Cilixyl® - a new trend in the treatment of rhinosinusitis

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Objective: Evaluation of the efficacy of the treatment with Cilixyl® nasal spray containing 3% xylitol and 1% glycerine in chronic rhinosinusitis (CRS).
Patients and methods: In the single-centric prospective, randomized, controlled, double-blind study 30 subjects (22 females and 8 males) with a mean age of 50.26 years (standard deviation 15.24 years) participated. After the intranasal use of a spray at a dose of 1-1 puff 4 times a day for 6 weeks, the subjective grade of satisfaction was assessed on a 5-score scale. In the control group, a nasal spray containing physiological salt solution containing was used.
Results: After 6 weeks of treatment, the increase of the subjective grade of satisfaction at the least with 2 scores could be found in the Cilixyl® group in 100% of the cases ($p<0.0001$), while in the control group this value was 69%. At the same time, the increase with 3 scores was 60% and 23% ($p=0.09$).
Conclusion: After the 6-week regular use of the Cilixyl® nasal spray applied in the course of our study, the subjective complaints of the patients in connection with the nasal breathing were significantly improved as compared to the control group.
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Introduction

The chronic rhinosinusitis (CRS) is a clinical picture having significant impact on the quality of life which affects the population irrespective of age and gender. By definition, the complaints persisting for more than 12 months are considered as of chronic in course: such as inhibited nasal breathing, discharge leakage in the pharynx, reduced sense of smell, feeling of facial “fullness” or “tightness” [1]. This term includes the chronic rhinosinusitis developed with or without nasal polyposis, respectively. Due to the disease-related visits to the physicians, the use of many different diagnostic and therapeutic procedures, this group of diseases imposes a considerable burden on the healthcare system. The estimated prevalence of the CRS is 15-16% in the USA [2], approximately 1 in 7 adults is affected; however, because of the heterogeneity of this group of diseases, the exact determination of the prevalence is difficult and mostly speculative [3].

In the decade past, a great emphasis was laid on the development of the guidelines related to the treatment and treatment strategies of the CRS. On the basis of the current consensus [4], the efficacy of the intranasal steroids and nasal lavage with physiological salt solution are supported by an evidence of Ia level, in case of a non-polypous CRS the long term macrolide therapy is efficient (Ib evidence) [5], in case of polypous CRS the inefficient massive dose therapy with steroid is an indication for surgery (Ib evidence) [6].

While the CRS was earlier thought to be the consequence of the not fully cured acute infectious sinusitis, by today this viewpoint has changed a lot. The researches define the CRS such a complex, multi-factorial disease state of heterogeneous aetiology which is featured by complex disturbance of the ostiomeatal function, persistent inflammation of the mucous membrane, reduced mucociliary clearance, biofilm formation, microbial resistance, osteitis, atopy [7].

As a consequence of the chronic inflammation, a very important element of the protection of the airways, the mucociliary clearance is severely damaged, thus a secondary ciliary dyskinesia is developed [8]. The cilium inhibitory effect of the inflammatory mediators, the effect of the toxins produced by respiratory pathogens (H. influenzae, P. aeruginosa) and the mucosa film layer breaking up because of the change in the secretion are among the cilium damaging effects [9]. Disintegration of the bronchial mucous membrane barrier gives scope to the entry of foreign proteins, stimulating the mucosal immune system through this, as well as the expression of the tight junction proteins (occludin) among the epithelial cells are reduced, increasing the ion-permeability of the mucous membrane as a result of this [10]. In addition to the cilium function, a further protective mechanism of the sinonasal mucous membrane is that it excretes numerous soluble proteins with antimicrobial effect into the mucous film layer (.e.g. lysosime, lactoferrin, human ß-defensins, phospholipase A2) which provide protection against the entered pathogens.

Biological effects of the polyols

The xylitol is a pentacarbon-atomic, pentahydric alcohol, is a strongly hygroscopic [11] and sweetish tasting material. It can be found in vegetables and fruits, but the human body itself also produces it. It is used as sweetening agent, its use as food additive is permitted (e.g. in chewing gums) [12]. It can be safely used for human consumption without restriction. Its overconsumption (in a single dose exceeding 30 grams), because of its osmotic activity, may cause diarrhoea. Its intravenous administration to human at a dose of 25 grams had not any kind of severe toxic effects [13]. The xylitol has been orally administered in a quantity of 15-20 grams a day for roughly 1 month as well [14, 15]. Its dental importance is proved, the xylitol content of the chewing gums, tooth pastes reduces the plaque formation, thus the development of the dental caries [16]. This is explained by the phenomenon that in the course of the decomposition of the xylitol the bacteria of the mouth cavity flora are not capable to produce ATP, thus their proliferation is stopped, therefore the cariogenic acids are formed only in a smaller extent as well [17].

