INTRANASAL ULTRAVIOLET PHOTOTHERAPY IN THE TREATMENT OF ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS

PhD Thesis

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Publications related to the PhD Thesis:

I. **Ágnes Kiricsi**, László Tiszlavicz, Zsolt Rázga, Magdolna Krasznai, Ida Vóna, Andor Hirschberg, Zsolt Szabó, Lajos Kemény, László Rovó, Edit Kadocsa, Zsolt Bella: Prospective, multicenter, randomized clinical study to evaluate the clinical efficacy and tolerability of long term mixed ultraviolet and visible light phototherapy in eosinophil nasal polyps. Journal of Photochemistry and Photobiology B: Biology 2017; 176: 118-123

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II. Zsolt Bella, **Ágnes Kiricsi**, Éva Dósa-Rácz Viharosné, Attila Dallos, Ádám Perényi, Mária Kiss, Andrea Koreck, Lajos Kemény, József Jóri, László Rovó, Edit Kadocsa: Rhinophototherapy in persistent allergic rhinitis. European Archives of Oto-Rhino-Laryngology 2017; 274: 1543–1550 (shared first authorship)

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IV. Bella Zsolt, **Kiricsi Ágnes**: Korszerű orrcseppek és használatuk; Háziorvosi továbbképző szemle 2016; 21: 29-33

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V. István B. Nemeth, Otto Zsiros, Andrea I. Koreck, Zsolt Bella, **Ágnes Kiricsi**, Ferenc Ignacz, Edit Kadocsa, Lajos Kemeny: Ultraviolet light and photodynamic therapy induce apoptosis in nasal polyps. Journal of photochemistry and photobiology B Biology 2012, 117: 179-184.

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Bella Zsolt, **Kiricsi Ágnes**, Szabó Zsolt, Kemény Lajos, Jóri József, Rovó László, Kadocsa Edit: Open, prospective, multicentric study to evaluate the efficacy of postoperative intranasal phototherapy in the prevention of recurrence of nasal polyps, 25th Congress of European Rhinologic Society 22-26 Jun, 2014 Amsterdam

ABBREVIATIONS

AR: allergic rhinitis

ARM: acoustic rhinometry

CD4+: major classification of T lymphocytes, referring to those that carry the CD4 antigen; most are helper cells, also called CD4 T lymphocytes.

CPD: cyclobutane pyrimidine dimer

CRS: chronic rhinosinusitis

CRSwNP: chronic rhinosinusitis with nasal polyps

DNA: deoxyribonucleic acid

ECP: eosinophil cationic protein

GM-CSF: granulocyte-macrophage colony-stimulating factor 1

ICAM1: intercellular adhesion molecule 1

IL: interleukin

mUV/VIS: mixed ultraviolet and visible light

NB-UVB: narrow-band ultraviolet B

NER**:** nucleotide excision repair

NIPF: nasal inspiratory peak flow

NO: nitrogen monoxide

NOSE: nasal obstruction symptoms evaluation

PAR: persistent allergic rhinitis

PCR-RFLP**:** polymerase chain reaction restriction fragment length polymorphism

PUVA: psoralen and ultraviolet A

RANTES: Regulated on Activation, Normal T Expressed and Secreted

RL: Rhinolight®

SNP: single nucleotide polymorphism

TGFβ1: transforming growth factor β1

TNS: total nasal score

UV-A: ultraviolet-A

UV-B: ultraviolet –B

UVDE: ultraviolet DNA endonuclease

VCAM-1: vascular cell adhesion molecule 1

VAS: visual analog scale

VIS: visible light

CONTENT

1. INTRODUCTION

1.1. Allergic rhinitis and chronic rhinosinusitis with nasal polyps

The nasal airways and their closely associated paranasal sinuses are an integral part of the respiratory tract. The nose protects the lungs by filtering and humidifying air prior to entry to the lungs. The nose senses airborne volatile compounds via pattern recognition and olfactory receptors. Olfaction can be essential in avoiding exposure to toxins and pathogens in the air or food. The filtering function of the nose initiates immune sensitization to potential pathogens. These functions play an essential role in normal upper airway functioning (1,2).

Chronic upper airway inflammation can be roughly divided into two major clinical entities, rhinitis and rhinosinusitis. Both can be separated into mild, moderate and severe subgroups, and for both anti-inflammatory medication is the first-line treatment. The allergic phenotype is the best characterized phenotype of rhinitis from a pathophysiologic point of view (1,2).

Allergic rhinitis is an allergen-induced, IgE-mediated inflammatory disease of the nasal mucosa. The development of the disease is characterized by an initial sensitization phase to a specific allergen. Later on, the encounter of the same allergen by sensitized individuals is followed by the activation of effector mechanism and specific immune response (1,3). Previously it was established that a shift toward T helper 2 (Th2) cells plays a role in the initiation and maintenance of the disease. Eosinophils, mast cells, and basophils are considered to be the major effector cells in hay fever. These cells release inflammatory mediators such as histamine, prostaglandins, cytokines, tryptase, leukotrienes and eosinophil cationic protein (ECP). These mediators are responsible for most of the pathological processes occurring in the nasal mucosa. (3, 4, 5) Rhinitis is defined as an inflammation of the lining of the nose and is characterized by nasal symptoms including anterior or posterior rhinorrhea, sneezing, nasal blockage, and/or itching of the nose. These symptoms occur during two or more consecutive days for more than 1 hour on most days. The diagnosis of allergic rhinitis is based on the typical history of allergic symptoms, nasal examination and confirmation of the suspicious allergen by diagnostic tests. *In vivo* and *in vitro* tests are used

to diagnose allergic diseases by the detection of free or cell-bound IgE (skin prick test and serum-specific IgE).

The management of allergic rhinitis encompasses patient education, pharmacotherapy and allergen-specific immunotherapy. Medical condition aims at controlling the disease, including clinically significant symptom reduction with improvement of quality of life and the reduction of socio-economic impact of the disorder (1). A therapeutic plan is needed according to the symptoms of the patient, the severity, the co-morbidities and availability of treatment (2). It is advised to evaluate the degree of symptom control regularly. Intranasal glucocorticosteroids are recommended for the treatment of allergic rhinitis in adults and children, (1,7) since these are the most effective drugs for the treatment of allergic rhinitis. Second-generation oral or intranasal H1-antihistamines are recommended as well. Leukotriene antagonist is suggested in the treatment of seasonal allergic rhinitis in patients over 6 years of age (1,2). In some selected cases, immunotherapy provides the basis of progressive treatment adjusted to the grades of severity. Intranasal decongestants may be used for a short period of time in patients with severe nasal obstruction (1,2,8). A number of paramedicinal products have been advocated, but their applicability awaits confirmatory evidence (9).

Chronic rhinosinusitis (CRS) is classically divided into two phenotypes: chronic rhinosinusitis with and without nasal polyps evaluated by nasal endoscopy (10).

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a multifactorial disease. The majority of CRSwNP cases are the eosinophil-type, in which the eosinophils represent more than 60% of the inflammatory cell population. The persistence of tissue eosinophilia is very important in the pathogenesis of CRSwNP. Thus apoptosis of eosinophils and T cells may represent a therapeutic target in nasal polyps (10).

Chronic rhinosinusitis (CRS) describes a heterogeneous group of diseases of the nose and the paranasal sinuses that is characterized by two phenomena: inflammation and tissue remodeling. According to the European Position Paper on rhinosinusitis and nasal polyps, CRS is defined by the presence of at least two of the following symptoms: nasal obstruction, nasal secretion and/or post-nasal drip (PND), headaches and/or facial pains, a reduction of smelling for more than 12 weeks during the last year, when at least one of the first two mentioned symptoms should also be observed (1). For the diagnosis positive nasal endoscopic and/or CT findings are essential. The burden of the symptoms, the associated reduction of the quality of life and the influence of the disease on work productivity are often underestimated (10,12). Histologically, CRSsNP is characterized by fibrosis of the mucosa and the basal

membrane while nasal polyposis is characterized by important edema with deposition of albumin and the development of pseudocysts (13).

The European Position Paper on Rhinosinusitis and Nasal Polyps 2012 lists the following factors associated with CRSwNP and CRSsNP:

- *ciliary impairment*: ciliary function plays an important role in the clearance of the sinuses and the prevention of chronic inflammation
- epidemiologic data show an increased prevalence of *allergic rhinitis* in patients with CRS, but the role of allergy in CRS remains unclear
- CRSwNP and *asthma* are also frequently associated in the same patients
- patients with *aspirin sensitivity* have radiographic changes affecting their paranasal sinuses
- *immunocompromised state*
- *genetic factors*
- *environmental factors (cigarette smoking)*
- *endocrinal state, hormonal factors*
- *iatrogenic factors*
- *antimicrobial responses, biofilms.*

Increasing evidence suggests the heterogeneity in CRS manifestations may be explained by a variety of molecular and cellular pathways that result in the mucosal inflammation of CRS. The understanding of different pathophysiologic mechanisms in CRS allows the identification of disease variants as endotypes (14). Endotyping relies on immunohistologic biomarkers involved in disease pathophysiology and provides a more comprehensive approach to classify CRS variants (12). Approximately 80% to 85% of CRSwNP patients in the United States and Europe have shown a strong predilection for a skewed type 2 immune response, which is characterized by a high presence of eosinophils, mast cells, basophils, and T-helper 2 (Th2) cells, and comorbid associations with asthma and atopy (13). Released by type 2 innate lymphoid cells, Th2 cells, and mast cells, IL-5 is a common cytokine that coordinates the local influx, maturation, and survival of eosinophils. The important role of IL-5 in CRSwNP pathophysiology was demonstrated by Tomassen et al (15). Another mean of endotyping CRS patients is through the identification of predominant immune cells in the sinonasal mucosa. In Caucasian CRSwNP patients, the inflamed sinonasal mucosa is characterized by eosinophils, whereas patients from East Asia are featured by neutrophils (16). Eosinophils express more than 30 cytokines and chemokines,

which are rapidly released following cellular activation and lead to a unique inflammatory signature.

