



Comparison of cefixime and amoxicillin plus metronidazole in the treatment of chronic periodontitis

Poređenje cefiksima i kombinacije amoksicilina sa metronidazolom u lečenju parodontopatije

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Abstract

Background/Aim. Despite significant advances in current medicine and improvement of overall health education, chronic periodontitis is still a widespread disease. Losing teeth is the most serious complication of this particular illness. The aim of this study was to examine patients with chronic periodontitis in order to evaluate the efficacy of non-surgical therapy and combination of amoxicillin and metronidazole compared with cefixime, which has not been so far used for the treatment of this disease. **Methods.** Adult patients with chronic periodontitis ($n = 90$) underwent non-surgical periodontal treatment (zero-day) and then randomly divided into three groups. The group I served as a control, the group II was additionally treated with the combination of amoxicillin and metronidazole (for 7 days), while the group III was treated with cefixime (also for 7 days). To assess the condition of periodontium before and seven days after the therapy, four clinical parameters were used: gingival index (GI), bleeding on probing (BOP), probing depth (PD) and clinical attachment level (CAL). **Results.** On the day 7 after the beginning of the therapy, we found that all the three

groups of patients had statistically significant clinical improvement of three parameters: GI, BOP and PD, but not of the CAL. However, the improvement of PD was only statistically, but not clinically significant. The improvement in the control group of patients on the day 7 was 19% in BOP and 28% in GI; this improvement was statistically highly significant after the addition of amoxicillin plus metronidazole (71% in BOP and 77% in GI) or cefixime (62% in BOP and 82% in GI). Compared to the combination of amoxicillin and metronidazole, cefixime was statistically significantly more effective for GI ($p < 0.05$), while for the other three clinical parameters their effects were equal. **Conclusion.** The conjunction of amoxicillin plus metronidazole or cefixime to the causal treatment of patients with chronic periodontitis led to statistically significant improvement in efficacy in relation to GI and BOP parameters, while cefixime was statistically significantly more efficient than the combination of amoxicillin and metronidazole for GI.

Key words:

periodontal diseases; cephalosporins; amoxicillin; metronidazole; treatment outcome.

Apstrakt

Uvod/Cilj. I pored značajnog napretka u savremenoj medicini i poboljšanja opšteg zdravstvenog obrazovanja, parodontopatija je još uvek veoma rasprostranjena. Gubitak zuba je najteža komplikacija ovog oboljenja. Cilj našeg rada bio je da kod bolesnika sa parodontopatijom ispitamo efikasnost kauzalne terapije i kombinacije amoksicilina i metronidazola u poređenju sa cefiksimom, koji do sada nije primenjivan kod te kategorije bolesnika. **Metode.** Odrasli bolesnici sa hroničnom parodontopatijom ($n = 90$) prvo su podvrgnuti kauzalnoj terapiji (nulti dan), a zatim randomizacijom podeljeni u tri jednake grupe. Prva grupa bila je kontrolna, druga grupa dodatno je lečena kombinacijom amoksicilina i metronidazola (AMO-MET) tokom 7 dana, a treća grupa bolesnika cefiksimom, takođe, tokom 7 dana. Za procenu stanja pa-

rodoncijuma na početku lečenja i sedam dana kasnije, primenjena su četiri klinička parametra: gingivalni indeks (*gingival index* – GI), indeks krvarenja gingive (*bleeding on probing* – BOP), dubina parodontalnih džepova (*probing depth* – PD) i nivo pripojnog epitela (*clinical attachment level* – CAL). **Rezultati.** Sedmog dana od početka terapije ustanovljeno je da je kod sve tri grupe bolesnika došlo do statistički visokoznačajnog poboljšanja kliničkog stanja procenjenog parametrima GI, BOP i PD ($p < 0,001$), ali ne i parametrom CAL. Međutim, to poboljšanje PD kod sve tri grupe bolesnika bilo je samo od statističkog, ali ne i kliničkog značaja. Posle kauzalne terapije, poboljšanja GI i BOP sedmog dana u odnosu na nulti dan iznosila su 28% i 19%, a nakon primene AMO-MET 71% (BOP) i 77% (GI), odnosno 62% (BOP) i 82% (IG) posle primene cefiksima, što je bilo statistički visokoznačajno bolje u odnosu na kauzalnu terapiju (u oba slučaja $p <$

0,001). Poređeni međusobno, cefiksima je u odnosu na kombinaciju amoksicilina i metronidazola bio statistički značajno efikasniji za GI ($p < 0,05$). **Zaključak.** Dodatna primena amoksicilina u kombinaciji sa metronidazolom ili cefiksima kauzalnoj terapiji kod bolesnika sa parodontopatijom dovela je do statistički visoko značajnog poboljšanja parametara GI i BOP, dok je cefiksima

bio statistički značajno efikasniji od kombinacije amoksicilina i metronidazola u odnosu na parametar GI.

