Influence of Local Application of Immunomodulator Cycloferon on the Clinical Course of Chronic Odontogenic Maxillary Sinusitis

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Abstract: 94 subjects aged from 23 to 54 years with diagnosis of "Chronic odontogenic maxillary sinusitis, oro-antral fistula" were under the supervision in the period from 2008 to 2013. During the comprehensive treatment of these patients clinical and immunological parameters were analyzed as well as the effectiveness of local immunotherapy by cycloferon. Based on the obtained results it was concluded that signs of adverse clinical course and outcome of the disease were detected in patients suffering from chronic odontogenic maxillary sinusitis for more than two months. It was concluded that adding cycloferon to conventional treatment makes postoperative course of chronic odontogenic maxillary sinusitis more favorable in comparison with a control group of patients. The most pronounced positive effect of cycloferon can be observed in patients with lingering course of chronic process, while its effectiveness is lower in patients with continuous course that raises the prospect of finding more adequate and more effective immunotherapy in this pathology.

Key words: Sinusitis • Cycloferon • Chronic • Odontogenic • Maxillary Sinusitis • Neutrophil Traps • Phagocytic Number

INTRODUCTION

Urgency of the Problem: A new conception of odontogenic pathogenesis of inflammation has developed in recent years [1-7]. Previously most researchers have associated the severity of inflammatory diseases of maxillofacial area with etiological factor of the disease-change in the spectrum of microflora, variability of its pathogenic properties, appearance of antibiotic-resistant strains of microorganisms. However today pathogenic mechanisms of odontogenic inflammatory process, namely a nonspecific immunological reactivity [8-11] play a leading role. Everyone is familiar with the fact that the presence of fistula between oral cavity and maxillary sinus leads to persistent contamination of sinus by oral microflora and its derivatives. This in turn affects the parameters of mucosal immunity, creating disadvantaged conditions for surgery-maxillary sinusotomy with fistula plasty. Although there are many existing ways of surgical closing of oro-antral fistula and development of new conservative techniques, the relapse rate in the last decade was in the range from 4% to 27% [3, 4, 10, 12]. It is logical to conclude that the longer the oro-antral fistula will present, the more doubtful the prognosis for treatment of odontogenic maxillary sinusitis will be.

Purpose: To evaluate the clinical and immunological effectiveness of topical application of cycloferon as a part of the comprehensive treatment and its impact on local immunity in patients with chronic odontogenic maxillary sinusitis.

MATERIALS AND METHODS

94 people aged from 23 to 54 years who were treated in the period from 2008 to 2013 in the Department of Maxillofacial Surgery of State Budget Healthcare Institution "Regional Clinical Hospital No. 1" of Chelyabinsk with the following diagnosis: "Chronic odontogenic maxillary sinusitis, oro-antral fistula". An average age of patients was 34 years (28; 52, 75) years. Among the subjects of the study there were
51 women (54.2%) and 43 men (45.8%). Patients were divided into two groups (base group (n = 45), the comparison group (n = 49), each of which was divided into two subgroups depending on the duration of the disease: lingering course (up to 2 months) and continual course (from 2 months or more) [8, 9]. The control group included 14 clinically healthy individuals having comparable gender and age characteristics who agreed with sampling of the biological material. All patients underwent surgical treatment - maxillary sinusotomy with plasty of oro-antral fistula (sinusotomy by Konduell-Luc) as well as comprehensive conservative treatment: preoperative antibiotic prophylaxis, nonsteroidal anti-inflammatory drugs, use of vasopressors in the nasal course of the disease, on the 5th day [4, 5] in patients from the comparison group. In patient with continual process there were no reliable differences-disappearance of swelling was observed on the 4th [3, 5] and the 5th [4, 5] day respectively. On the 4th [3, 4] day in patients with lingering course of the disease that received cycloferon it was noted disappearance of hyperemia and edema of the mucous membrane in the area of the wound edges, whereas in patients from a comparison group these signs decreased on the 5th [5, 6] day. Similar rates were found in patients with continual course of the disease-in the test group edema and hyperemia of the wound eliminated significantly faster than in the comparison group of patients: after the 5th [4, 6] and the 7th [6, 7] day respectively. Absence of exudation from the nasal cavity in patients from the test group was observed on the 3rd [2, 3] day in those with lingering course of the disease, on the 4th [3, 4] day in those with continual course and in patients with traditional topical treatment-on the 6th [5, 7] and the 7th [6, 8] day of the disease. In patients that didn’t receive local immunotherapy suture line disruption was also taken into account as well as appearance of an infiltration. Collecting specimens for the study of mucosal immunity of maxillary sinus was performed on the 2nd day (on admission to the clinic), 6th and 12th days of post-operative treatment. On admission the contents of the sinus was collected via the oro-antral fistula, in the postoperative period-through the fistula in the lower nasal meatus. In the control group biopsy specimens were collected in the area of middle nasal meatus [8]. We studied neutrophil functional activity in the maxillary area (activity and intensity of phagocytosis, phagocytic number) followed by determination of neutrophil extracellular traps (NETs) (%) - neutrophil traps containing bacterial cells calculated from 100 net-like structures [7, 13, 14, 15].

Data processed by the methods of variation statistics was expressed as median and percentiles (M [Q1; Q2]), where n is the number of cases in the sample. Statistical significance was assessed by nonparametric Wilcoxon and Mann-Whitney criteria. Statistical differences were considered significant at p < 0.05. Results of the study were processed by a PC using the software package «BioStat».

