,” “alveolitis,” “alveolar osteitis,” “dry socket,” “third molar surgery,” and “oral surgery.” Each abstract identified was evaluated before to obtain the full article. Reports published up to October 2016 were eligible. The study design is shown in Fig. 1.

The Criteria for Evaluating the Full Papers

Inclusion criteria were as follows: (1) randomized, double-blind, clinical trial; (2) study comparing pre- and/or post-operative metronidazole with a placebo group in third molar surgery; (3) healthy patients; (4) diagnosis of wound infection, alveolar osteitis, and/or adverse effects; and (5) English or Spanish report. Exclusion criteria included: (1) loss to follow-up more than 20% of those entered and (2) use of immunosuppressive drugs.

Two researchers did independently evaluate each full-text report. Thus, both researchers performed the evaluation of inclusion and exclusion criteria of each study. Once the researchers made this evaluation, the information by one researcher was checked by the other. Any disagreement was resolved by consensus with the aid of another experienced researcher. The authors were contacted by email for additional or unclear information.

Evaluation of Quality

The studies were assessed using the Oxford Quality Scale [17], as was done in previous studies [16, 18]. The obtained information by one researcher was checked by the other. The differences were resolved as it was explained above. Those studies meeting the inclusion criteria without exclusion points plus an Oxford Quality Score ≥ 3 were included in our qualitative and quantitative analysis.

Assessment of Bias

The internal validity of the included clinical trials was evaluated using the Cochrane Collaboration’s risk of bias tool examining seven points: (1) random sequence

Fig. 1 Study flow diagram

generation; (2) allocation concealment; (3) masking (blinding of participants and personnel); (4) blinding outcome assessment; (5) incomplete outcome data; (6) reporting bias; and (7) other bias.

Data Extraction

The extracted data of each included study were author, design study (parallel or crossover groups), treatment groups, size sample, dose and administration route, period of evaluation, patients with surgical wound infections, alveolar osteitis, and patients reporting adverse effects (Table 1).

For general analysis of data when a study had two groups using the metronidazole, the infection cases were integrated in a same group and were compared with a placebo group, e.g., as in the case of Sekhar et al. [4].

Statistical Analysis

For the statistical assessments, the unit of analysis was the odd ratio (OR). First, we did the overall evaluation of the risk of surgical infection, alveolar osteitis, and adverse effects using metronidazole in comparison with a placebo group. The absolute risk reduction (ARR), number needed to treat (NNT), absolute risk increase (ARI), number

needed to harm (NNH), and 95% confidence intervals (CIs) were calculated using the Risk Reduction Calculator [19].

Each meta-analysis employed the Mantel–Haenszel method under a random-effects model using the Review Manager 5.3., from the Cochrane Library. This statistical method was used to obtain an appropriate analysis of data with few events and to consider the heterogeneity [20]. Two *p* values were obtained using this approach. One was related to the summary effect of the meta-analysis (*Z* value), and other was related to heterogeneity. For an adequate interpretation of the results, the *p* values were presented alongside the estimates of effect (OR) and associated 95% CI [21]. For the evaluation of heterogeneity, the Cochrane's *Q* (χ^2) statistic was determined by summing the squared deviations of each study's estimate from the overall estimate taking into account the weight of each study's contribution. Meanwhile, the static *I*² was employed for the quantification of inconsistency between the included trials. An *I*² value ranged from 0 to 30% might indicate an unimportant inconsistency, whereas values ranged from 30 to 100% may represent a moderate, substantial, or considerable inconsistency [20, 22]. A significant risk reduction was assumed when the upper limit of the 95% confidence intervals was <1 and the lower limit did not cross zero (negative number) alongside a *p* value of

Table 1 Details of studies included

First author and study design	Interventions (<i>n</i>)	Adverse effects	Conclusion
Barclay [10] Randomized, double-blind, parallel clinical trial	Experimental group: Metronidazole 400 mg 1 h before surgical removal and then ever 8 h for 8 days postoperatively (<i>n</i> = 45) Control group: Placebo 1 h before surgical removal and then ever 8 h for 8 days postoperatively (<i>n</i> = 50)	Twenty patients receiving metronidazole and 14 receiving placebo reported adverse effects	Therapeutic success
Bergdahl and Hedström [6] Randomized, double-blind, parallel clinical trial	Experimental group: a single dose of metronidazole 1600 mg orally 45 min before surgery (<i>n</i> = 59) Control group: Placebo 45 min before surgery (<i>n</i> = 60)	Not evaluated	Therapeutic failure
Pasupathy and Alexander [5] Randomized, double-blind, parallel clinical trial	Experimental group: a single dose of metronidazole 800 mg orally 1 h before surgery (<i>n</i> = 29) Control group: Placebo 1 h before surgery (<i>n</i> = 29)	Not evaluated	Therapeutic failure
Ritzau et al. [7] Randomized, double-blind, parallel clinical trial	Experimental group: Metronidazole 1000 mg orally 30 min before surgery (<i>n</i> = 135) Control group: Placebo tablets 30 min before surgery (<i>n</i> = 135)	No adverse effects	Therapeutic failure
Sekhar et al. [4] Randomized, double-blind, parallel clinical trial	Experimental group 1: a single dose of metronidazole 800 mg orally 1 h before surgery (<i>n</i> = 44) Experimental group 2: Metronidazole 400 mg orally eight hourly for 5 days postoperatively (<i>n</i> = 47) Control group: Placebo 1 h before surgery and then eight hourly for 5 days postoperatively (<i>n</i> = 34)	Not evaluated	Therapeutic failure