International guidelines recommend regular local nasal steroids (Ia evidence), short period systemic steroids (III), nasal lavage (Ib) and functional endoscopic sinus surgeries in combination for the treatment of chronic rhinosinusitis with nasal polyps. About 38% to 51% of CRS patients fail to respond to these recommended medical therapies (17,18). New treatment methods, which decrease eosinophil cell numbers and IL-5 levels are supposed to be of outstanding therapeutic importance in CRSwNP (19,20).

1.2. Genetic predisposing factors for Chronic rhinosinusitis with nasal polyps (CRSwNP)

Inflammation has been demonstrated to play a central role in the pathogenesis of CRSwNP, and TNFα is a key pro-inflammatory cytokine in these processes. In collaboration with the Department of Genetics at the University of Szeged, genomic DNA were obtained from buccal swab samples in order to determine whether TNFA –308 G>A SNP has a role in a genetic predisposition to CRSwNP in the Hungarian population. Patient and control samples were genotyped for the TNFA -308 G>A (rs1800629) SNP by the PCR-Restriction Fragment Length Polymorphism method. Altogether 169 controls and 375 CRS patients were genotyped for the TNFA –308 G>A SNP. Aspirin sensitivity (ASA+) was detected in 18.4% (n = 60) of the CRSwNP patients. After careful stratification of the patient group on the basis of clinical symptoms, we found a significantly higher carriage rate of the rare A allele-containing genotypes among the CRSwNP who also exhibited sensitivity to aspirin (acetylsalicylic acid, ASA+). The genetic variants of the TNFA gene may affect the risk of CRS in a clinically well-defined group of CRSNP+ASA+ patients in the Hungarian population. Their carried genetic predisposing factors, and as a result, the exact molecular events leading to the development of various forms of CRS, may differ. The clinical and genetic data suggest that the overall group of CRS patients is indeed heterogeneous. Many differences have been described in the clinical characteristics of these patients and severe cases often exhibit extreme treatment resistance and the recurrence of symptoms after the surgical resection of polypoid tissues. All these data suggest that not only the genetic predisposing factors but also

the actual disease pathogenesis at the molecular level may differ in the various CRS subgroups (21).

After these findings Szabo et al performed a case-control study for examining the frequency of 8.1AH carriers in subgroups of CRS and control. They found that the presence of the 8.1AH may be responsible for the development of severe CRSwNP ASA+ forms (22).

1.3. Effects of UV phototherapy

The therapeutic effect of UV light is generally attributed to its immunosuppressive and immunomodulative effect. It is used worldwide for the treatment of immunomediated inflammatory skin diseases like psoriasis or vitiligo (23,24). One of the most important mechanisms explaining the immunosuppressive effect of UV light is DNA damage inducing apoptosis in infiltrating T cells, the reduction in the number and function of Langerhans cells, and the induction of immunomodulatory cytokines such as IL-10. UV irradiation leads to the formation of photoproducts (cyclobutane-pyrimidine dimer, 6-4 photoproducts, Dewar isomers), which are the major triggers of UV-induced apoptosis (25). Inflammatory processes are very similar in the nose and in the skin; therefore rhinophototherapy is a promising, noninvasive treatment option for a number of inflammation-related pathological nasal conditions (26).

Hungarian inventors have experimented with the most efficient light composition to be applied in the nose in order to reduce allergic symptoms or even to treat various forms of nasal problems (27). Mixed ultraviolet light (Rhinolight®) is composed of more than 70% of visible light, 25% of UV-A light, and less than 5% of UV-B. Figure 1 shows the frequency and wavelength ranges of visible light and UV light.

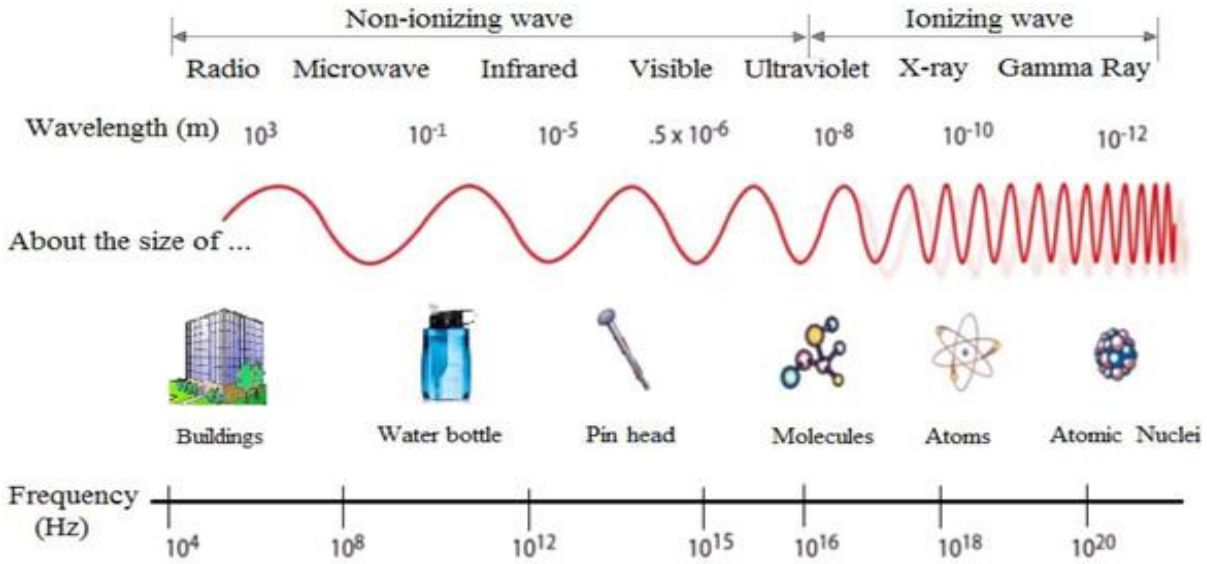


Figure 1: Frequency and wavelength of microwaves compared with that of visible light, UV light and X Rays (adapted from http://mynasadata.larc.nasa.gov/science-processes/electromagnetic-diagram/)

During the initial research, photosensitizing drugs (psoralen) and phototherapy were combined (PUVA psoralen and ultraviolet A). Csoma et al proved that intranasal PUVA therapy significantly reduced the symptoms of patients suffering from allergic rhinitis (26).
The UVB range mainly provides the immunosuppressive effect of UV light. Narrow-band UVB (NB-UVB: 305-315nm wavelength) light sources are not only the most widely used in phototherapy, but are also considered to be the gold standards for the treatment of inflammatory skin diseases as well (29).

Our previous publication revealed that mixed ultraviolet light/visible light (mUV/VIS) intranasal phototherapy was safe and effective in intermittent allergic rhinitis. UV phototherapy induced a dose-dependent increase of eosinophil and T-cell apoptosis (28). In a preliminary study, polyps were *in vivo* irradiated with mUV/VIS and then surgically removed. The penetration of UV light in the polyp tissue proved to be dose-dependent. This data indicated that light penetrates into the polyp tissue to a sufficient depth (200-900um) to reach the inflammatory cells in the stroma; therefore a proper therapeutic effect can be achieved (29). The formation of photoproducts after UV irradiation, and the subsequent induction of apoptosis establish the molecular mechanism to reduce inflammatory infiltration in the polyps. Different light sources - broad-band and narrow-band UV light (NB-UVB) exposures – were applied: broad-band UV light increased the apoptosis of inflammatory cells and polyp epithelium, whereas narrow-band UV light penetrated deeper (30).

The first *in vitro* and *in vivo* studies assessing the applicability of UV phototherapy in allergic rhinitis were conducted in Szeged, Hungary (28). UV-induced DNA damage response of the respiratory epithelium was very similar to the response of the human epidermis, since the nasal mucosa could efficiently repair UVB induced DNA damage (28,31).

Surface epithelial cells have an important role in polyp formation. They produce cytokines and growth factors, and their proliferation capacity is related to the recurrence rate of CRSwNP. In an *ex vivo* study, the effect of different phototherapeutic methods on apoptosis induction in epithelial cells and inflammatory cells were evaluated in CRSwNP. Nasal polyp tissue was collected from 21 CRSwNP patients. The polyps were cut into pieces and then irradiated with lights of different wavelengths and doses. The mUV/VIS treated group showed a dose-dependent increase in apoptotic surface epithelial cells and in subepithelial leukocytes of nasal polyps. The photodynamic therapy group resulted in the highest surface apoptosis in the epithelial cells and in the subepithelial leukocytes. In the control non-treated samples only a few apoptotic surface cells and apoptotic subepithelial leukocytes were detected. These data proved that mUV/VIS can effectively increase apoptosis of the therapeutic target epithelial cells in a dose-dependent manner. The 5-delta-aminolevulinic acid (DALA) presensitized photodynamic group had the most dramatic effect on surface epithelial apoptosis. Both methods are effective and can be options for treatment of CRSwNP (32).

