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REVIEW ARTICLE

A review of the literature: antibiotic usage and its relevance to the infection in periodontal flaps

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ABSTRACT

Objective: This study aimed to investigate the systemic antibiotic usage in the perioperative period of periodontal flaps and its relevance to the infection after surgeries through reviewing the papers of the last decade.

Materials and methods: A search was conducted for the studies of randomized clinical trials between 2005 and 2014 that reported periodontal flaps in chronic periodontitis patients. Data were extracted and the rate of the systemic antibiotic use, the infection rate after surgeries and the number needed to treat (NNT) to prevent one infected case were calculated. The impact of antibiotic use and materials used in surgeries on the infection was evaluated.

Results: Eighty-three trials were included. Antibiotics were used in 73.7% of the patients and 75.4% of the flaps. Infection occurred in only five flaps where enamel matrix proteins (EMD) or EMD + bone grafts were used in intrabony defects. Only 0.170% of the surgeries got infected in total. When all kinds of surgeries were included for analysis, the infection rate was 0.073% for the surgeries using antibiotics, which was lower than the infection rate 0.693% for the surgeries not using antibiotics ($p < .05$). The infection rate was very low in general. NNT was 203 when all the surgeries were included for analysis. Therefore, the difference of the infection rates between using antibiotics and not might lack clinical significance.

Conclusions: Considering the very low incidence of the infection and the disadvantages of the systemic antibiotic use, we suggest not using systemic antibiotics in the perioperative period of periodontal flaps to prevent infection.

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Introduction

Periodontal surgery is an important periodontal therapy. One of the complications that may occur after surgeries is wound infection. A surgeon may choose to use systemic antibiotics to prevent this complication, which is often empirical. Endocarditis prophylaxis is reasonable for patients with the highest risk of adverse outcomes who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa [1]. For patients without special medical history, it is controversial whether to use systemic antibiotics to prevent wound infection after periodontal surgeries. Some authors thought that the use of systemic antibiotics could reduce pain [2,3] and swelling [3] as well as improve wound healing [3,4]. However, other authors indicated that the use of systemic antibiotics might not help to improve wound healing [5], decrease the infection rate [6–8] and reduce pain [7,9,10], the amount of inflammation [10] and postsurgical swelling [7]. Although some researchers found systemic antibiotics could improve the clinical results of the periodontal surgical procedure such as more attachment gain [11,12], some found that it could not help to get better clinical outcomes beyond that of the surgery alone [7,9,13,14]. We need to be cautious about the use of systemic antibiotics because of the low incidence of the infection after periodontal surgeries [15,16] and the possible risk of the systemic antibiotic use such as induction of bacterial resistance, hypersensitivity or allergic reaction and drug interactions with concomitant medications [17].

Many new materials such as various bone grafts [18], enamel matrix proteins (EMD) [19] and growth factors [20,21] have been used in periodontal surgeries for stimulating periodontal regeneration during the last decade. The application of new materials may influence the decision of surgeons on using systemic antibiotics in perioperative period and may cause changes in the infection rate. This review of the literature aimed to investigate the use of systemic antibiotics in the perioperative period of periodontal flaps and its relevance to the infection after surgeries through reviewing randomized clinical trials (RCTs) about periodontal flaps in chronic periodontitis patients from 2005 to 2014.

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Supplemental data for this article can be accessed here.

Materials and methods

Inclusion and exclusion criteria

We selected RCTs of periodontal surgeries in chronic periodontitis patients published in English from 2005 to 2014. Three sorts of studies were included: (1) studies aiming to compare different periodontal surgeries; (2) studies aiming to investigate the changes of some unconventional indicators such as molecular indicators in periodontal surgeries; (3) studies aiming to explore the effect of systemic antibiotics or other drugs without anti-inflammatory or immunologic effects in periodontal surgeries. Studies were excluded according to the following exclusion criteria: (1) studies that used drugs or materials with antibiotic, anti-inflammatory or immunologic effects except for systemic antibiotics; (2) studies in which laser was used; (3) studies of mucogingival surgeries; (4) studies that included patients who needed endocarditis prophylaxis; (5) studies where the teeth were scheduled for extraction and the tissue of the surgical area was collected for histological evaluation; (6) studies without abstract; (7) studies where we could not get the accurate information we needed such as postoperative care and wound healing.