<0.05 for the overall test. Moreover, probabilities of <0.05 were accepted as statistically significant.

Results

Identification and Included Studies

A total of 11 relevant clinical studies employing metronidazole in comparison with placebo in third molar surgery were identified. After fully evaluation, only five clinical trials were used for the risk analysis because they met all the requirements (Table 2).

Assessment of Bias

Overall evaluation of the risk of bias was adequate or satisfactory for six of the evaluated points. However, a high risk of attrition bias was observed (Fig. 2).

Surgical Site Infection

We analyzed the data of 183 patients which were obtained only of two of the five clinical trials that met all the requirements because assessed the number of patients presenting surgical wound infection. A total of 120 patients was given metronidazole of whom 2 (1.66%) developed a surgical infection. Of the 63 patients administered with placebo, 3 (4.76%) patients presented an alveolar infection. The ARR showed that 2.46% (95% CI −3.14 to 8.06%) of patients will not present surgical infections receiving metronidazole that they would have with placebo. The NNT estimates that 41 (95% CI 12.4 to Infinity) patients must be treated with metronidazole to prevent one infection

case that would have happened under placebo. The overall evaluation of risk of surgical wound infection showed no statistical difference (Fig. 3).

Alveolar Osteitis

The data of 667 patients with alveolar osteitis from five clinical studies were assessed. A total of 359 patients were administered with metronidazole of which 24 (6.68%) patients presented alveolar osteitis compared to 308 patients receiving placebo of whom 37 (12%) developed a dry socket. The ARR indicates that 4.89% (95% CI 0.47–9.31%) of patients will not experience alveolar osteitis using metronidazole that they would have using placebo. The NNT shows that 20 (95% CI 10.7–212.1) patients must be treated with metronidazole to prevent one case of dry socket that would have occurred under placebo. The overall assessment of the alveolar osteitis showed no statistical difference (Fig. 4).

Adverse Effect

Data of 365 patients of two studies who reported adverse effects were analyzed. In the metronidazole groups 20 (11.1%) of 180 patients presented adverse reactions, while in the placebo groups 14 (7.56%) of 185 patients reported adverse effects. The ARI indicates that 5.95% (−0.28 to 12.17%) of patients will experience adverse events receiving metronidazole that they would not have with placebo. The NNH estimated that for every 17 (8.2 to infinity) patients treated with metronidazole, one adverse effect will occur beyond those that would have happened using placebo. In addition, the meta-analysis showed an OR 2.06 and 95% CI between 0.88 and 4.83.

Table 2 Assessment of relevant studies

Study	Criteria		Oxford Quality Scale	Included
	Inclusion	Exclusion		
Al-Rousan et al. [11]	2–5	0	4	No
Barclay [10]	1–5	0	5	Yes
Bergdahl and Hedström [6]	1–5	0	4	Yes
Kaziro [8]	1, 2, 5	0	3	No
Lloyd and Earl [3]	4, 5	2	3	No
Olojede et al. [1]	4, 5	0	1	No
Olusanya et al. [2]	4, 5	0	2	No
Pasupathy and Alexander [5]	1–5	0	5	Yes
Ritzau et al. [7]	1–5	0	5	Yes
Rohit and Reddy [9]	3–5	0	2	No
Sekhar et al. [4]	1–5	0	4	Yes

Fig. 2 Assessment of risk of bias of the included clinical trials

Discussion

This is the first systematic review and meta-analysis to our knowledge assessing the clinical effectiveness of metronidazole in front of surgical site infection and dry socket compared to placebo in healthy patients undergoing third molar removal. Our results indicate that there is no reduction in the risk of surgical infection or alveolar

osteitis when metronidazole was given in comparison with placebo in third molar removal. The outcomes of our systematic review and meta-analysis show that the routine clinical use of metronidazole to prevent surgical wound infection and/or dry socket is not recommended in third molar surgery because the results of this report indicate that it is necessary to treat approximately 40 patients to prevent one case of surgical site infection or 20 patients for

Fig. 3 Overall assessment of surgical wound infection **Fig. 4** Overall evaluation of alveolar osteitis

preventing a case of alveolar osteitis. It is very important to note that the lower 95% IC of ARR of surgical infection crosses zero, which implies that the ARR is not significant; and it is possible that metronidazole may actually increase risk of infection. Table 2 summarizes the characteristics of the five quality studies included in our meta-analysis of which four clinical trials showed therapeutic failure when metronidazole was compared with placebo to evaluate its prophylactic effect against a surgical infection and/or alveolar osteitis.