The glycerine is a three-carbon-atomic, three-hydric alcohol, is a strongly hygroscopic [11], sweetish tasting material, it is the constituent of the triglycerides and the phospholipids in the human organism. It is used as sweetening agent, solvent, humidifier, thickener. Consumed orally in a larger quantity, it has a diarrhoeic effect. Making use of its osmotic activity, it is used in the treatment of intracranial pressure increase and as diuretics, respectively. Similarly to the xylitol, the cariogenic bacteria cannot decompose the glycerine either.

In the recent years, greater and greater attention is paid to the intracellular effect of the above mentioned polyol compounds and their effect having influence on the gene expression. Apart from the fact that due to their chemical properties they are efficient humidifiers, hydrating agents, they have an impact on biochemical

processes at cell level as well. It has been demonstrated in tests carried out on normal human keratinocytes [18] that the xylitol boosts the synthesis of filaggrin which is a molecule having key importance in the epithelial integrity and the normal barrier function. The glycerine significantly reduces the HLA-DR expression of the human epithelial cells which is an epithelial inflammation marker, thus it has an anti-inflammatory effect. During all these, they have no influence on the viability of the cells, cell volume and the intracellular calcium concentration.

Having discovered by Finnish scientists that the xylitol inhibits the proliferation of the Streptococcus mutants playing a key role in the cariogenesis [19], the attention was focused on its role filled in relation with the otopathogen bacteria. Under in vtiro circumstances, the xylitol inhibits the proliferation of the S. pneumoniae [20] and its capability of adhesion [21]. In the background of it, the inhibitory effect of the xylitol on the capsular gene expression of the bacterium was discovered [22]. In the course of a controlled, double blind study carried out in the circle of nursery-school children (n=306), the xylitol-containing chewing gum used for two months (five times daily, in a total of 8.4 grams) significantly reduced the prevalence of the development of the acute otitis media [23]. In their study carried out with a higher number of cases 2 years later (n=857), they came to the same conclusion [24], besides they pointed out that the xylitol had no influence on the frequency of the symptom-free nasopharyngeal carrying of the S. pneumoniae. Administration three times a day had no significant effect in the prevention of the acute otitis media [25].

In the Weissman's research [26], a prospective, double-blind study was carried out in relation with the efficacy of the nasal lavage with xylitol 5% aqueous solution in patients suffering from CRS (n=15), used isotonic salt solution as control. According to the result of this, the nasal lavage with xylitol significantly improved the subjective complaints in the course of the SNOT-20 test (p=0.0437).

The activity of the soluble protective proteins of the liquid film layer covering the surface of the airways is inhibited by the increased salt concentration (the case of the cystic fibrosis is an illustrative example of it because of the mutant CI channel). Through its osmotic activity, the xylitol reduces the ion strength of the liquid layer as well as it increases the volume of the liquid film, improving the cilium function through this [27].

Patients and methods

A single-centric, prospective, randomised, controlled, double-blind study was carried out. The primary objective of the research was to evaluate the efficacy of the treatment with Cilixyl® nasal spray at a dose of 1-1 puff into both nostrils 4 times a day. The secondary objective of the research was to collect data on the tolerability and safety properties of the treatment with the nasal spray applied at a dose of 1-1 puff in both nostrils 4 times a day.

In the course of the study having the permission number ETT-TUKEB 5638-0/2010-1018EKU (383/PI/10.), the informed consent to the study, readiness to cooperate, age between 18 and 75 years, grade 1 or 2 on the 5-grade subjective satisfaction scale used for the subjective assessment of the quality of the nasal breathing, consequently, a wrong or pure qualification were the enrolment criteria. A chronic disease of the lower respiratory system and the use of another intranasal preparation within one month prior to the study were obstacles to the enrolment. A previous lasting intranasal treatment with steroid and a FESS operation carried out because of nasal polyposis earlier than half a year ago were not exclusion criteria. In our study, between November 2011 and April 2013, 30 voluntary subjects, 22 females and 8 males, with a mean age of 50.26 years (standard deviation 15.24 years) participated. From among the patients selected into 7 subjects did not finish the study.