Search strategy

A search was conducted on electronic databases, without language restrictions: PubMed, EMBASE through Ovid and Cochrane Central Register of Controlled Trials from 1 January 2005 to 31 December 2014. The search was performed with the following strategy: ((((((Pericementitides* [All Fields]) OR Periodontitides* [All Fields]) OR Periodontitis* [All Fields])) AND surgery* [All Fields])) OR 'Periodontitis/surgery' [Mesh]. This was complemented by a hand search of the Journal of Periodontology, Journal of Clinical Periodontology, and Journal of Periodontal Research from January 2005 to December 2014.

Trial selection

Eligibility assessment was performed through the title, abstract and full text. If a trial was described by several reports, the most original report or the one meeting with the criteria was chosen.

Data collection

The primary outcomes were the rate of systemic antibiotic use in the perioperative period of periodontal flaps and the infection rate after surgeries. Following information was collected: (1) trial design and trial duration; (2) defect type; (3) the severity of periodontal disease; (4) materials used in the surgery; (5) antibiotic usage: if there was not any description about antibiotic usage in the perioperative period, we classified it as non-antibiotic treatment; (6) the number of the patients for analysis: it was defined as the number of the patients at the baseline in the report; (7) the number of the flaps: it was defined as the number of the flaps at the baseline in the report; (8) the number of the flaps for calculating the infection rate: it was the same as the number of the flaps except that it was the number of flaps in adverse events analysis when the paper reported it and that a patient was eliminated if the patient was lost in the first two weeks after the surgery; (9) description of the wound healing in the article; (10) the number of the infected surgeries: it was defined as an infected surgery when the EHI (Early Wound-Healing Index [22]) was higher than 3 (partial or complete necrosis of the interproximal tissue) or WHI (wound healing index score [23]) was 3 (poor wound healing with significant gingival edema, erythema, patient discomfort, flap dehiscence, or suppuration) in the first 2 weeks after the surgery if the two indexes were used; a surgery was considered as an infected one according to the description of the papers like significant gingival oedema, erythema or suppuration in the first 2 weeks after the surgery if no indexes were used; (11) location of the trial; (12) inclusion criteria about oral hygiene and oral hygiene before the periodontal surgeries. Aggressive periodontitis patients were eliminated from all the analysis.

Statistics

Data analysis was performed using SPSS 17.0 statistical package (SPSS Inc., Chicago, IL). When the rate of systemic antibiotic use in the perioperative period of periodontal flaps was calculated, studies for exploring the effect of systemic antibiotics in periodontal surgeries were excluded. We used both patient and flap as statistical unit to calculate the rate of systemic antibiotic use in general, in both developing countries and developed countries. The rates of antibiotic use were also calculated in different kinds of defects and surgeries, taking flap as the statistical unit. The type of a surgery was classified according to the type of materials used. These types included bone grafts, barrier membrane, growth factors and EMD. The impact of a country's level of development on the rate of systemic antibiotic use was examined using Fisher's exact test and Pearson's chi-square test. The rate of systemic antibiotic use was calculated as follows:

$$\text{the rate of systemic antibiotic use} = \frac{\text{the number of the patients or the flaps using antibiotics}}{\text{the number of the patients for analysis or the flaps}}$$

The infection rate after surgeries was then calculated in each and every type of surgery and defect. We only used flap as the statistical unit, when we calculated the infection rate. The impact of antibiotic use and materials used in surgeries on the infection rate was examined using Fisher's exact test and Pearson's chi-square test and studies of different designs were analysed separately. The infection rate after surgeries was calculated as follows:

$$\text{the infection rate after surgeries} = \frac{\text{the number of the infected cases}}{\text{the number of the flaps for calculating the infection rate}}$$

The number needed to treat (NNT) with antibiotics to prevent one infected case compared to no antibiotics was

calculated when all kinds of surgeries were included for analysis and it was calculated as follows:

$$\mathrm{NNT} = \frac{1}{\begin{pmatrix}\text{the infection rate when not using antibiotics}\\ -\text{the infection rate when using antibiotics}\end{pmatrix}}$$

The significance level of all the statistical hypothesis testing procedures was preset at $p < .05$.