RESULTS AND DISCUSSION

In patients who underwent local immunotherapy by cycloferon the disappearance of swelling of soft tissues of the face was observed significantly earlier than in those who was on traditional local treatment: on the 3rd day [2, 3] in patients from the test group with the lingering course of the disease, on the 5th day [4, 5] in patients from the comparison group. In patient with continual process there were no reliable differences-disappearance of swelling was observed on the 4th [3, 5] and the 5th [4, 5] day respectively. On the 4th [3, 4] day in patients with lingering course of the disease that received cycloferon it was noted disappearance of hyperemia and edema of the mucous membrane in the area of the wound edges, whereas in patients from a comparison group these signs decreased on the 5th [5, 6] day. Similar rates were found in patients with continual course of the disease-in the test group edema and hyperemia of the wound eliminated significantly faster than in the comparison group of patients: after the 5th [4, 6] and the 7th [6, 7] day respectively. Absence of exudation from the nasal cavity in patients from the test group was observed on the 3rd [2, 3] day in those with lingering course of the disease, on the 4th [3, 4] day in those with continual course and in patients with traditional topical treatment-on the 6th [5, 7] and the 7th [6, 8] day of the disease. In patients that didn’t receive local immunotherapy suture line disruption was observed on the 5th [4, 5] day of postoperative period associated with recurrent of oro-antral fistula (in 2 patients of the test group with lingering course of the disease (6%) and in 5 patients (23%) with continual course). In the group of patients treated with cycloferon no adverse reactions and inflammatory complications have been identified-their wounds were healed on the 10th [9, 12] day by first intention.

In the studies of local immunity (Table 1) a statistically considerable increase in phagocytic number was showed for the patients of the test group, while in the comparison group this parameter remained almost unchanged throughout the treatment. It is known that the intensity of neutrophil reactions is reduced by restimulation, so "hyperstimulation" of neutrophils by microorganisms of the maxillary sinus and their metabolic products may cause reducing of their reactivity [13, 16].
Table 1: Parameters of mucosal immunity in patients with chronic odontogenic maxillary sinusitis being on the comprehensive treatment

<table>
<thead>
<tr>
<th></th>
<th>Comparison group (n=49)</th>
<th>Test group (n=45)</th>
<th>Control (n=14)</th>
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<tbody>
<tr>
<td></td>
<td>Lingerer course (n=26)</td>
<td>Continual course (n=23)</td>
<td>Lingerer course (n=24)</td>
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<tr>
<td>Local immunity</td>
<td>Day 2</td>
<td>Day 6</td>
<td>Day 12</td>
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<tr>
<td>RCN, %</td>
<td>66,5</td>
<td>64,5</td>
<td>62.8</td>
</tr>
<tr>
<td></td>
<td>[65; 68]</td>
<td>[63; 67]</td>
<td>[61; 67]</td>
</tr>
<tr>
<td>PN, %</td>
<td>1,9</td>
<td>2,3</td>
<td>2,3</td>
</tr>
<tr>
<td></td>
<td>[1,2; 2,7]</td>
<td>[1,5; 2,8]</td>
<td>[1,8; 3]</td>
</tr>
<tr>
<td>PA, %</td>
<td>48</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>[25; 51]</td>
<td>[34; 51]</td>
<td>[32; 52]</td>
</tr>
<tr>
<td>IP, c. u.</td>
<td>0,94</td>
<td>1,1</td>
<td>1,19</td>
</tr>
<tr>
<td></td>
<td>[0,44; 1,87]</td>
<td>[0,78;1,56]</td>
<td>[0,7; 1,74]</td>
</tr>
<tr>
<td>NETs,%</td>
<td>29</td>
<td>27,5</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>[13,25;35]</td>
<td>[22,5; 37]</td>
<td>[20,34]</td>
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Note: RCN - relative content of neutrophilic granulocytes, PN - phagocytic number of neutrophilic granulocytes, PA - phagocytic activity, IP - intensity of phagocytosis, NETs - neutrophil extracellular traps; * - statistically considerable differences between test and control group of patients; # - statistically considerable differences between groups (time of treatment and type of course); ^ - statistically considerable differences on the 2nd and the 6th day of treatment in the group; ^ ^ - statistically considerable differences on the 2nd and 12th day of treatment in the group.

Initially low levels of phagocytosis activity in patients of the comparison group tended to decrease during treatment. The most considerable decrease was observed in patients with continual course of the disease. Such dynamics of this parameter is particularly unfavorable for the surgical stage of the treatment of odontogenic maxillary sinusitis-maxillary sinusotomy with plasty of oro-antral fistula. Statistically considerable increase in activity and intensity of phagocytosis of neutrophils was observed in the test group of the patients. Moreover, there was an increase in the number of neutrophil extracellular traps. However in the comparison group of patients there were no statistically considerable differences in the level of neutrophil extracellular traps during the treatment, which probably indicates hyporesponsiveness of the local immunity [13].

**CONCLUSION**

Based on the obtained results we can conclude that signs of adverse clinical course and outcome of the disease were detected in patients suffering from chronic odontogenic maxillary sinusitis for more than two months. Analyzing clinical and immunological parameters in patients with chronic odontogenic maxillary sinusitis receiving cycloferon during the comprehensive treatment, we can conclude that more favorable postoperative course in comparison with patients of the comparison group. The most pronounced positive effect of cycloferon was showed in patients with lingering course of chronic process, while its effectiveness in patients with continual course was less considerable that raises the prospect of finding more effective and more adequate immunotherapy in this pathology.

**REFERENCES**

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