

# TOPICAL ANTISEPTICS AS SYSTEMIC ANTIBIOTICS IN THE PREVENTION OF ALVEOLAR OSTEITIS AFTER EXTRACTION OF LOWER THIRD MOLARS

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## ABSTRACT

*Alveolar Osteitis (AO) and infection are common post-operative complications in third molar surgery. Topical antiseptics (chlorhexidine gluconate) and systemic antibiotics are the most commonly used antimicrobial agents to prevent these complications. However, their use is controversial in dental practice. The aim of this study is to evaluate the efficacy of topical antiseptics and systemic antibiotics in reducing the incidences of these complications and to compare them.*

*A systematic review and meta-analysis, based on clinical trials that were evaluating the efficacy of topical antiseptics and systemic antibiotics, was carried out. The primary outcome variable was AO. The relative risk (RR) of antiseptics and antibiotics as well as the total effect of all studies was calculated using random effect model.*

*The study included 20 clinical trials. A total of 3004 dental extractions, 868 in the antiseptic group and 2136 in the antibiotic group, were included in the quantitative analysis. The overall RR of all studies was 0.49[95% confidence interval (CI), 0.35-0.68;  $P < 0.001$ ]. The RR for antiseptics was 0.42 (95% CI; 0.28-0.64;  $P < 0.001$ ). The RR for antibiotics was 0.56 (95% CI; 0.34-0.91;  $P < 0.001$ ). The difference between two groups was not statistically significant ( $P = 0.28$ ).*

*The topical antiseptics and systemic antibiotics significantly reduce the risk of AO in third molar surgery. However, there was no difference between antiseptics and antibiotics regarding the efficacy in the prevention of AO.*

**Key Words:** Topical antiseptics, systemic antibiotics, alveolar osteitis.

## INTRODUCTION

Alveolar osteitis (AO), most commonly known as 'Dry Socket' is a postoperative painful, debilitating condition that occurs as a complication of tooth extraction in permanent dentition.<sup>1</sup> The frequency of AO in dental extraction normally ranges from 3% to 4%. However, very high incidences, from 25% to 30% of all

cases, occur after extraction of impacted mandibular third molar.<sup>2</sup>

The symptoms of AO appear after 24 to 48 hours of surgery as severe throbbing pain, that can last for up to three weeks.<sup>3</sup> The alveolar socket may contain partially or totally disintegrated blood clot with or without fetid breath.<sup>4</sup> Based on different theories for the causative factors, numerous techniques have been used for its prevention such as, the use of saline mouthwashes, topical placement of antibiotics, antiseptic rinses, anti-fibrinolytic agents, tranquilizer dressings, occlusive dressings as well as application of polylactic acid.<sup>5</sup> However, as the primary role of pathological bacteria for the development of AO has been constantly reported in the literature, the most effective method in the prevention of AO has been the use of agents that systemically or locally reduce the pathological microbes at the surgical site.<sup>6-7</sup>

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The efficacy of systemic antibiotic as well as topical antiseptic agents have been studied and analyzed by different researchers. For example, Ramos et al<sup>8</sup> have performed a systematic review and meta-analysis and concluded that systemic antibiotics significantly reduce the risk of dry socket after extraction of lower third molar. Similarly, Reza and Khazaei<sup>9</sup> have reviewed and performed a meta-analysis to determine the efficacy of 0.2% chlorhexidine bio adhesive gel for prevention of AO incidence after extraction of lower third molar. However, I have not found any study that makes a comparison of efficacy of systemic antibiotic and topical antiseptic agents for the prevention of AO. The aim of this study is to review and analyze published studies and compare the effectiveness of systemic antibiotics and topical antiseptics such as chlorhexidine for the prevention of AO after extraction of lower third molar.