Results

Study selection and study characteristics

We identified 83 eligible studies. A list of the 111 excluded articles and the reasons for exclusion were shown in Appendix S1. The details of the included studies were shown in Appendix S2 and S3. Among the studies included, there was only one paper that used both parallel group and split-mouth designs [24]. Most papers aimed to compare different periodontal surgeries. There was one paper exploring the use of teriparatide [25] and two papers exploring the effect of systemic antibiotics in the periodontal surgeries [7,26]. Three of the 83 papers aimed to study the changes of unconventional indicators in periodontal surgeries [27–29]. Most of the studies included the patients with acceptable oral hygiene and only one study did not give any information about the oral hygiene of the included patients [30]. Totally, 2421 patients and 2951 surgeries were analysed. The characters of the surgeries included in this study were shown in Appendix S4. According to the main function of each material, we classified the marginal pedicle periosteum [29,31–33] and the human cultured periosteum [34] as barrier membrane and the autogenous periodontal ligament grafts [35] as growth factors.

Analysis of the usage of systemic antibiotics in the periodontal flaps

Most of the studies which used antibiotics chose amoxicillin or doxycyclin but the dosage varied. The details of antibiotic usage in the selected studies were shown in the Appendix S5. For pre-surgical antibiotic usage, amoxicillin was used 1 hour or 1 day pre-operatively or doxycyclin was used 2 h or 1 day pre-operatively. The number of the patients and surgeries using pre-surgical or post-surgical antibiotics was shown in Table 1. When the prevalence of systemic antibiotic use was analysed, two reports [7,26] were excluded because they aimed to explore the effect of systemic antibiotics in periodontal surgeries, thus leaving 99 cases unanalysed in the following statement. In general, 73.7% of patients and 75.4% of surgeries used systemic antibiotics in the perioperative period of the periodontal flaps (Table 1). The rates of systemic antibiotic use in different kinds of defects and surgeries were calculated (Tables 2 and 3). The rates of systemic antibiotic use in developed and developing countries were shown in Table 4. Most surgeons from both developing and developed countries chose to use antibiotics. The rate of antibiotic use was lower in developed countries compared with developing countries, whether a patient or a flap was used as the statistical unit ($p < .001$).

Table 1. The use of systemic antibiotics.

Statistics unit	Antibiotics[a]			Antibiotics[b]		
	N (rate %)	*Y* (rate %)	Total	Pre-surgical	Post-surgical	Total
Patient	610 (26.3)	1712 (73.7)	2322	147	1622	1769
Flap	703 (24.6)	2149 (75.4)	2852	171	2035	2206

N=not using antibiotics; *Y*=using antibiotics.
[a]Two reports which aimed to explore the effect of systemic antibiotics in periodontal surgeries were excluded.
[b]Two reports which aimed to explore the effect of systemic antibiotics in periodontal surgeries were included.

Table 2. The use of systemic antibiotics in different kinds of defects.

Defect	Antibiotics		Total
	N (rate %)	*Y* (rate %)	
Furcation defect	51 (24.9)	154 (75.1)	205
Intrabony defect	580 (33.0)	1945 (77.0)	2525
Supra-alveolar-type defect	0 (0)	50 (100)	50
Deep pocket	72 (100)	0 (0)	72

N=not using antibiotics; *Y*=using antibiotics.

Table 3. The use of systemic antibiotics in different kinds of surgeries.

Surgeries	Antibiotics		Total
	N (rate %)	*Y* (rate %)	
Open flap debridement	274 (40.1)	409 (59.9)	683
Bone grafts	121 (19.2)	508 (80.8)	629
Barrier membrane	52 (24.4)	161 (75.6)	213
Growth factors	0 (0)	90 (100)	90
EMD	126 (42.7)	169 (57.3)	295
EMD + bone grafts	73 (30.7)	165 (69.3)	238
EMD + barrier membrane	9 (100)	0 (0)	9
Bone grafts + barrier membrane	45 (16.2)	232 (83.8)	277
Bone grafts + growth factors	12 (4.4)	262 (95.6)	274
Bone grafts + barrier membrane + growth factors	0 (0)	131 (100)	131
EMD + bone grafts + growth factors	0 (0)	13 (100)	13

N=not using antibiotics; *Y*=using antibiotics.

Table 4. Systemic antibiotic use in developed and developing countries.

Statistical unit	Developed countries		Developing countries		Significance of Difference
	N (rate %)	*Y* (rate %)	*N* (rate %)	*Y* (rate %)	
Patient	542 (34.0)	1054 (66.0)	68 (9.4)	658 (90.6)	$p < .001$[a]
Flap	579 (32.7)	1192 (67.3)	124 (11.5)	957 (88.5)	$p < .001$[a]

N=not using antibiotics; *Y*= using antibiotics.
[a]Pearson's chi-square test.