1.4. Efficacy of mixed ultraviolet light and visible light (mUV/VIS) therapy in persistent allergic rhinitis

Considering that phototherapy using combined wavelengths is successfully used in the treatment of severe atopic dermatitis and that allergic rhinitis and atopic dermatitis are characterized by several common pathogenic features, we aimed to investigate whether phototherapy using mUV/VIS light may represent a therapeutic alternative in patients with persistent allergic rhinitis.

34 patients with moderate or severe persistent allergic rhinitis were enrolled and randomized. Allergy to house dust mite and mold was confirmed with a specific immunoglobulin E (IgE) or skin prick test. The patients were enrolled and randomized into two groups, namely to Rhinolight (RL) group and to placebo group in a 2:1 ratio (33).

The probe of the light source was inserted into the right nostril first and then into the left one. The light was spread over the mucosal surface by constant and gentle movements within the nose. Treatment duration was from 2 minutes to 3 minutes. The patients received a total of 13 intranasal treatments during 6 weeks. The dose of phototherapy was 1.6–2.7 J/cm^2/nostril/treatment. In the placebo group low-intensity VIS was administered. Patients had medical check-ups by an ENT specialist on week 3 (visit #2), 24 h after the last treatment (visit #3), and one month later (visit #4). Patients recorded their nasal symptoms in the morning and evening (rhinorrhoea, nasal itching, sneezing, and nasal obstruction on a visual analog scale (VAS scale of 0–10). For the examination of nasal breathing, nasal inspiratory peak flow (NIPF) measurements were made twice a day in their homes. Application of supplementary medication, i.e., oral antihistamine (levocetirizine 195 mg/day), side-effects, and adverse events were also recorded. For quantitative assessment of the smell threshold, the University of Pennsylvania Smell Threshold test was used. The mucociliary transport function was measured by means of a saccharin test. Nasal mucosal sampling was taken for determination of the intracellular adhesion molecule 1 (ICAM-1) expression of the nasal mucosal epithelial cells. Samplings were obtained before start of treatment (visit #1), after completion of the treatment period (visit #3) and at the end of the follow-up phase (visit #4). The number and percentage of ICAM-1 and cytokeratin 5/8-positive cells of each sample were determined relative to the isotype control samples (32).

Both the initial morning and evening nasal symptom scores improved significantly in the two groups by the end of the treatment compared with baseline and this was observed during the 1-month follow-up. By the end of the treatment phase, the morning scores for sneezing, rhinorrhea, nasal obstruction and the calculated total nasal score (TNS) and NIPF, and the evening scores for sneezing and NIPF demonstrated a significant improvement in the RL group relative to the placebo group. By the end of the 4-week follow-up, a significant improvement was seen in the morning and evening scores for nasal itching, the evening rhinorrhea score, and the TNS in the RL group. By the end of the follow-up, there was no significant difference between the morning and evening sneezing scores, both of which had improved significantly. The evening nasal obstruction proved to be the most resistant symptom. Although it improved considerably, it did not improve significantly as compared with the placebo group at any time examined. The measured mucociliary function and quantitative smell threshold data exhibited considerable variation and no significant change was observed either in time or in intergroup comparisons. The permitted levocetirizine consumption per person did not differ significantly in the RL group (4.21 tbl/person/treatment

cycle) and in the placebo group (3.45 tbl/person/treatment cycle). The number of ICAM-1-positive cells was appreciably lower in the RL group than in the placebo group even at visit #3 and the difference became more marked at visit #4, yet it did not reach a significant level at any time. No severe side-effects were found. Three patients in the RL group reported mild dryness of the nasal mucosa, which disappeared in a few days with the use of ColdastopTM nasal drops. Two patients in each group experienced mild nosebleed when blowing the nose; this was not directly treatment-related, and did not require any particular treatment. Temporary and spontaneously resolving nasal pain occurred in the RL group and in the placebo group too. There was no statistically measurable difference between the frequencies of the side-effects in the two groups (33).

1.5. Safety of ultraviolet (UV) phototherapy

The DNA-damaging effect of high-energy ultraviolet light irradiation is well known, and this effect may indicate the first step of carcinogenesis. The majority of literature data refer to the damage formed after UV irradiation of the skin. The mutagenic risk of DNA photodamage has stimulated interest to determine the wavelength-dependent distribution of different DNA photodamage types. UV light is able to cause DNA damage by direct mechanisms (absorption of photons by the DNA) or by indirect mechanisms such as generation of reactive oxygen species (34,35,36). Cells possess various repair mechanisms in response to UV-induced DNA damage. Although skin diseases are successfully treated with phototherapy and data from the literature support that no significant increase in skin cancer risk is present in patients treated for decades with UVB light, no data were available regarding the effect of UV light on nasal mucosa.

Koreck et al detected the effect of the intranasal mUV/VIS phototherapy on DNA damage and repair mechanisms *in vivo*. In their studies, they processed the nasal mucosa samples of 26 allergic rhinitis patients in a double-blind experimental system using a Comet assay. Their results have shown that in the chosen experimental study design the UV/VIS phototherapy did not cause significant DNA damage. They found that skin and airway mucosa exhibit similar kinetics in repairing UV-induced DNA damage. Nasal mucosa exposed to UV light possess the capacity to repair DNA damage which suggests that the multistep process of carcinogenesis has not been triggered (27,30).

Mitchell et al performed a safety study as well. Radioimmunoassay was used to quantify cyclobutane pyrimidine dimers (CPDs) and (6–4) photoproducts in DNA purified from nasal mucosa samples from subjects exposed to intranasal phototherapy and human airway (EpiAirwayTM) and human skin (EpiDermTM) tissue models. Immunohistochemistry was used to detect CPD formation. In subjects exposed to broadband ultraviolet radiation, DNA damage frequencies were determined prior, immediately after treatment and at increasing times post-treatment. Twenty-six allergic rhinitis subjects were included in the study. The study was performed during ragweed pollen season. Subjects were randomized to either receive intranasal phototherapy using Broadband-UV light (BB-UV) source or low-dose visible light placebo therapy 3 times per week for 3 weeks. Nasal mucosa samples were collected from the antero-medial surface of the inferior turbinate before treatment, immediately after last exposure, 1 week after the last treatment and 1 month after. DNA was extracted from the nasal mucosal samples. EpiAirway and EpiDerm tissues were exposed to three different doses from narrow-band germicidal UVC source, narrow band UVB (NB-UVB), broadband UV (BB-UV) lights. Both placebo-treated and UV-treated subjects exhibited similar histological changes, most probably associated with the chronic inflammatory process associated with allergic rhinitis of the nasal mucosa. CPD positive cells were not detected in the tissue samples from subjects exposed to multiple UV treatments or in placebo-treated subjects. Their data suggest that the human respiratory epithelium can efficiently remove lesions in DNA resulting from exposure to UV radiation (25).

1.6. Special instrumentation for targeted intranasal phototherapy

Based on our previous studies we planned a 12 week long intranasal phototherapy in early stage CRSwNP. In order to achieve a targeted, precise, and easily adjustable and controllable intranasal phototherapy, we needed to implement some developments in the instrumentation and the design and application of new devices was necessary.

Since in the case of CRSwNP the planned treatment needed to be performed under endoscopic supervision in narrow areas of the nasal cavity, therefore the development of a curve-ended handler device was required. This handler device had to be capable of transmitting the light in a targeted manner onto the surface of the polyp.

The most precise measurement procedure of the nasal polyp surface was also required since the treatment should affect only the polypoid mucosa, without impacting the normal mucosa. The polyps had to be separately measured by a special measurement instrument in both halves of the nasal cavity.

In case of large polyps, even in a targeted approach, the duration of intranasal phototherapy is more than 30 minutes. Throughout this treatment period both the operator and the patient has to be in a stable position, which causes inconvenience for both parties.

For the solution of these problems, novel devices and equipment had to be designed for the planned clinical study.

AIMS OF THE THESIS

2.1. To evaluate the efficacy and tolerability of intranasal mixed ultraviolet and visible light (mUV/VIS) phototherapy in nasal polyposis

Mixed UV/VIS light resulted in the induction of apoptosis in eosinophils *in vitro* and phototherapy reduced the clinical symptoms in patients with CRSwNP.

The aim of the study was to *evaluate the capacity* of mUV/VIS light *in suppressing the clinical symptoms* of patients with eosinophilic polyposis with a follow up of 3 months. As primary endpoints the changes in total nasal score and nasal symptoms and the polyp size according to videoendoscopic images were considered. Secondary endpoints were the improvement in the ability of smelling, in the quality of life and the volume of nasal cavity measured by acoustic rhinometry.

We aimed to *specify the side effects* and their severity, and rescue treatment, if needed.

2.2. To investigate the efficacy of postoperative intranasal mUV/VIS phototherapy in preventing the recurrence of nasal polyposis

Intranasal mUV/VIS phototherapy decreased significantly the nasal symptoms and the size of eosinophil nasal polyps. The aim of this study was to evaluate *in vivo* the *clinical effect* of mixed UV light (Rhinolight®) *on the recurrence* of nasal polyps during a 12-week treatment period with a follow up of 6 months. Primary endpoints were the ratio of patients without recurrent nasal polyps in the two groups according to the videoendoscopic images and the changes in nasal symptom scores.