## METHODOLOGY

This review is composed of publications that were published during 2006 to 2017, reporting on systemic antibiotics and/or topical antiseptics in the prevention of AO after extraction of lower third molar. Only studies that were based on randomized clinical trials and had at least one control group have been included in the review. The literature search was carried out with questions structured in the Patient, Intervention, Comparison and Outcome (PICO) format.<sup>10-11</sup>

### Eligibility Criteria

- 1 **Patient:** This review includes the studies with individuals of any age and gender, who had lower third molar extraction, regardless of how much were the degree of impaction. All patients were otherwise healthy, without any underlying medical problem.
- 2 **Intervention:** The included studies had tested the efficacy of different systemic antibiotics, administered through oral or parental route as well as topical antiseptics in the form of oral rinses or bio adhesive gel. However, the only antiseptic that was evaluated was the chlorhexidine gluconate.
- 3 **Comparison:** All studies were randomized clinical trials having a control group. The controls were the placebo in the same form and shape of active regime. However, the controls were in the same patients (split-mouth technique) or in different patients.
- 4 **Outcome:** This review includes those studies who studied alveolar osteitis (dry socket) or infection or both as post-operative complication, occurring after 3 to 5 days of surgery. It is likely that investiga-

tors tested other outcomes such as inflammatory conditions (pain, fever, size of mouth-opening etc.) along with alveolar osteitis or infection. However, only alveolar osteitis or infection fragment was included in this review.

### Characteristics of studies

All included studies were randomized clinical trials having at least one control where the control group received placebo replica of active ingredient. However, in some studies the control group did not receive any placebo.<sup>12</sup> In such studies, the patients or extracted tooth sockets without any placebo were considered as control. Similarly, the control was either an another group of identical patients or it was the same patient where corresponding tooth in the opposite side of the mouth (studies using split-mouth technique) was considered as control. Though majority of the studies were double blinded, in some studies the investigator's blinding was not mentioned. However, there was one study that was single-blinded.<sup>13</sup> There existed a large variation in the type and administration of experimental material. For instance, the route of administration of antibiotics was either oral or parental but the route of administration of chlorhexidine was always topical, either in the gel or in the mouth rinse form. Similarly, the timing of administration was either pre-operative where the drug was given before surgery or post-operative when the drug was administered after the surgery. All included studies tested a single regimen at one time, testing either antibiotic or chlorhexidine gluconate. However, one study<sup>14</sup> tested the effects of 0.2% chlorhexidine gluconate as well as 0.2% chlorhexidine gluconate in combination with amoxicillin plus clavulanic acid in two different groups. To avoid the complication, the results of 0.2% chlorhexidine gluconate from first group were included in this review and results from the second group were discarded. The outcome was alveolar osteitis. The AO was established if there was severe pain after 24 to 48 hours of extraction with exposed bony socket. Similarly, surgical wound infection was diagnosed if there was purulent discharge from the wound along with symptoms of the infection such as pain, fever and lymphadenopathy.

### Statistical analysis

The extracted data from selected studies were analyzed using statistical software R (version 3.3.2)<sup>15</sup> and package 'metafor'.<sup>16</sup> The effect of treatment was analyzed with a random effect model, using the Relative Risk (RR) as effect size of individual studies. Treatment antibiotic or antiseptic were used as a

TABLE 1: RANDOM EFFECT MODEL FOR OVERALL EFFECT OF ALL STUDIES

Model Results					
Estimate	Standard Error (SE)	Z-value	P-value	ci.lb	ci.ub
-0.7110	0.1672	-4.2530	<.0001	-1.0386	-0.3833
Test for Heterogeneity					
Q (df = 19)			P-value		
29.5734			0.0575		
Random-Effects Model (k = 20; tau <sup>2</sup> estimator: REML)					
I <sup>2</sup> (total heterogeneity / total variability)		32.12%			
H <sup>2</sup> (total variability / sampling variability)		1.47			