Ključne reči:

periodontalne bolesti; cefalosporini; amoksicilin; metronidazol; lečenje, ishod.

Introduction

Periodontitis is a severe illness with clinical features manifesting in gingival inflammation, gum recession, formation of periodontal pockets with corresponding pathological content and appearance of subgingival concretions, teeth loosening and pathological teeth migration. Untimely treated, periodontitis leads to teeth loss as the major complication of the illness¹.

Formerly, periodontitis was predominantly the illness of the elderly. However, in the past few decades, there has been an increase in the number of diseased children and adolescents². The main etiological cause of periodontitis is bacterial infection. Until the introduction of antibiotics, the therapy was only based on scaling and root planning. Afterwards, a widespread use of antibiotics has begun in dentistry, too. In the meantime the range of used antibiotics has been most commonly reduced to the combination of amoxicillin (AMO), broad spectrum antibiotic, and narrow spectrum metronidazole (MET) acting on anaerobes as the main co-causative agents of the infection.

Related to antibiotic therapy, Zandbergen et al.³ stated that the efficacy of AMO-MET combination with and without non-surgical periodontal treatment was the topic of examination in 526 publications. Their statement is in accordance with meta-analysis data of Villagrana et al.⁴ and Sgolastra et al.⁵, as well as with recent systematic review of Kolakovic et al.⁶. According to them, combination of these two antibiotics has significantly improved the efficacy of non-surgical periodontal treatment proclaimed as "gold standard". Nevertheless, according to a systematic review and meta-analysis, Sgolastra et al.⁵ are of the opinion that additional studies are needed to confirm these results.

As a representative of the third generation of cephalosporins – cefixime (CEF), which is an antibiotic with wide spectrum of effect on Gram-positive and Gram-negative bacteria, was used in cases of oral infections^{7,8}, but not in the treatment of periodontitis. In studies *in vitro* on 178 bacterial strains isolated from 74 patients with pyogenic infections of odontogenic origin, some strain isolates were fairly susceptible, with CEF MIC ranging from 8 to 16 µg/mL. Therefore, the aim of our study was to examine the efficacy of CEF in comparison with AMO-MET as the most common combination of antibiotics, and in both cases after the conduction of non-surgical therapy.

Methods

The clinical study was conducted at the Department of Periodontology, Clinic for Dentistry of the Military Medical Academy in Belgrade. It involved 90 patients with the pro-

gressed form of periodontitis (35 females and 55 males, the mean age 49.3 years). Criteria for including patients in the study entailed newly, previously untreated and systemic healthy patients, selected on the basis of clinical inspection, whereby a prerequisite was to have at least 23 natural teeth, four of which were first molars and each of the examinees had minimally three teeth in each quadrant, with periodontal pocket depth of 5 mm and larger and also gingival bleeding after periodontal probing.

All the participants underwent a clinical examination of the oral cavity as well as periodontal examination. Adequate clinical and anamnestic data were taken for all the participants and also personal data, general medical and dental anamnesis. All the patients first underwent non-surgical periodontal treatment (day zero) and then they were randomly divided into three equal groups. The first group served as a control, the second one was additionally treated by the combination of AMO and MET, and the third one by CEF.

In order to assess the condition of periodontium, we used the level of gingival inflammation which is expressed through gingival index (GI) according to Löe and Silness⁹, bleeding on probe (BOP), according to Mühlemann and Son¹⁰, probing depth (PD) and clinical attachment level (CAL). As a part of periodontal examination, we performed measuring on all permanent teeth. Measurement was done by the graduated periodontal probe (CPITN:US, WILLIAMS; Pro-Dentec, Batesville, Ark) by the routine method. All listed clinical parameters were noted at the beginning as well as seven days after the treatment.

AMO (500 mg) and MET (400 mg) were given perorally, three times a day, and CEF (400 mg) perorally, once a day. Antibiotics were administered over a period of seven days and immediately after the causal treatments of periodontium had been performed. The patients were advised to observe any adverse reaction during the use of antibiotics. All three antibiotics are registered in Serbia in the form of oral use⁸.

Statistical analysis was performed by Student's *t*-test for differences between the groups, with statistically significant results for $p < 0.05$.

Results

The results of the study are shown in Table 1 and Figure 1.

Table 1 shows that the values of three (GI, BOP and PD) out of four examined clinical parameters were statistically significantly improved on the seventh day since the beginning of non-surgical therapy. Nevertheless, the fourth clinical parameter (CAL) showed only negligible improvement after seven days and it did not reach statistical significance in relation to the control value.