Sekhar et al. [4] had a considerable loss of follow-up; 23 patients in the metronidazole group and three in placebo group. The authors of that study analyzed the influence of the demographic and surgical variables of patients who did not complete the study and reported that there were no important differences between the study groups [4]. However, the causes for which the patients did not finish the study were not reported and could have influenced the results obtained. It is possible that the high loss of follow-up in the metronidazole group of the study by Sekhar et al. [4] has been by using of this drug, perhaps due to adverse effects. Despite the high number of follow-up losses, we included this study because these losses do not exceed 20%. In the same manner, the study by Ritzau et al. [7] reported 11 follow-up losses, but these were not included in the statistical analysis because the number of losses in each group was not indicated. The authors did not disclose the

reason for the loss of follow-up. The clinical study by Barclay [10] indicates that five patients in the metronidazole group no finish the trial while that in the placebo group there were no losses-up. The follow-up losses from Sekhar et al. [4] and Barclay [10] were considered in our analysis of risk on alveolar osteitis and adverse effects. On the other hand, two studies were not included in our meta-analysis because they did not meet the required languages [23, 24].

Our systematic review and meta-analysis used specific inclusion and exclusion criteria; high quality randomized, double-blind, clinical studies only; assessment of cases of infection or dry socket separately; adverse effects; an individual systemic antibiotic (metronidazole) compared to placebo in healthy patients undergoing third molar removal; a conservative statistical method (random-effects model); and the follow-up losses were considered in the statistical analysis. The reports showing a positive effect to antibiotics ignored one or several of these important points to perform the risk evaluation [13–15, 25].

The main objective of a meta-analysis is supporting physicians in their clinical decisions in situations of controversy through the rigorous evaluation of existing evidence [16, 17]. The meta-analyses performed with several kinds of antibiotics do not fulfill this main purpose which involves assisting in making a clinical decision on which antibiotic to use when a healthy patient undergoes third molar surgery. These reports have been

conveniently performed using different types of antimicrobials to increase the sample size or assessing different variables such as post-surgical wound infection and dry socket in the same analysis as if these variables were the same, increasing the sample size. Unfortunately, these meta-analyses cause more confusion in this regard [13–15, 25].

According to international data reported in different clinical trials [12, 26, 27] and meta-analyses [13–16], the percentage of surgical site infection after third molar surgery is low in patients with or without antibiotics. In this sense, several clinical studies performed in different oral care centers from India have reported variable results (0–7.29%) on surgical site infection in third molar removal similar to those of other international populations [28–30]; and for this reason, our clinical research group does not recommend the routine use of these drugs in third molar surgery. The indiscriminate use of antibiotics increases bacterial resistance [4]. The normal microbiome widely exposed to antimicrobials develops great number of resistance genes. The dysbiosis is another disturbance in the human microbiome producing altered functions of microflora, which can be produced by antibiotic exposure and other factors. Dysbiosis can cause health harmful changes, including antimicrobial resistance, susceptibility to infectious diseases, altered immune homeostasis (including allergic reactions), and abnormal metabolism [31]. Moreover, it has been estimated that approximately 6–7% of patients receiving an antibiotic have any adverse effects [4, 16]. In the present report, the ARI, NNH, and overall meta-analysis did not indicate a difference between metronidazole and placebo. However, the pre- and post-operative administration of metronidazole exhibited a high incidence of adverse reactions compared with the pre-operative administration of this drug.

The main drawback of this report is the number of randomized, double-blind, clinical trials included in the statistical analysis because the controversy about the efficacy of antibiotics in prophylaxis of an infection in third molar surgery could be due to the low number and low quality of the studies performed.

Considering the low incidence of surgical infection [26, 27] and alveolar osteitis [7] in the third molar removal as well as the lack of evidence in the literature supporting the use of metronidazole in this kind of surgical procedure, we concluded that the routine use of systemic metronidazole to prevent surgical site infection and/or dry socket in healthy patients undergoing third molar surgery is not recommended. Likewise, new randomized, double-blind, clinical trials using metronidazole in comparison with placebo with appropriate methodology and standardized evaluation of important outcomes should be performed.

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