TABLE 2: MIXED EFFECT MODEL FOR THE COMPARISON OF ANTISEPTICS AND ANTIBIOTICS

Model Results						
	Estimate	Standard Error (SE)	Z-value	P-value	ci.lb	ci.ub
	-0.5239	0.2242	-2.3369	0.0194	-0.9633	-0.0845
	-0.3503	0.3202	-1.0942	0.2739	-0.9778	0.2772
Test for Residual Heterogeneity						
QE (df = 18)			P-value			
25.3386			0.1159			
Test of Moderators (coefficient(s) 2)						
QM (df = 1)			P-value			
1.1973			0.2739			
Mixed-Effects Model (k = 20; tau <sup>2</sup> estimator: REML)						
I <sup>2</sup> (residual heterogeneity / unaccounted variability)		32.12%				
H <sup>2</sup> (unaccounted variability / sampling variability)		1.47				
R <sup>2</sup> (amount of heterogeneity accounted for)		18.55%				

TABLE 3: MIXED EFFECT MODEL FOR THE COMPARISON OF THE CONTROL TYPES

Model Results						
	Estimate	Standard Error (SE)	Z-value	P-value	ci.lb	ci.ub
Intercept	-0.5974	0.2672	-2.2360	0.0254	-1.1210	-0.0738
Treatment (T Antiseptic)	-0.3426	0.3327	-1.0298	0.3031	-0.9947	0.3094
Control Type (T Same)	0.1343	0.3373	0.3981	0.6905	-0.5268	0.7954
Test for Residual Heterogeneity						
QE (df = 17)			P-value			
25.0788			0.0930			
Test of Moderators (coefficient(s) 2,3)						
QM (df = 2)			P-value			
1.1799			0.5544			
Mixed-Effects Model (k = 20; tau <sup>2</sup> estimator: REML)						
I <sup>2</sup> (residual heterogeneity / unaccounted variability)		34.61%				
H <sup>2</sup> (unaccounted variability / sampling variability)		1.53				
R <sup>2</sup> (amount of heterogeneity accounted for)		2.92%				

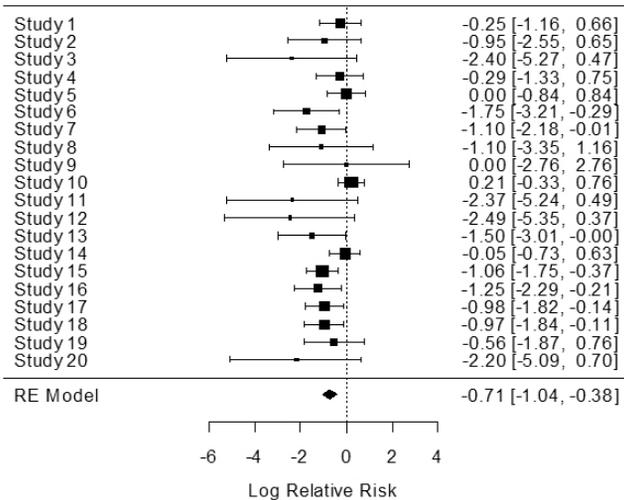


Fig 1: Forest plot of the overall effect of antiseptics and antibiotics

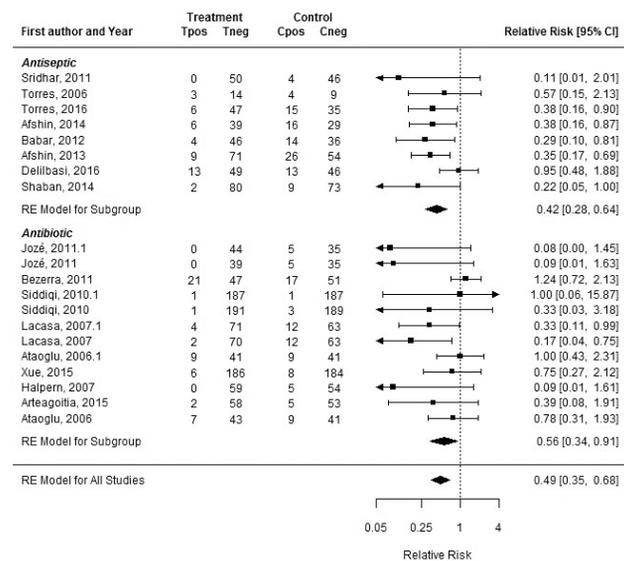


Fig 2: Forest plot of the subgroup analysis of the type of treatment

modifier. A funnel plot was designed to check the precision and/or existence of publication bias of the selected studies.