Analysis of the infection after the periodontal surgeries

Two surgeries using bone grafts and two surgeries using both bone grafts and growth factors were not included in the infection analysis because their records in the paper's adverse events analysis were not found, although their records at the baseline was obtainable [36]. Infection occurred in five surgeries and the wound healing was evaluated by EHI. For these five infected surgeries, three cases from one report used EMD in intrabony defects. Among the three cases, one case used systemic antibiotics post-surgically and two did not use antibiotics [26]. In another report [37],

Table 5. The impact of systemic antibiotic use on the infection rate.

	Both designs		Parallel-group design		Split–mouth design	
Surgery type	*Y*	*N*	*Y*	*N*	*Y*	*N*
All surgeries	1/2202 (0.045)	4/745 (0.537)	1/1362 (0.073)[a]	4/577 (0.693)[a]	0/840 (0)	0/168 (0)
EMD in intrabony defects	1/196 (0.510)	2/153 (1.307)	1/147 (0.680)	2/121 (1.653)	0/49 (0)	0/32 (0)
EMD + bone grafts in intrabony defects	0/165 (0)	2/73 (2.740)	0/131 (0)	2/73 (2.740)	0/34 (0)	0/0 (0)

N=not using antibiotics; *Y*=using antibiotics.
Each unit showed the number of the infected cases/the number of the total procedures (infection rate %).
[a]Results of Fisher's exact test: there is a significant difference of the infection rates between the surgeries using antibiotics and not.

two cases using EMD + bone grafts in intrabony defects had post-surgical infection without antibiotics used during the treatment.

When the parallel-group design studies were analysed, 0.258% of the surgeries got infected. There was no infected case in the studies of the split-mouth design. When the studies of both designs were included, 0.170% of the surgeries got infected. Since the infected cases did not occur in the studies of the split-mouth design, the impact of antibiotic use and materials on the infection was analysed in the studies of parallel-group design. When all kinds of surgeries were included for analysis, the infection rate for the cases using antibiotics was lower than the cases not using antibiotics ($p = .03$). Noticing that all the five infected cases occurred in the surgeries using EMD or EMD + bone grafts in intrabony defects, we investigated the impact of systemic antibiotics on the infection rate of these specific kinds of surgeries. The infection rate for the cases using antibiotics was lower, but the difference was not statistically significant (Table 5). The number needed to treat to prevent one infected case was 203 when all kinds of surgeries of both designs were included for analysis and this number was 161 when all kinds of surgeries of parallel-group design were included.

As for the impact of materials used in surgeries on the infection, the difference of the infection rates between different types of surgeries was not statistically significant ($p = .093$) (Appendix S6).

Discussion

A search was conducted for RCTs about periodontal flaps from 2005 to 2014. When the rate of systemic antibiotic use was calculated, studies which aimed to explore the effect of antibiotics had to be excluded because these studies were supposed to use antibiotics in one group and not in the other. Therefore, it was not suitable to include these studies if we wanted to investigate the true prevalence of antibiotic use.

A total of 147 patients were prescribed antibiotics preoperatively for. All these patients were systemically healthy and did not need to use antibiotics preoperatively for special medical history. None of them got postsurgical infection. The reason for using antibiotics preoperatively might be to ensure the adequate concentration of antibiotics in the periodontal tissue to inhibit or eliminate bacteria during the surgeries.

About 73.7% of patients and 75.4% of surgeries used systemic antibiotics in the perioperative period of the periodontal flaps, which indicates that most surgeons may prefer to use antibiotics. Interestingly, the rates for systemic antibiotic use differed between the developing and developed countries. The rate turned out to be lower in developed countries, indicating that antibiotics are less likely to be chosen by surgeons in those countries. This result is consistent with the increasing antibiotic consumption in the developing countries. An analysis of national pharmaceutical sales data showed that antibiotic consumption increased substantially (36% increase between 2000 and 2010), mainly in developing countries. Antibiotic consumption was stable or had moderately decreased in high-income countries between 2000 and 2010 except Australia and New Zealand [38]. This increase in antibiotic consumption is driven by economic growth and prosperity, particularly in Asia and Latin American countries [39]. Inappropriate knowledge on use of antibiotics, poor modelling by seniors, economic incentives and fear of poor clinical outcomes could play a role in the overuse of antibiotics [40].