2.2.1. Development of a new measurement and handler device for intranasal phototherapy under endoscopic supervision

To develop a *new measurement* method and a *handler device,* which permits easier, faster and safer phototherapy with the mUV/VIS equipment under endoscopic supervision

METHODS AND SUBJECTS

3.1. **Efficacy and tolerability of intranasal mUV/VIS phototherapy in nasal polyps**

SUBJECTS

87 subjects with bilateral nasal polyposis (stage II-III) who regularly take local nasal steroid were included. They all previously underwent functional endoscopic sinus surgery, and obtained the histopathological diagnosis of eosinophil polyposis (Table 1). Eleven subjects were excluded from the study because of their poor compliance or withdrawal. The data from the drop-outs were not included in the evaluation. The investigations were performed in six centers in Hungary. The subjects gave written informed consent and the study was approved by the local Ethics Committee.

Polyp stage	
0	none
I	small polyp in the middle meatus
II	more polyps in the middle meatus
III	polyps beyond the middle meatus or elsewhere
IV	polyps obstructing the nasal cavity

Table 1: Stage of polyps evaluated by nasal endoscopy (E. Meltzer et al. Rhinosinusitis: Developing Guidance for clinical trials. Journal of Allergology and Clinical Immunology 2006; 118: S17-S61)

The subjects were divided into two groups: in Group A, subjects received only local nasal steroid (mometasone furoate 2x200 μg per day) for the duration of the study. In Group B, local nasal steroid were administered (mometasone furoate 2x200 μg per day) to the subjects, combined with intranasal mUV/VIS phototherapy 3 times per week for 12 weeks. The used mUV/VIS device (Rhinolight Inc, Hungary) contained 5 % ultraviolet B, 25 % of ultraviolet A and 70 % of visible light, with the spectrum between 280 and 650 nanometers. The dose of phototherapy was proportional to the measured surface of the polyps 6 J/cm2 in

the first two weeks, and then 9 J/cm2. Depending on the size of the polyps the irradiation time varied between 5 to 40 minutes.

METHODS

During the study, demographical data, nasal endoscopy images and clinical data were collected; nasal inspiratory peak flow, acoustic rhinometry, smell threshold test, and exhaled nasal nitrogene-oxide (NO) measurements were performed (Figure 2, Table 2).

Nasal symptom score and the total nasal symptom score (TNS): subjects evaluated nasal obstruction, rhinorrhea, facial/headache, loss of the sense of smell separately by pointing on a 0-6 visual analogue scale, cumulative value of symptom scores 0-24, from the inclusion until the 3 months follow-up period once a week (37,38,39).

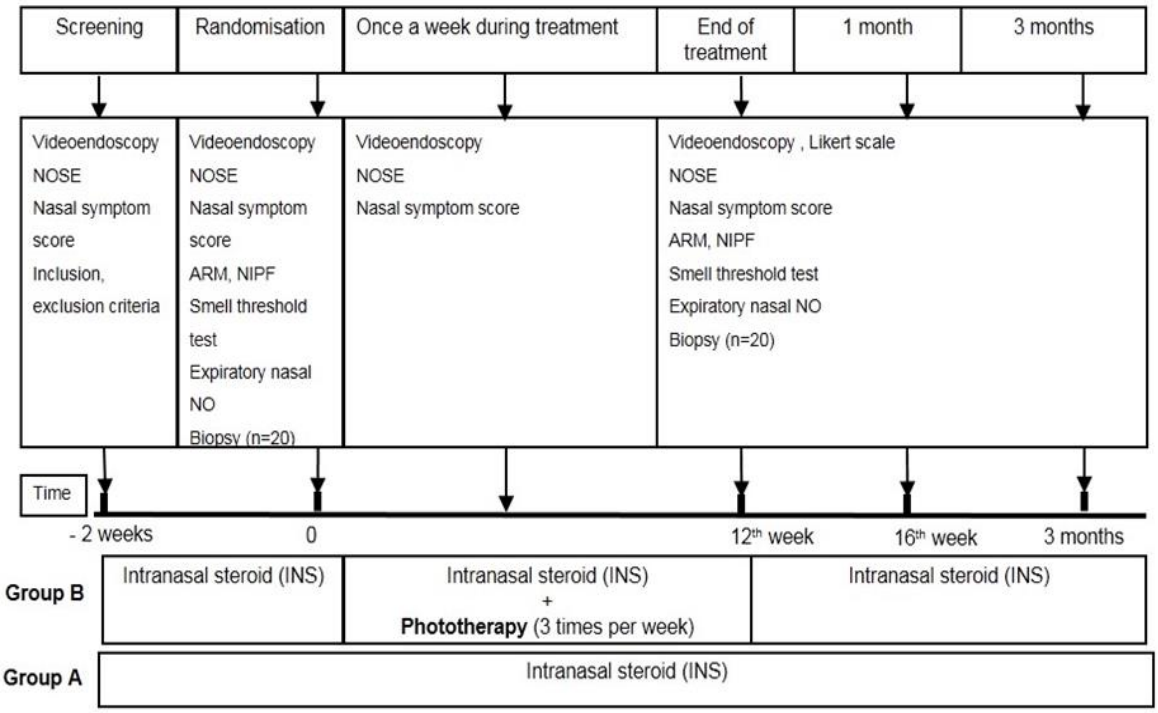


Figure 2. Study procedure: shows the visits and examination on a timeline (NOSE QoL: nasal obstruction evaluation score, Nasal symptom score, visual analog score (VAS:0-6), ARM acoustic rhinometry (Volume 0-7 cm (V0-7) and Volume 2-5 cm (V2-5), NIPF nasal inspiratory peak flow, Smell threshold test (UPSIT), Expiratory nasal NO (Kiricsi Á et al. Prospective, multicenter, randomized clinical study to evaluate the clinical efficacy and tolerability of long term mixed ultraviolet and visible light phototherapy in eosinophil nasal polyps. Journal of Photochemistry Photobiology B 2017; 176: 118-123)

NOSE questionnaire for the study of nasal congestion-specific quality of life: Subjects scored from 0 to 4 the influence of nasal congestion on everyday life or sport, with a cumulative value of 0-20 (37,38).

Smell threshold test: For quantitative assessment of the smell threshold, the standardized Smell Threshold Test developed by the University of Pennsylvania was used. The threshold was determined by stimulating the olfactory nerve with a standardized solution series of phenylethyl alcohol, separately in each nostril, in several steps. The average determined threshold concentration of each nostril was then compared to the average for the age group in the healthy population (39,40,41).

Videoendoscopy: The surface of polyps in the treated zones was measured. The change of the endonasal image and the polyp stage (Table 1) was recorded then evaluated according to a 5-point Likert scale by two specialists independently (39,42).

Nasal inspiratory peak flow: Patients measured the flow in their homes (the highest value of three measurements was recorded) with a Youlten (Clement Clark, England) instrument (39).

Acoustic rhinometry: The mid-third and the total volume of the nasal cavity was measured using acoustic rhinometry (GM INSTRUMENTS Acoustic rhinometer/rhinomanometer A1+NR6 clinical/research). V2, 2-5,4 and V0-7 values were determined in both nasal cavities, and the data of the two were added (39).

Exhaled nasal NO level: The NO level of the expiratory nasal air was measured, in 22 volunteers, from Group A - 7, and from Group B - 15 subjects. The measurements were conducted using a NIOX MINOR instrument (Aerocrine AB, Solna, Sweden), and an attachment (CPAP) suitable for the nose was installed to the filter (43-45).

Histological examination, biopsy

In restricted number of subjects (8) biopsy was taken from the nasal polyps. The cellular composition of the surface respiratory epithelium, the subepithelial basal membrane (subepithelial fibrosis) and the condition of the mucous glands, the inflammatory cellular

composition of the stroma were investigated. The semiquantititve determination of tissue eosinophil granulocytes and mastocytes were carried out.

Statistical analysis

The subsequent data was analyzed using SPSS 23 and Statistica 12 software. The symptom scores on the visits were analyzed with the Friedman test, a p value less than 0, 05 was considered statistically significant. As a post hoc test, the Wilcoxon Signed test was used with the Bonferroni correction ($p<0$, 0083 was statistically significant).

Evaluation	**Screening/ inclusion**	**Randomization**	**1-36 treatments**	**Once a week during the treatments**	**24 hours after last treatment**	**1 and 3 month follow-up**
Eligibility criteria	x	x				
Nasal symptom scores (VAS:0-6)	x	x		x	x	x
Nasal endoscopy	x	x		x	x	x
UV phototherapy			x in Group B			
General physical examination	x				x	
Urine Pregnancy Test		x			x	
NIPF/ ARM		x			x	x
NOSE QoL	x	x		x	x	x
UPSIT		x			x	x
Unwanted events		x	x	x	x	x
Expiratory nasal NO (n= 30)		x			x	x
Drugs	x	x	x	x	x	x

Table 2: Study plan shows the visits, and examinations performed during each visit (NIPF nasal inspiratory peak flow, ARM acoustic rhinometry NOSE QoL: nasal obstruction evaluation score, UPSIT University of Pennsylvania smell threshold test, Nasal symptom score, visual analog score (VAS:0-6)) (Kiricsi Á et al. Prospective, multicenter, randomized clinical study to evaluate the clinical efficacy and tolerability of long term mixed ultraviolet and visible light phototherapy in eosinophil nasal polyps. Journal of Photochemistry Photobiology B 2017; 176: 118-123)

3.2. Efficacy of postoperative intranasal mUV/VIS phototherapy in the prevention of recurrence of nasal polyps

SUBJECTS

Thirty patients were enrolled from 16 to 65 years of age taking standard dose of intranasal steroid with bilateral recurrent nasal polyps. They were divided in two groups, in group A they received only intranasal steroid (mometason furoate, 2x100-100 ug) during the study. In group B they received combined UV light (6 J/cm2) 3 times per week for 12 weeks and intranasal steroid. They were not randomized, but selected in the two groups according to the history, atopy, the number of previous surgeries and the polyp size before present functional endoscopic surgery for the equal distribution.