**RESULTS**

Out of 31 potentially eligible full-text studies, 16 were selected for quantitative analysis. However, some studies<sup>17,18</sup> used more than 1 group to check the efficacy of the treatment. In such cases, every group was taken as a single study, thus making 20 suitable trials for meta-analysis. Fig 1 shows the selected studies and the flow chart of the selection process. Fifteen studies failed to fulfill the inclusion criteria and, therefore, were excluded. The excluded studies and the reason for their exclusion are summarized in appendix A.

**Analysis of efficacy**

This quantitative analysis included 2136 tooth extractions in antibiotic group and 868 tooth extractions in antiseptic group, thus making total 3004 dental extractions for meta-analysis. Out of 2136 dental extractions in antibiotic group, 1089 cases received antibiotics with 53 infections (4.87%) and 1047 were in control group with 91 infections/dry sockets (8.69%). Similarly, 439 cases were treated with antiseptics where 43 cases developed infections/dry sockets (9.79%) whereas 101 resulted with infections out of 429 extractions in control group (23.54%). The overall RR was 0.49, with 95% confidence interval, ranging from 0.35 to 0.68. This was statistically significant (P < 0.0001) and different from RR=1, indicating that the overall effect of all treatment was significant and both antibiotics and antiseptics can prevent AO. The overall effect of antibiotics and antiseptics are plotted in Fig 2 and results of random effect model are shown in Table 2.

**Subgroup Analysis: Types of Treatment**

Based on type of treatment, the 20 clinical trials were classified into two main groups, antibiotic and antiseptic. The antiseptic group included 8 clinical trials where topical antiseptic, the chlorhexidine gluconate, was tested either in the gel or liquid form.

The substance was topically applied either pre or post operatively. The antibiotic group comprised of 12 clinical trials, that were testing systemic antibiotics, administered via oral or parental rout either pre or post operatively. In all clinical groups either a placebo substance was used in control groups or patients were considered as control when neither an antiseptic/antibiotic nor placebo substance was used.

As shown in Table 3, subgroup antiseptic and antibiotic treatment yielded similar results as total effect of both treatment, i.e. both antiseptic and antibiotic are effective in reducing AO. However, when both groups were compared with each other, a statistically less significant result (P = 0.28) was obtained. It means there was no significant difference between antiseptic and antibiotic treatment regarding prevention of AO after third molar surgery.

**Subgroup Analysis: Types of Control**

In this meta-analysis, the included clinical trials used two types of control groups. The first group (different) comprised 13 trials where the placebo was given to different patients with similar surgeries. The

second group (Same) included 7 trials where control was in the same patient. In these patients, the lower third molars were extracted using split-mouth technique. The corresponding tooth on the opposite side in same patient was considered as control. When compared with each other, a less significant result ( $P = 0.69$ ) was generated. It means both control types have approximately similar effects on the analysis in the effectiveness of the treatments. The results of mixed effect model for the comparison of the control types are shown in Table 4.

## DISCUSSION

In this meta-analysis, the results from 20 randomized clinical trials were analyzed. From the analysis, it is evident that topical antiseptic (chlorhexidine gluconate) reduces the risk of dry socket/infection by 58% (RR = 42; 95% CI; 0.28-0.68) and antibiotics by 44% (RR= 56; 95% CI; 0.34-0.91). Though the infection rate in the antiseptic group was twice as high (9.79%) as the infection rate in the antibiotic group (4.87%), a similar pattern was also observed in their control groups, respectively. The infection rate was almost three times higher (23.54%) in the antiseptic controls than the antibiotic controls (8.69%). The possible reason for higher value in the control may be due to variation in the criteria used to define 'infection' in these clinical trials. However, this resulted in a comparatively lower RR in the antiseptic group compared to antibiotic group, indicating that antiseptics are relatively more effective than antibiotics. However, when both groups were compared within the mixed effect model, no significant difference ( $P = 0.28$ ) was observed.

