The Laryngoscope

Controlled Trial for Long-Term Low-Dose Erythrom Surgery for Chronic Rhinosinusitis

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Objectives/Hypothesis: The efficacy of macrolides in chronic rhinosinusitis (CRS) is s only two double-blind, placebo-controlled studies have been published with differing results. gated the possible benefit of macrolides in the postoperative period. We conducted an investig 250-mg erythromycin once a day over a period of 3 months, beginning the administration of 2 weeks after a surgical intervention for CRS.

Study Design: Randomized double-blind, placebo-controlled trial.

Methods: The concentrations of eosinophilic cationic protein (ECP) and myeloperoxidase as primary outcome measures. Additionally, as a secondary outcome measure, changes in t score, olfaction, saccharin transit time, nasal endoscopy score, and self-rating of nasal healt were evaluated.

Results: Sixty-seven patients after surgery for CRS with or without nasal polyps were s randomized to the study groups. For the primary outcomes, the concentrations of ECP cha 226.1 µl/l ± 200.6 in the erythromycin group and from 186.9 µl/l ± 36.0 to 192.9 µl/l ± 189. tistical differences were found. Of the secondary outcomes, only the nasal endoscopy score s improvement in the erythromycin group (from 2.6 ± 1.4 to 1.9 ± 1.5 points) compared to the to 2.6 ± 1.5 points). The subgroup of patients without nasal polyps in the erythromycin group ment in some secondary outcome criteria.

Conclusions: A general recommendation for long-term, low-dose erythromycin treatmer be given. In patients with CRS without nasal polyps, a tendency to improved parameters was c

Key Words: Macrolides, sinus surgery, CRS, evidence-based medicine.

Level of Evidence: Ib.

Laryng

INTRODUCTION

Rhinosinusitis is regarded as a multifactorial disease that causes different symptoms such as nasal obstruction, headache, nasal discharge, and olfactory dysfunction. Chronic rhinosinusitis (CRS) is defined as a state of inflammatory disease that occurs for longer than 12 weeks and is diagnosed by nasal endoscopy and computed tomography (CT) scan of the sinuses. CRS can present as cases with nasa out nasal polyps (CRSsNP ent underlying pathophysi inflammation in the nasal superantigen, aspirin-exa biofilm, or fungi, just to Present and future resear ces in individual phenotyp kine levels in nasal secre between different speci inflammatory disease.[5,6]

Therapeutic options roids, antibiotics in acute

Additional Supporting Information may be found in the online version of this article.

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oral steroids. In patients w
servative treatment, a s
endonasal sinus surgery) i

Surgery is effective
and improves the quality
by long-term topical ste
CRSwNP patients, the risk
than in CRSsNP patients,

In some studies, long
proposed for medical treat
lides are thought to have
modulatory capacities besi

This is based on the observation of blockage of the production of interleukin-8 (IL-8) and tumor necrosis factor, the effects on neutrophil migration and adhesion, and modulation of synthesis and secretion of mucus.[11]

In clinical trials of CRS, macrolides showed improvements in symptoms and endoscopic findings, decrease in polyp size, decrease of radiologically conspicuous mucosal changes in the sinuses on CT scan, and reduction in neutrophils and interleukin (IL)−8 levels in nasal discharge—as well as an improvement in saccharine transit time.[10,12]

Although these results showed promising effects of macrolides in CRS, most of these studies were conducted as open and noncontrolled clinical trials. To date, only two double-blind, placebo-controlled (DBPC) studies have been published with differing results.[13,14] In the Wallwork study, CRS patients without topical or systemic treatment 4 weeks prior to the start of the macrolide therapy were included; whereas in the Videler study, patients who suffered from recalcitrant CRS despite previous surgery and intensive medical treatment were evaluated.[13,14] None of these studies investigated the possible benefit of macrolides in the immediate postoperative period. In the 2012 European Position Paper on Rhinosinusitis (EPOS) guidelines, macrolides for treatment of CRS is recommended for patients with CRSsNP (level of evidence Ib, strength of recommendation C).[1]

We conducted a randomized, double-blind, placebo-controlled clinical trial with low-dose erythromycin over a period of 3 months directly after a surgical intervention for CRS. The changes in concentrations of eosino-

Gutenberg University, Main
initiated study.

Study Medication

As study medication, 25
placebo was administered ove
2 weeks after the surgical in
tion list was generated by a c
plinary Center for Clinical Tr
in this institution. A copy of t
pharmacy of the university
the packing and blinding of t
mycin 250-mg tablets were
empty capsules served as plac

Concomitant Medicati

All patients used nasal i
a day and were treated with
furoate) once a day (27.5 μg),
vention and continuing for th

Primary and Secondar

The concentrations of EC
were chosen as primary outc
nasal endoscopy score, sacchari
Outcome Test (SNOT-20) score
tus determined by a visual anal

Additionally, the preope
sinuses were analyzed and th
as well as the status of atopy
vitro methods (specific immu

study period. The amount of the difference of 1 point (out of 7 possible) also seems to be clinically relevant. In the follow-up period of an additional 3 months, this endoscopy score also decreased to lower values in the placebo group (Fig. 4). The other evaluated secondary parameters (including SNOT-20 score, self-rating of nasal health on a VAS, olfaction, and saccharin transit time) decreased in both groups over time and showed no statistically significant differences between the two treatment groups. Additionally, no positive effect on the primary criteria (ECP and MPO in nasal secretions) was found.

In our study, no severe side effects were seen, and the study medication did not cause higher rates of severe adverse events compared to placebo. These results are in accordance with previous reports.[13,26,27] But the ratio of side effects, especially of the gastrointestinal tract, was higher in the erythromycin group, which lead to a higher number of dropouts. Therefore, a higher dosage as used in other studies might cause even more side effects.

It might well be possible that a macrolide medication over 12 weeks, as used in our study, is not long enough. As in another nonplacebo-controlled postsurgical study, the visual analogue scale scores for rhinorrhea and postnasal drip at 12 months after surgery were lower in a group that was treated with clarithromycin (200 mg/day) for 6 months than in the group with 3 months of treatment.[28]

One general problem in these types of studies is the limited number of patients who can be included. Both previously published DBPC studies showed similar patient numbers to the present study, one even in a multicenter design. Therefore, the results must always be discussed with caution because more included patients would mean more statistical power. On the other hand, investigator-initiated trials often are confronted with critical funding and duration is limited.

CONCLUSION

In conclusion, the nasal markers for inflammation (ECP and MPO) could not be influenced by a long-term, low-dose erythromycin therapy in patients after sinus surgery. Despite a positive effect on the nasal endoscopy score in the treatment group, no other clinical advantage of the study medication over placebo could be proven. Therefore a general recommendation for the use of long-term, low-dose erythromycin therapy after surgery for CRS cannot be advocated. A presumably relevant improvement in the subgroup of patients without nasal polyps (CRSsNP) and specific endotypes (neutrophilic inflammation) should be further investigated.

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