We started the 12 week treatment 2-4 weeks after functional endoscopic sinus surgery, depending on the recovery of the mucosa. During the study, demographical data, nasal endoscopy images and clinical data were collected. We recorded total nasal score, NOSE quality of life, nasal inspiratory peak flow and acoustic rhinometry. The follow up interval was 6 months. For the evaluation of short-term safety and tolerability we recorded side-effects, unwanted events and nasal endoscopic video images.

METHODS

Nasal symptom score and the total nasal symptom score (TNS): subjects evaluated nasal obstruction, rhinorrhea, facial/headache, loss of the sense of smell separately by pointing on a 0-6 visual analogue scale, cumulative value of symptom scores 0-24, from the inclusion until the 6 months follow-up period once a week (39).

NOSE questionnaire for the study of nasal congestion-specific quality of life: Subjects scored from 0 to 4 the influence of nasal congestion on everyday life or sport, with a cumulative value of 0-20 (38,39).

Videoendoscopy: The surface of the ethmoid region to be treated was measured. The change of the endonasal image and the size of recurrant polyp was recorded then evaluated according to a 5-point Likert scale by two specialists independently (39,42).

Nasal inspiratory peak flow: Patients measured the flow in their homes (the highest value of three measurements was recorded) with a Youlten (Clement Clark, England) instrument (39).

Acoustic rhinometry: The mid-third and the total volume of the nasal cavity was measured using acoustic rhinometry (GM INSTRUMENTS Acustic rhinometer/rhinomanometer A1+NR6 clinical/research). V2, 2-5,4 and V0-7 values were determined in both nasal cavities, and the data of the two were added (39).

Exhaled nasal NO level: The NO level of the expiratory nasal air was measured, in 22 volunteers, from Group A - 7, and from Group B - 15 subjects. The measurements were conducted using a NIOX MINOR instrument (Aerocrine AB, Solna, Sweden), and an attachment (CPAP) suitable for the nose was installed to the filter (43-45).

Statistical analysis

The data were analyzed using IBM SPSS Statistics 20. software. The significance level was 0,05. The clinical data showed no normal distribution with one sample Kolmogorov-Szmirnov probe in the two groups, they were compared with Mann-Whitney and Fisher's exact probe. The symptom scores on the visits were analyzed with the Wilcoxon Signed test used with the Bonferroni correction.

RESULTS

4.1. **Efficacy and tolerability of intranasal mUV/VIS phototherapy in nasal polyposis**

76 of the 87 enrolled patients finished the study (average age 49, 61 ± 11, 23 years; female/male ratio 26/50). In Group A consisted of 24 patients (average age 49, 61 ± 11, 23 years; female/male ratio 10/14), and Group B consisted of 52 patients (average age 48, 19 ±11, 95 years; female/male ratio 16/36). Eleven subjects were excluded from the study: in Group A, 6 patients (2 systemic steroid use, 4 compliance problems) and in Group B, 5 patients (3 compliance problems, 2 intercurrent infections). Data from the drop-outs were not included in the evaluation. Patients who were taking drugs (i.e., photosensitizers, non-steroidal anti-inflammatory drugs, and antibiotics) were excluded, washout periods for medications were strictly considered.

Nasal symptom score and total nasal symptom score

In the phototherapic Group B, significant improvement was observed in all of the nasal symptom scores and in the total nasal score both at the end of phototherapy and during follow-up (1 and 3 month) In Group A, no significant improvement was measured (Figure 3).

Nasal obstruction symptom evaluation

In Group B, significant improvement was found after phototherapy and at the two check-ups occasions during follow up, whereas in Group A, no significant change was observed (Figure 4).

Smell Threshold Test

In group B, the results of the smell threshold test showed a significant improvement after phototherapy, which was maintained even 3 months after phototherapy. In group A, no significant change was observed (Figure 4).

The fact that no decrease in smell function was observed in any of the patients in Group B indicates that intranasal mUV/VIS phototherapy treatment in the applied dose does not damage the olfactory epithelium.

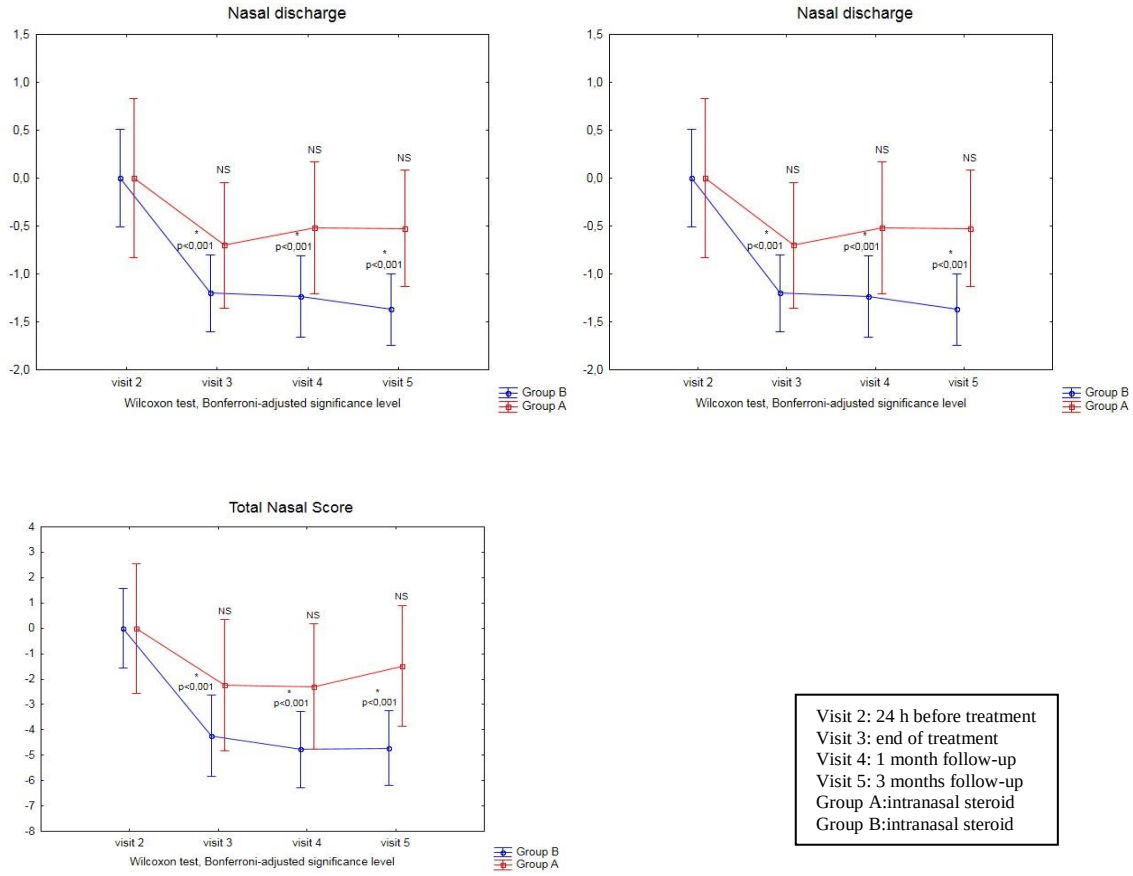


Figure 3. Nasal symptoms: nasal congestion, nasal discharge, total nasal score relative to baseline before treatment (visit 2), at the end of treatment (visit 3), at one month follow up (visit 4) and three months follow up visit (visit 5) in the two groups. Group A red line, Group B (phototherapy) blue line.

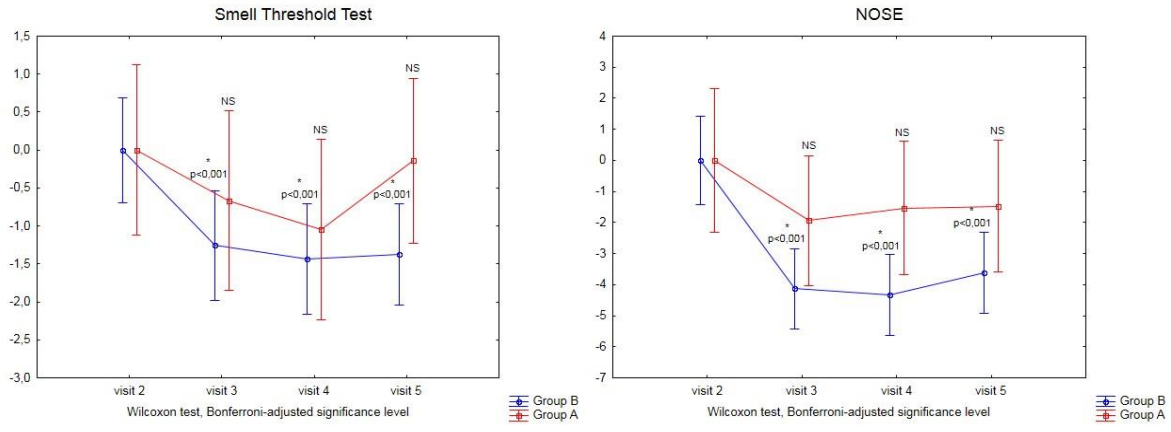


Figure 4. *Nasal symptoms*: UPSIT smell threshold test and the nasal obstruction evaluation score (NOSE) relative to baseline before treatment (visit 2), at the end of treatment (visit 3), at one month follow up (visit 4) and three months follow up visit (visit 5) in the two groups. Group A red line, Group B (phototherapy) blue line. (Visit 2: 24 h before treatment; Visit 3: end of treatment; Visit 4: 1 month follow-up; Visit 5: 3 months follow-up; Group A:intranasal steroid; Group B:intranasal steroid + mUV/VIS)

Videoendoscopy

The videoendoscopic images showed significant improvements in polyp stage and grade on both nostrils of patients in Group B after phototherapy. No significant change was detected in patients belonging to Group A (Figure 5 and 6).