The Cilixyl® nasal spray manufactured and commercialized by Videomed Kft. is a product controlled and approved by the (Hungarian) National Institute for Quality- and Organizational Development in Healthcare and Medicines – National Institute of Pharmacy among the components of which 3% xylitol, 1% glycerine, 0.01% L-alanine can be found in an aqueous solution of neutral pH by using 0.01% benzalkonium chloride as preservative. In the control group, a nasal spray containing isotonic salt solution was used. The grade of subjective satisfaction was determined on a 5-grade scale on the basis of the answers given to the following question: "You are kindly requested to evaluate the sensation of your nasal dryness taking into account how much you are satisfied with the quality of your nasal breathing?" (answers: 1 – bad, 2 – poor, 3 – moderate, 4 – good, 5 – excellent). In the course of the study, the 10-ml presentation of the Cilixyl® nasal spray was applied at a dose of 1-1 puff into both nostrils 4 times a day for 6 weeks, and then with 2 weeks, 4 weeks and 6 weeks, respectively, after starting the treatment the grade of the subjective satisfaction was assessed again.

Results

In the group of the Cilixyl® nasal spray users, the mean score of the subjective satisfaction was 1.53 before starting the treatment. After 6 weeks of using the nasal spray regularly, this value increased to 4.2. The improvement within the group was highly significant (pair test, $p<0.0001$).

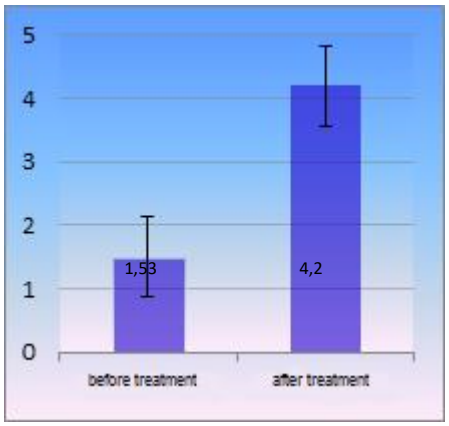

Figure 1: Distribution of the subjective satisfaction scores in the group of the Cilixyl® nasal spray users. The subjective satisfaction index of 1.53±0.64 measured prior to the treatment was 4.2±0.63 six weeks after starting the treatment ($p<0.0001$)

The comparison of the Cilixyl® nasal spray and the isotonic sodium chloride solution was made in two approaches. As the first, it was investigated whether the Cilixyl® nasal spray is of more favourable effect as compared to the isotonic sodium chloride solution on the condition that the successful treatment **increased** the starting score **with 2 scores**. The result may be seen in the figure 2. In the course of the evaluation, the Fischer test was used. The result is not significant, but it shows a definite tendency (one-sided $p = 0.08$).

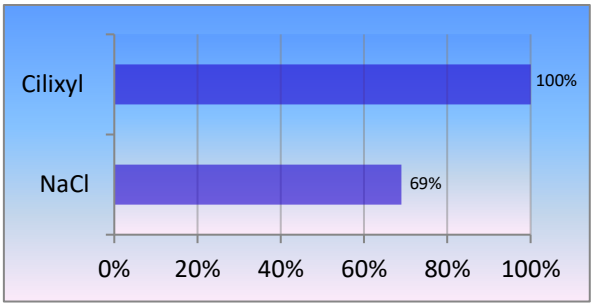

Figure 2: The Fischer test in the comparison of the Cilixyl® nasal spray and the isotonic sodium chloride solution. In the Cilixyl group, the subjective index increased with 100%, while in the control group with 69%. The difference between the two groups is not significant, but it shows a definite tendency (p=0.08).

Secondly, it was investigated whether the Cilixyl® nasal spray is of more favourable effect as compared to the isotonic sodium chloride solution on the condition that the successful treatment **increased** the starting score **with 3 or more scores**.