No complaints or major side effects of chlorhexidine were reported in 8 clinical trials. Only Delilbasi et al<sup>19</sup> reported staining of oral tissues, an alteration of the taste and bad taste of the solution in around 30% patients. Similarly, the reported adverse reaction after the use of antibiotics were diarrhea, gastric pain, nausea and vaginal candidiasis.<sup>20-21</sup> However, like antiseptic group, most of the selected clinical trials in antibiotic group failed to report the associated adverse effects. Even though there is no clear evidence of adverse effects of antibiotics in the selected studies, their indiscriminate use is not free from hazards. Their extensive use is associated with antimicrobial resistance, secondary infection, allergic reaction and drug-related toxicity.<sup>22</sup> One study reported 9 cases of nausea and 21 with diarrhea after use of amoxicillin in combination with clavulanic acid.<sup>23</sup> Similarly, the

common side effects of chlorhexidine gluconate were staining of tongue and dental fillings and soreness of oral mucosa.<sup>24-25</sup> These effects are comparatively mild, local and easy to manage.

Most of the post-operative complications are associated with bacterial contamination, it seems reasonable to prescribe antibiotics to prevent or reduce the incidence of AO. On the other hand, the incidence of dry socket is relatively low and usually not life-threatening. Moreover, in this analysis some studies<sup>26-27</sup> have not recommended the routine use antibiotics in third molar surgery. This raises the question if and how antibiotics should be used to prevent AO. The purpose this meta-analysis is to collect all available evidence to prevent the alveolar osteitis in third molar surgery.

The complications associated with third molar surgery especially with AO is very painful and disabling, that affects the quality of life and productivity of the patients.<sup>28</sup> Thus, the cost associated with these complications is much higher than the cost of antibiotic. In this scenario it seems reasonable to promote the prophylactic use of antibiotics from the cost-benefit perspective only. Moreover, the findings of this meta-analysis indicate no difference among the topical antiseptics and systemic antibiotics in the prevention of AO. Thus, it makes sense to prefer topical antiseptics over systemic antibiotics because of their mild, local and comparatively less adverse effects.

Regarding other published meta-analysis, Torres et al<sup>29</sup> concluded that systemic antibiotics can reduce the risk of post-operative complications by approximately 57%. (RR = 0.43, 95% CI,  $P < 0.0001$ ). However, in current meta-analysis, the risk-reduction of AO using antibiotics was 44% (RR = 56, 95% CI,  $P < 0.0001$ ), a lower efficacy observed than the efficacy of the antibiotics used in Ramos's meta-analysis. Similarly, a meta-analysis conducted by Zeitler DL<sup>30</sup> & Flotra L et al<sup>31</sup> have concluded that 0.2% chlorhexidine gel, placed in the tooth socket after removal of third molar, can reduce the risk of alveolar osteitis by approximately 72%.

Despite a highly significant reduction of AO after use of antiseptics/antibiotics, the results of this analysis should be interpreted carefully because of the limitations regarding their generalizability. As current research has shown<sup>32-33</sup>, bacterial invasion is not the sole cause of AO. Rather it is a healing disturbance due to disintegration of blood clot at the extraction site and bacterial infection could be one of many factors that lead

to AO<sup>34</sup>. Moreover, the experience of the surgeon and the complexity of the surgery due to angulation of the tooth within the alveolar bone as well as the duration of the treatment also plays an important role for the development of AO.

## CONCLUSION

On the basis of the results presented in this analysis, it is concluded that the prophylactic use of both antiseptic and antibiotics can substantially reduce the risk of AO after extraction of lower third molar. However, these antimicrobial agents are not significantly different from each other regarding the risk-reduction of AO. On the other hand, systemic antibiotics exert more adverse effects than topical antiseptics. So, because of the potential systemic adverse effects and increasing trend of drug resistance towards antibiotics, it is recommended that the topical antiseptics should be considered as viable alternative over systemic antibiotics.

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