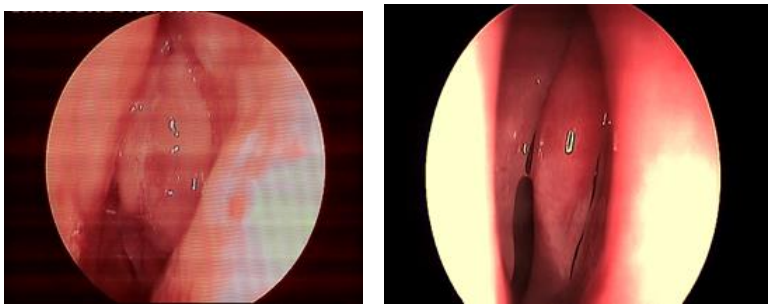


Figure 5: *Endoscopic view:* a) before treatment, b) after treatment (the same patient)

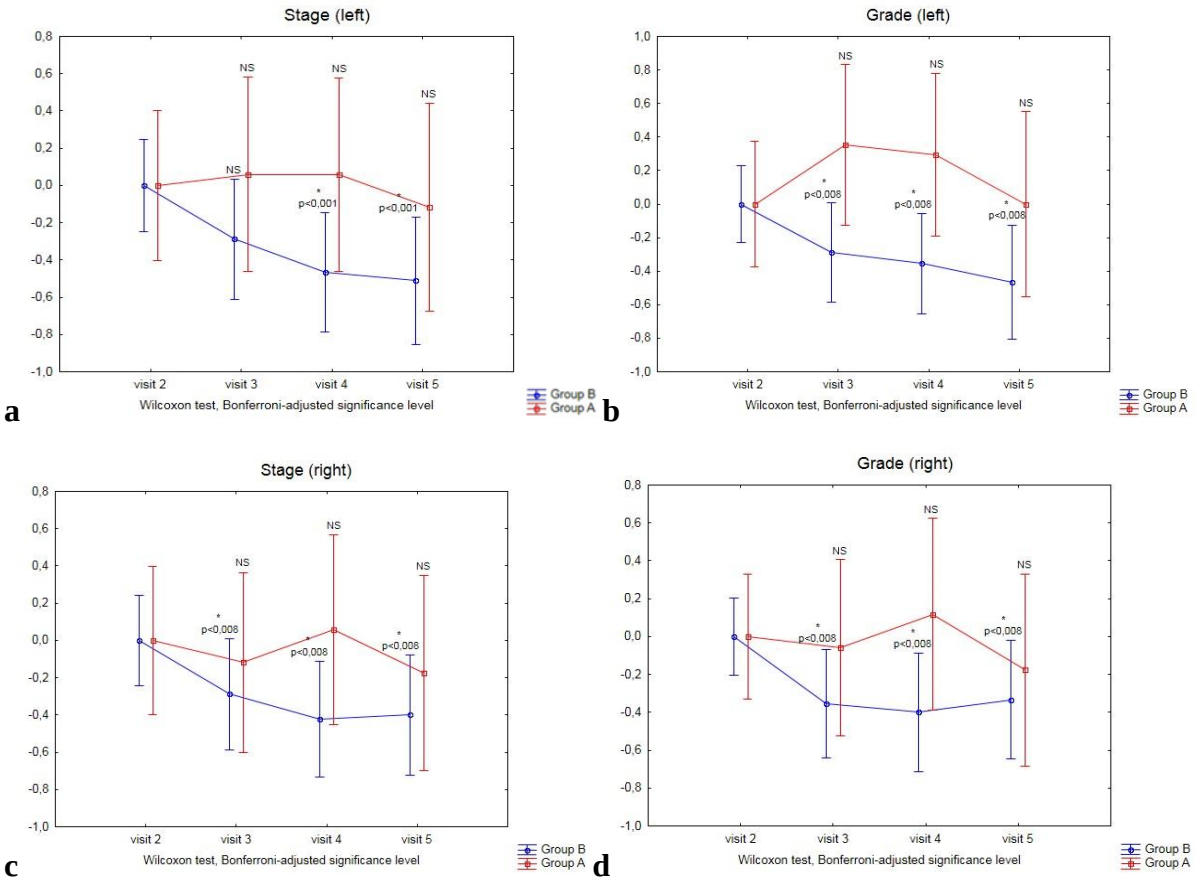


Figure 6: Polyp size a) stage left side, b) grade left side, c) stage right side and d) grade right side before treatment (visit 2), at the end of treatment (visit 3), at one month follow up (visit 4) and three months follow-up visit (visit 5) in the two groups. Group A red line, Group B (phototherapy) blue line. (Visit 2: 24 h before treatment; Visit 3: end of treatment; Visit 4: 1 month follow-up; Visit 5: 3 months follow-up; Group A:intranasal steroid; Group B:intranasal steroid + mUV/VIS)

Nasal inspiratoriy peak flow

In Group A, no significant improvement was found. In Group B, a significant increase was measured between the screening visit and the 3 month follow-up (Figure 7).

Acoustic rhinometry

In group B, a tendency of improvement was measured, but this was not significant. In group A, no improvement could be identified (Figure 7).

Exhaled nasal NO

Neither of the groups showed significant changes in the expiratory nasal NO level (Figure 7).

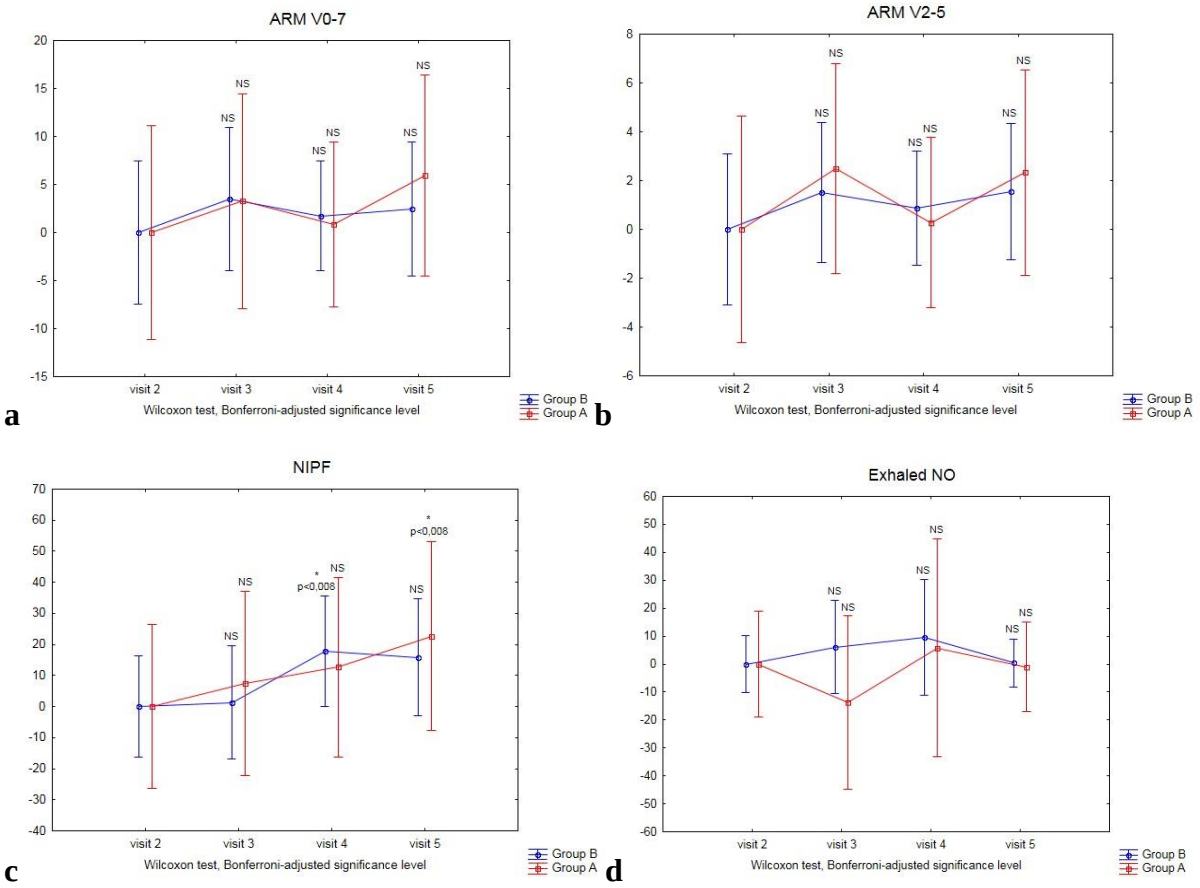


Figure 7: *Nasal volume, nasal inspiratory peak flow and exhaled NO:*Acoustic rhinometry (ARM) **a**)Volume 0-7 cm(V0-7) and **b**)Volume 2-5 cm(V2-5) and **c**) nasal inspiratory peak flow and **d**) exhaled NO test relative to baseline before treatment (visit 2) at the end of treatment (visit 3), at one month follow-up (visit 4) and three months follow-up (visit 5) in the two groups. Group A red line, Group B (phototherapy) blue line. (Visit 2: 24 h before treatment; Visit 3: end of treatment; Visit 4: 1 month follow-up; Visit 5: 3 months follow-up; Group A:intranasal steroid; Group B:intranasal steroid + mUV/VIS)

Biopsy

The histopathological examination showed thick basal membrane in each sample. We observed the decrease of eosinophilia and inflammation after phototherapy and 3 months follow up. No intraepithelial lymphocytosis, stromal fibrosis or myofibroblast proliferation occurred (Figure 8).