Table 1

The influence of the type of treatment on clinical periodontal parameters				
Groups (before/after) treatment	GI	BOP	PPD	CAL
	$\bar{x} \pm SD$			
Control				
Day 0	1.950 ± 0.437	0.850 ± 0.140	4.296 ± 0.179	3.607 ± 0.918
Day 7	1.408 ± 0.502	0.616 ± 0.260	4.290 ± 0.174	3.389 ± 1.171
p_1	< 0.001	< 0.001	< 0.001	n.s.
AMO-MET				
Day 0	1.783 ± 0.618	0.750 ± 0.254	4.269 ± 0.162	3.579 ± 1.128
Day 7	0.525 ± 0.427	0.175 ± 0.209	4.241 ± 0.153	3.201 ± 1.013
p_1	< 0.001	< 0.001	< 0.001	n.s.
p_2	< 0.001	< 0.001	n.s.	n.s.
Cefixime				
Day 0	1.700 ± 0.680	0.816 ± 0.404	4.309 ± 0.125	3.543 ± 0.992
Day 7	0.316 ± 0.346	0.133 ± 0.182	4.268 ± 0.175	3.199 ± 1.115
p_1	< 0.001	< 0.001	< 0.001	n.s.
p_2	< 0.001	< 0.001	n.s.	n.s.
p_3	< 0.05	n.s.	n.s.	n.s.

p_1 – significance within the groups before and after the treatment; p_2 – significance between the antibiotics and control group after treatment; p_3 – significance between the antibiotics groups after the treatment; GI – gingival index; BOP – bleeding on probing; PD – probing depth; CAL – clinical attachment level; AMO-MET – amoxicillin-metronidazole.

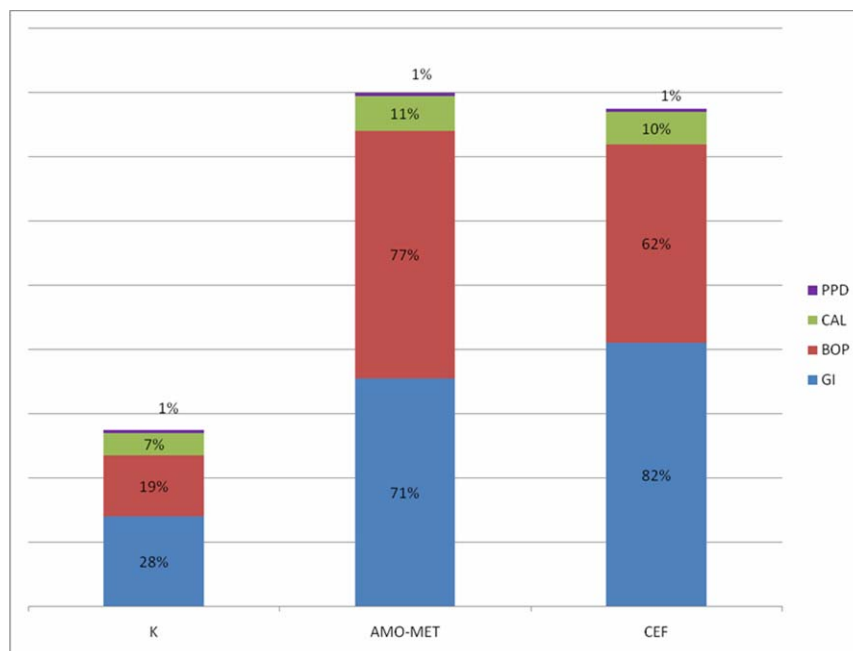


Fig. 1 – The percentage of relative values of clinical parameters improvement based on the results shown in Table 1 at the end of the treatment (Day 7) in relation to the initial values (Day 0) taken as 0%.

Each column represents one of the three tested groups. The values of the tested parameters at day 0 were represented as 0%, and those of day 7 were calculated as the increase of the corresponding percentage for each of the four tested clinical parameters shown in Figure 1.

PPD – periodontal probing depth; CAL – clinical attachment level; BOP – bleeding on probing; GI – gingival index.

When antibiotics AMO-MET or CEF were added to non-surgical therapy, the treatment results of GI and BOP showed statistically significantly higher improvement compared to the control values on the zero day. Simultaneously, concerning two other clinical parameters, there was a statistically significant improvement in the PD, but not in the CAL. On the other hand, when the effects of the antibiotics were compared to the values of the control group on the day zero (P_2), then a statistically significant improvement was registered only in values of GI and BOP. However, contrary to the administration of antibiotics, differences of

other two indexes (PD) and (CAL) were not statistically significant compared to their control values on the day zero. Comparing the results between the two groups of antibiotics (P_3), it was found that CEF was statistically significantly more efficient than the combination of AMO and MET for GI. The other three parameters (BOP, PD, CAL) were not statistically significantly different comparing two antibiotic regimes.