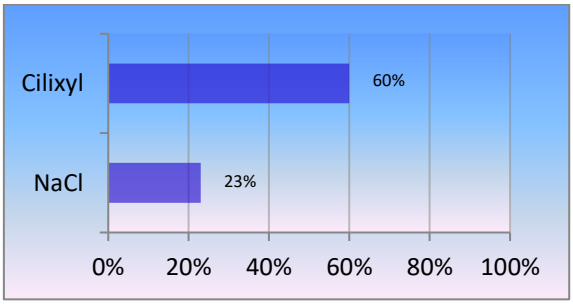

Figure 3: The Fischer test in the comparison of the Cilixyl® nasal spray and the isotonic sodium chloride solution. In the Cilixyl group, the subjective index increased with 60%, while in the control group with 23%. The difference between the two groups is not significant, but it shows a definite tendency (p=0.09).

Discussion

On the basis of the comparison of the data found before and after the investigation it can be stated that the Cilixyl® nasal spray is of active effect, it significantly improves the subjective satisfaction index of the nasal breathing, sensation of nasal dryness in the patients suffering from CRS (p=0.0001).

The components of the product, Cilixyl indicated in our objective together, i.e. the joint effect of the xylitol and glycerine, has not been investigated earlier yet, this investigation is accounted as a novel one in the professional literature. Weissmann, in his research [26], has earlier given an account of the beneficial effects of the nasal lavage containing only xylitol. Our current results are in accordance with the results of this research. By way of influencing the tissular HLA-DR synthesis and filaggrin expression, the combination of the glycerine and xylitol has an individual effect which is anti-inflammatory on the one hand and promoting the tissular integrity on the other hand.

The statistical analysis of the data originating from the comparison of the Cilixyl® and the isotonic salt solution shows a definite trend (p=0.08) in favour of the Cilixyl®. The lack of reaching the significance level can be led back to the number of patients examined in both cases. When the investigation plan was drawn up, we counted with the involvement of 30 subjects. Supposing the same distribution, the significance level (p=0.02) would have been reached with this number of patients.

In the Cilixyl®, the bezalkonium chloride is the preservative the effect of which exerted on the mucous membrane was found harmful is several studies [28, 29], with special respect to the mucociliary function. The fact, that the satisfaction with the chronic treatment 4 times a day for 6 weeks was almost the maximum highest (Figure 1), does not support the negative effect of the benzalkonium chloride. The explanation of this may be that the glycerine inhibits the negative effect of the benzalkonium chloride [30].

Furthermore, our objective was to collect data on the safety and tolerability in the course of the clinical investigation of the product. In the course of the study, no adverse event occurred. The use of the nasal spray was easy, the administration 4 times a day was not a burden to the patients. In the Cilixyl® group, in the minutes after spraying into, a sweetish sensation was reported. No account was given of the known laxative effect of the xylitol and glycerine by the subjects, this was not expected either with respect to the fact that the quantity of the materials getting into the alimentary canal is insignificant.

There are several factors which are limits in the evaluation of our study. These are the low number of subjects (n=30) and the drop-outs due to the lack of compliance (n=7). It was earlier described that in the case of the planned number of subjects the difference found between the results of the Cilixyl® and control group would have reached the significance level. Taking the trends into account, by further increasing the number of patients, the significance level of the current results would continue to increase.

While investigating the patients' satisfaction, we have lent on the subjective evaluation in a great extent. Our questionnaire consists of only one question, a 5-grade subjective scale, mostly related to the quality of the nasal breathing and the subjective sensation of the nasal dryness. The complaints can be analysed with higher accuracy with the use of the SNOT-20 questionnaire developed for the subjective evaluation of the CRS [31], because it evaluates both the local and general complaints belonging to the clinical picture of CRS in a broader range.

We pointed out the increase of the subjective satisfaction index of a definite extent in the control group using physiological salt solution as well. The result is not surprising, because the nasal lavage with physiological salt solution is an accepted treatment method of the CRSs with clinically evidenced efficacy [32, 33]. The research group proved the beneficial effect of the hypertonic salt solution as well [34]. However, on the basis of the data obtained in this study it cannot be established whether the isotonic sodium chloride solution had an effect higher in any extent than the one expectable from the placebo (p=0.16).

Conclusion

The barrier function of the mucous membrane injured in the course of the CRS and the permanent mucous membrane inflammation can be improved with the use of the combination of xylitol and glycerine. In addition, the therapeutic options inherent in the humidification of the mucociliary layer playing a key a role in the pathogenesis and in the reduction of the biofilm formation may represent a new trend in the complex treatment of the CRS, beside the now available treatment options (see intranasal corticosteroids).

Literature

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