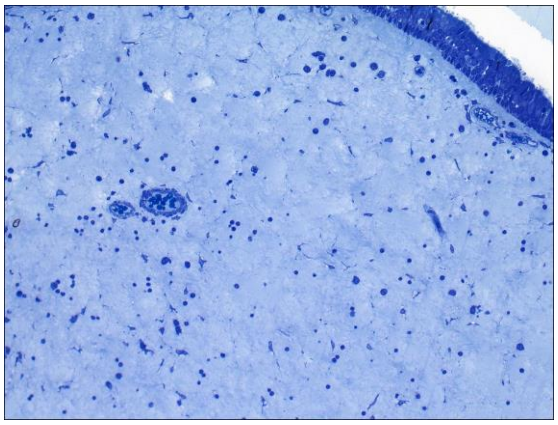
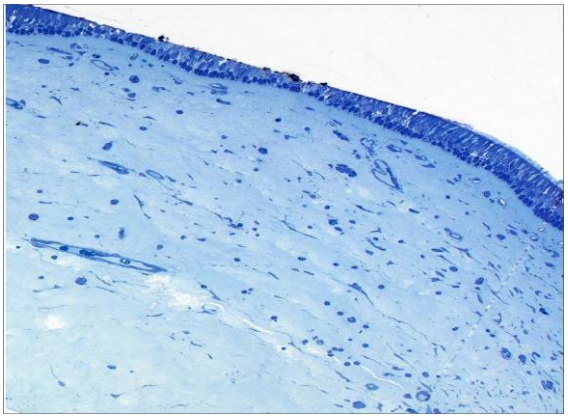
a  **b** 

Figure 8. Histopathological examination: edematous nasal mucosa with ciliated respiratory epithelial cells a) before and b) after treatment (Toluidin-blue, 20x)

Mixed ultraviolet and visible light (UV/VIS) phototherapy was well tolerated. No severe side-effects were found. Few patients reported mild dryness of the nasal mucosa, which disappeared in a few days with the use of Coldastop® nasal drops. No systemic rescue treatment was necessary.

4.2. **Efficacy of postoperative intranasal mUV/VIS phototherapy in the prevention of recurrence of nasal polyps**

There was no significant difference in the basic clinical and demografical data of the patients in the two groups. From the 30 enrolled patients 15 finished the study, eight in Group B (female/male ratio 1/7) and seven in Group A (female/male ratio 2/5).

We observed significant improvement in NOSE Quality of life (p=0,009) and in total nasal score (p=0,008) in Group B at six months follow up (Figure 9).

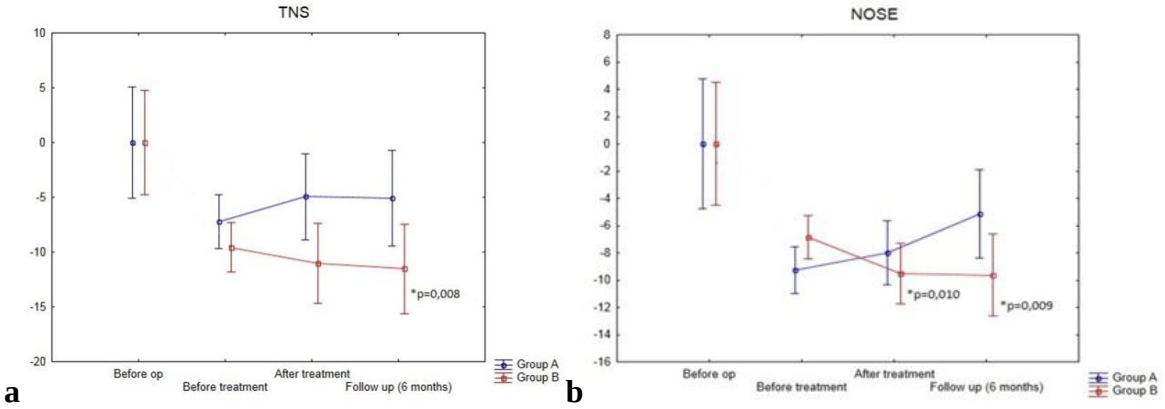


Figure 9. a) Total nasal score (TNS) and b) Nasal obstruction quality of life Questionarre (NOSE) in Group A(blue line) and Group B (red line) before treatment, after treatment and 6 months follow up.

In Group B 4 of eight patients had recurrent polyps 6 months after finishing mUV/VIS phototherapy. In Group A: all of 7 patients had recurrent polyps. This difference was significant between the two groups (p=0,0289) (Figure 10).

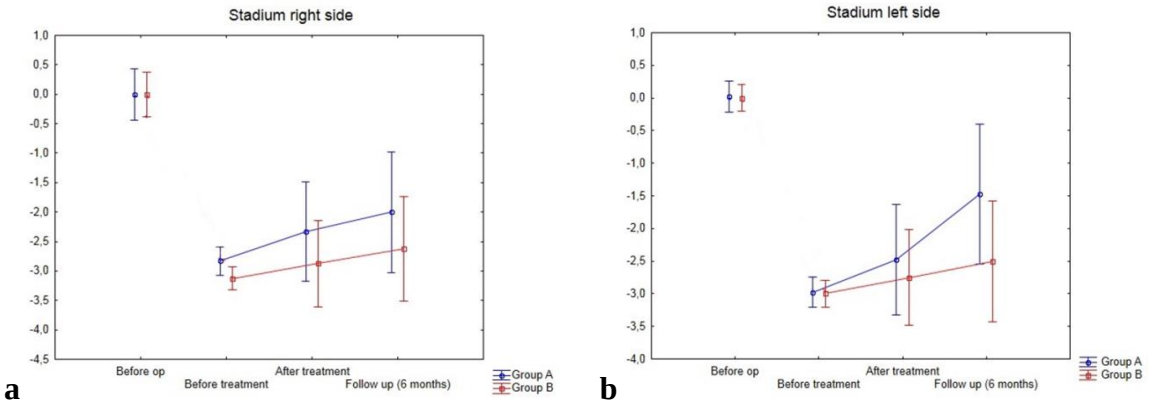


Figure 10: Size of nasal polyps a) right side and b) left side in Group A (blue line) and Group B (red line) before treatment, after treatment and the 6 months follow up.

Nasal inspiratory peak flow, acoustic rhinometry and exhaled nasal NO measurement: Neither of the groups showed significant changes in nasal inspiratoric peak flow and acoustic rhinometry.

Mixed ultraviolet and visible light (UV/VIS) phototherapy was well tolerated. No severe side-effects were found. Three patients reported mild dryness of the nasal mucosa, which

disappeared in a few days with the use of Coldastop® nasal drops. No systemic rescue treatment was necessary.

4.3 Development of a new handler, a measurement device and an armrest for intranasal phototherapy under endoscopic supervision

Mixed ultraviolet light (Rhinolight®) is composed of more than 70% of visible light, 25% of UV-A light, less than 5% of UV-B. The handler device and the target light fitted to the basic Rhinolight IV. device (Figure 11).

Figure 11. Rhinolight IV. device

The original Rhinolight IV device emitting cold light has been equipped with a target light. Prior to the application of the therapeutic light, this made the area to be treated well-visible. The target light was blue and fell into the visible light range (Figure 12).

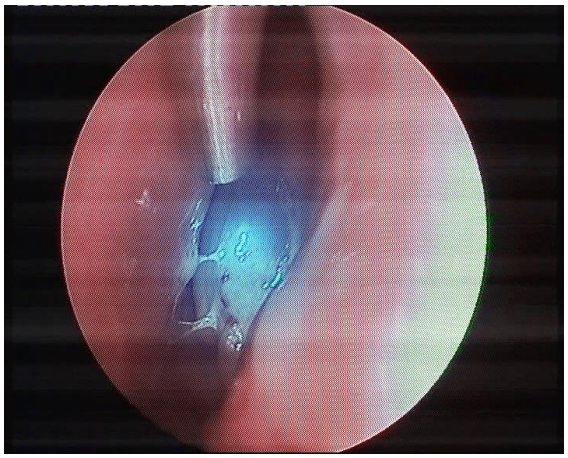


Figure 12. Target light (endoscopic view)

4.3.1. Measurement device

The nasal polyp surface area to be treated was separately in both halves of the nasal cavity in the following main zones: roof of the ethmoid cavity, medial wall of the ethmoid sinus, lateral wall of the ethmoid sinus, sphenoethmoidal recess. Under endoscopic supervision the size of the polyps was measured by a special instrument, an optical extension designed for the study by Ferencz Ignácz (Department of Optics and Quantum Electronics University of Szeged). This instrument made precise evaluation of the extension of the polyps possible (Figure 13).