On the whole, the infection rate was low in this study. When the studies of both designs were included, only 0.170% of the surgeries got post-surgical infection. The results were consistent with two previous studies. In the study of Checchi et al. [15], 231 patients and 498 surgical procedures were reviewed and the infection rate was 4.2% overall. In another retrospective study of Powell et al. [16], 395 patients and 1053 fully documented surgical procedures were included and the overall prevalence of the surgical infection was 2.09%. The infection rate in this study was lower than those in the two previous studies. It might result from more stringent asepsis over the decades [41]. What should be paid attention to is that the infected cases found in the two papers were all evaluated by EHI and EHI was used for evaluation only in these two papers in this study, which means that other papers with no infected cases evaluated the wound healing by other standards or just the author's experience. It is possible that this phenomenon is not related to EHI. It is also possible that EHI might make the authors pay more attention to some details that could be easily neglected. It means that most studies included in this study did not use a systematic recording and it is a disadvantage that should be improved in the future. In this study, the descriptions of the wound healing were believed to be all true and recorded by authors after evaluation in full. We strongly suggest the clinicians evaluate the postsurgical infection by some established standards in the future.

In the study of Checchi et al. [15], 4.4% of cases using tetracycline in surgical procedures reported infection, while

the rate was 3.8% in the group not using tetracycline. Statistical comparison showed no difference between the two groups. In the study of Powell et al. [16], 2.85% of the surgeries where antibiotics were used (pre- and/or post-surgically) resulted in signs of infection, while 1.81% of the surgeries where antibiotics were not used resulted in signs of infection. However, the difference was still not statistically significant. This study found that when analysing surgeries with EMD or EMD + bone grafts in intrabony defects, cases using systemic antibiotics had a lower infection rate and the difference was not statistically significant. When we added surgeries using all other materials into the analysis of infection and analysed the surgeries using all kinds of materials, the infection rate of antibiotic group remained lower, but the difference turned out to be statistically significant. Nevertheless, we believe this result can not indicate the necessity of antibiotic use for infection control. The infection rate remained to be low whether systemic antibiotics were used or not, indicating that the difference may lack clinical significance. Additionally, we notice that there were no infected cases reported in the added surgeries of other types, and most of them used antibiotics. For this reason, the non-infected group using antibiotics tended to be much larger, and the infection rate of the antibiotic group became much lower. Therefore, the difference was more likely to be statistically significant.

Considering that many studies included used various kinds of materias in the surgeries, we investigated the impact of materials on the infection. There were no infected cases in the studies of the split-mouth design and the difference of the infection rates between different surgery types was not statistically significant when the studies of the parallel-group design were analysed. Hence, there might be no relationship between the postsurgical infection and the materials used in surgeries.

The side effects of taking systemic antimicrobials range from common mild and short-lasting disturbances of physiology to the rare, but sometimes life-threatening reactions. For example, the most common adverse reactions for amoxicillin are diarrhoea, rash, vomiting and nausea and some rare but life-threatening reactions like toxic epidermal necrolysis and Stevens–Johnson syndrome can happen as well. More importantly, antimicrobial resistance has become a global threat and can have important consequence of human health such as threatening improvements made in child survival and higher economic burden of infectious disease [42]. In 2015, a global action planning to tackle growing antimicrobial resistance was endorsed at WHO's annual meeting in Geneva. Optimizing the use of antimicrobial medicines was one of the objects. The rational use of antimicrobials should always be kept in mind. Herrera et al. [43] pointed out that surgeons might use systemic antibiotics in the regenerative periodontal surgery to prevent post-operative complications when a foreign body was placed inside the periodontium and improve the regenerative outcomes by reducing bacterial contamination. However, the evidence did not seem to be convincing. In this study, we found that 73.7% of patients and 75.4% of surgeries received systemic antibiotics in the perioperative period of the periodontal flaps although the infection rate was very low whether antibiotics were used or not and the number needed to treat to prevent one infected case was very high. Considering the low infection rate, the potential risk of antimicrobial resistance and other disadvantages of systemic antibiotics use, we do not suggest surgeons to use systemic antibiotics in the perioperative period of the periodontal flaps to prevent infection for patients without special medical history.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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