Figure 1 shows that in respect of the periodontal pocket depth in the control group of patients there was practically no relative improvement (1%); a relatively better improvement

was registered in CAL (7%), and the best improvement was noted in BOP (19.9%) and GI (28%).

In the group of patients treated with AMO-MET combination, there was practically no relative improvement in PD (1%). A somewhat greater improvement was registered in CAL (11%), while the improvements in GI and BOP were statistically significant (71% and 77% respectively).

In the group of patients treated with CEF, there was practically no improvement regarding the periodontal pocket depth (1%), while it was somewhat higher in CAL (10%). Unlike those clinical parameters, there was a statistically significant improvement in clinical condition of GI (82%) and BOP (62%).

Reported side-effects were rare, mild and transient in nature. They mainly manifested as nausea, dizziness and/or anorexia and appeared in both groups of patients treated with antibiotics.

Discussion

The results of our study show that administration of AMO-MET or CEF statistically highly significantly improve the efficacy of non-surgical therapy concerning GI and POB, while all the three types of treatment are practically ineffective concerning PD and CAL. Furthermore, CEF is significantly more efficient than AMO-MET concerning GI. Since each of the three patient groups represented separate entities, the discussion is accordingly divided in that way.

Non-surgical therapy

Although non-surgical therapy was introduced long ago, it still represents the basis of periodontitis treatment¹¹. This kind of therapy removes biofilm (dental plaque), supragingival and subgingival concretions, which are the source of infection and the cause of illness, cures periodontal pockets and removes all factors that contribute piling plaque and decreases the overall resistance of bacteria¹.

From that point of view, the results of our study show that non-surgical therapy effectively improves GI and POB, has slight significance on PD and is practically ineffective concerning CAL. Our results are in accordance with the majority of authors who have also show that, seven days after the beginning of non-surgical therapy, a significant improvement in clinical condition in the values of GI and POB is achieved¹²⁻¹⁴. Furthermore, hitherto clinical experiences also show that the improvement in clinical condition in PD and in CAL, after three, six and twelve months also ensued¹⁵⁻¹⁹. We did not follow-up our patients longer than seven days as, according to our previous experience, after the improvement of clinical condition, they rarely regularly return for control examinations, making thus maintaining the initial number of patients in the formed groups difficult.

However, with non-surgical therapy it is impossible to remove all bacteria deposits. For example bacteria from deep unapproachable periodontal pockets or microorganisms from other areas of oral cavity, which are beyond the scope of non-surgical therapy, make results of this therapy to be unpredictable and dependent upon many different factors²⁰.

AMO-MET

At first, antibiotics were administered as monotherapy which was not enough effective due to the existence of mixed aerobic-anaerobic flora⁷. For this reason, a dual therapy consisting of AMO-MET was introduced. At the same time, this combination is considered to be the "golden standard" of antibiotic therapy¹⁶.

The results of our study show that the combination of AMO-MET has statistically significantly improved clinical efficacy of non-surgical therapy concerning two indexes (GI, BOP), but not the two others (PD, CAL). Our results are in accordance with the findings of other authors^{5, 6, 21}, as well as meta-analyses^{4, 22}. However, the mentioned benefit of AMO-MET treatment has to be balanced against their possible adverse reactions^{23, 24}.

CEF

Our results with CEF show significant improvement of non-surgical periodontal treatment in values of two clinical parameters (GI, BOP), while for the other two parameters (PD, CAL) it was practically ineffective.

CEF belongs to the third generation of cephalosporins with a broad spectrum of antibacterial activity. So far, it was studied only *in vitro* in relation to bacterial strains isolated from patients with pyogenic infections of odontogenic origin²⁵, but not in patients with periodontitis. CEF significantly improved the clinical condition of GI and in this respect was statistically significantly more effective than the AMO-MET combination. According to the data from Eusterman⁷, CEF is very effective against many oral infections. CEF also has several advantages over AMO-MET combination like: taking only one antibiotic instead of two, its dosage is much more comfortable (once instead of three times a day), and it could be more tolerant than the AMO-MET combination.

That is why we consider that whenever additional antibiotic therapy is needed in non-surgical therapy CEF might be useful alternative. Certainly, it should be pointed out that for definitive attitude, clinical experience with CEF on larger number of patients is needed.

Conclusion

Co-administration of amoxicilline plus metronidazole or cefixime in adult patients with periodontal disease significantly increases therapeutic effect of causal therapy concerning gingival bleeding and bleeding on probing indexes, but not probing depth and clinical attachment level. Between the two groups of antibiotics, the improvement of gingival index was significantly better in the group of patients treated with cefixime. Side effects of antibiotics were rare, mild and transient by nature.

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