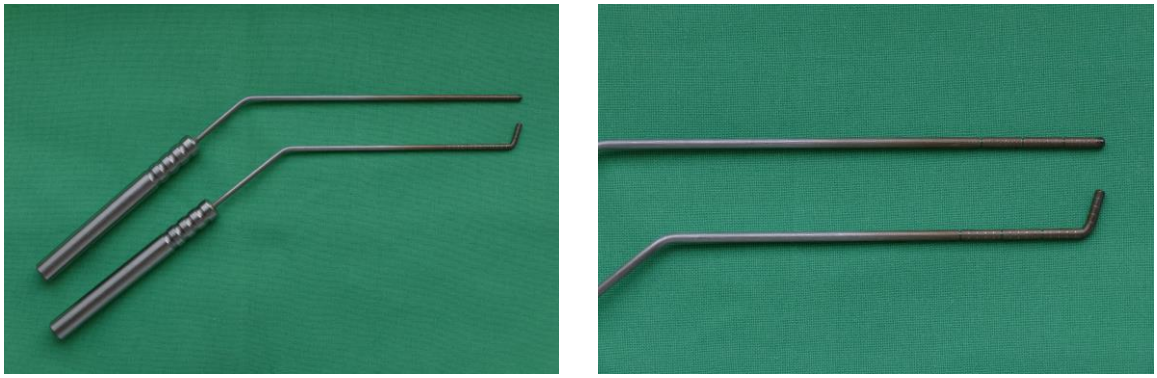


Figure 13. Measurement device

The area of each irradiated zone was measured every four weeks, and the phototherapy dosages were modified accordingly (Figure 14). If the treated polyp entirely regressed before the end of the 3-month treatment period, treatment had to be ended for that zone.

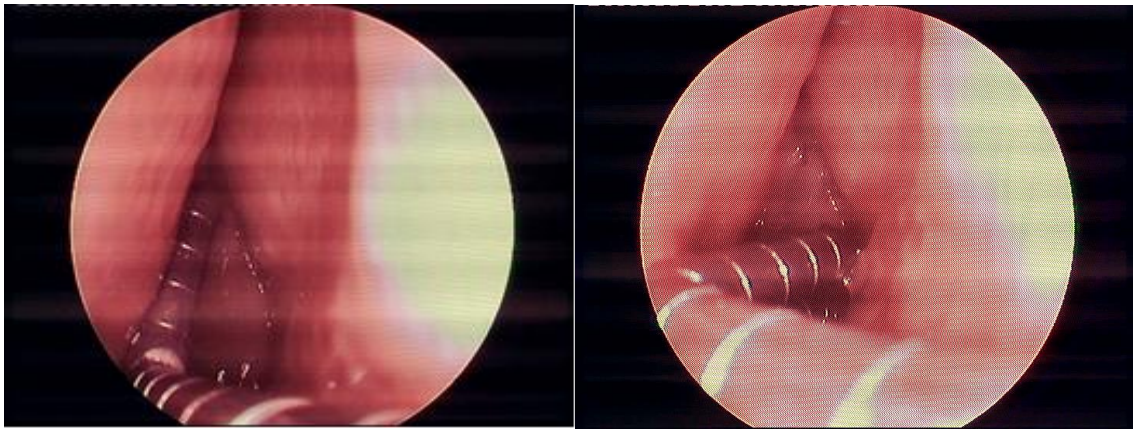


Figure 14. Measurement under endoscopic supervision

4.3.2. Handler device

We developed in cooperation with the Department of Optics and Quantum Electronics a handler device, which is curve-ended to reach even the narrowest parts of the nasal cavity (Figure 15). The handler device is made of fiber optic quartz bunch transmitting the UV spectrum, located in a stainless steel tube. It is capable of transmitting the light (both the target and the therapeutic) in a targeted manner onto the polyp's surface. It can be connected to the flexible light guide of the original device. It is compatible with cleaning, disinfection and sterilization procedures generally applied in clinical circumstances.

Figure 15. Handler device

After measuring the two dimensional extension of the isolated polyp surfaces, the treatment time was defined based on a dose-table. In the first 2 weeks the dosage was 6 J/cm^2 3 times

per week for each treated zone. In the following ten weeks 9 J/ cm^2 3 times per week for each zone. If a patient did not tolerate the given dose, 50% dosage reduction was made (Table 3).

4.3.3. Armrest

It is outstanding important to stay as fixed as possible during phototherapy, because the operator uses both hands at the same time, in the same nostril. The duration of the treatment was long, sometimes 30-40 minutes, and both patient and operator had to stay in a well-controlled head and arm position. A special armrest was designed to the 'exhausting' intervention more comfortable. The phototherapy was done in sitting position, so it was very important not to move more than 2-3 mms (Figure 16).

Figure 16. The armrest and its use during phototherapy

Together with all these new instruments it was possible to perform the phototherapy under endoscopic supervision precisely, securely and easily both for the patient and the doctor even in the narrowest parts of the nasal cavity (Figure 17).

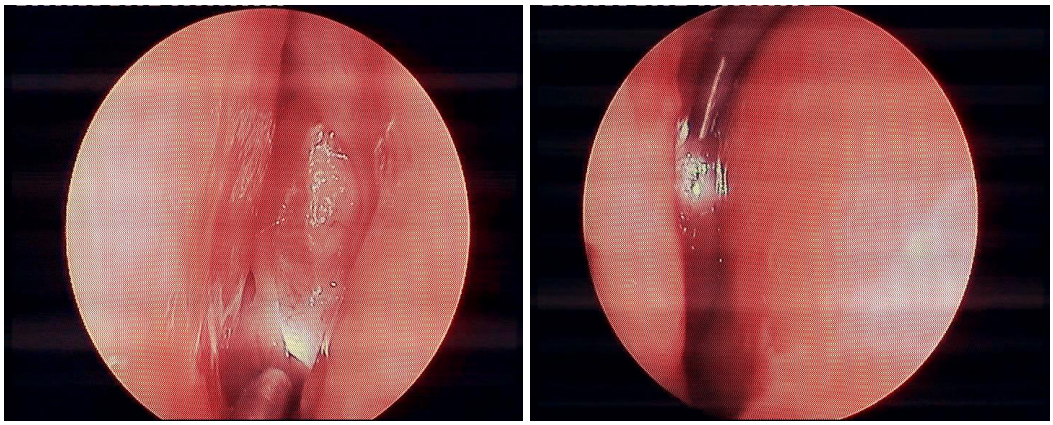


Figure 17. Phototherapy with the new handler device under endoscopic supervision

6 J/cm2																		
mm	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
3	26 s	34 s	43 s	51 s	60 s	69 s	77 s	86 s	94 s	103 s	111 s	120 s	129 s	137 s	146 s	154 s	163 s	171 s
4	34 s	46 s	57 s	69 s	80 s	91 s	103 s	114 s	126 s	137 s	149 s	160 s	171 s	183 s	194 s	206 s	217 s	229 s
5	43 s	57 s	71 s	86 s	100 s	114 s	129 s	143 s	157 s	171 s	186 s	200 s	214 s	229 s	243 s	257 s	271 s	286 s
6	51 s	69 s	86 s	103 s	120 s	137 s	154 s	171 s	189 s	206 s	223 s	240 s	257 s	274 s	291 s	309 s	326 s	343 s
7	60 s	80 s	100 s	120 s	140 s	160 s	180 s	200 s	220 s	240 s	260 s	280 s	300 s	320 s	340 s	360 s	380 s	400 s
8	69 s	91 s	114 s	137 s	160 s	183 s	206 s	229 s	251 s	274 s	297 s	320 s	343 s	366 s	389 s	411 s	434 s	457 s
9	77 s	103 s	129 s	154 s	180 s	206 s	231 s	257 s	283 s	309 s	334 s	360 s	386 s	411 s	437 s	463 s	489 s	514 s
10	86 s	114 s	143 s	171 s	200 s	229 s	257 s	286 s	314 s	343 s	371 s	400 s	426 s	457 s	486 s	514 s	543 s	571 s
11	94 s	126 s	157 s	189 s	220 s	251 s	283 s	314 s	346 s	377 s	409 s	440 s	471 s	503 s	534 s	566 s	597 s	629 s
12	103 s	137 s	171 s	206 s	240 s	274 s	309 s	343 s	377 s	411 s	446 s	480 s	514 s	549 s	583 s	617 s	651 s	686 s
13	111 s	149 s	186 s	223 s	260 s	297 s	334 s	371 s	408 s	446 s	483 s	520 s	557 s	594 s	631 s	669 s	705 s	743 s
14	120 s	160 s	200 s	240 s	280 s	320 s	360 s	400 s	440 s	480 s	520 s	560 s	600 s	640 s	680 s	720 s	760 s	800 s
15	129 s	171 s	214 s	257 s	300 s	343 s	386 s	429 s	471 s	514 s	557 s	600 s	643 s	686 s	729 s	771 s	814 s	857 s

9 J/cm2																		
mm	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
3	39 s	51 s	64 s	76 s	90 s	103 s	115 s	129 s	141 s	154 s	166 s	180 s	193 s	205 s	219 s	231 s	244 s	256 s
4	51 s	69 s	85 s	103 s	120 s	136 s	154 s	171 s	189 s	205 s	223 s	240 s	256 s	274 s	291 s	309 s	325 s	343 s
5	64 s	85 s	106 s	129 s	150 s	171 s	193 s	214 s	235 s	256 s	279 s	300 s	321 s	343 s	364 s	385 s	406 s	429 s
6	76 s	103 s	129 s	154 s	180 s	205 s	231 s	256 s	283 s	309 s	334 s	360 s	385 s	411 s	436 s	463 s	489 s	514 s
7	90 s	120 s	150 s	180 s	210 s	240 s	270 s	300 s	330 s	360 s	390 s	420 s	450 s	480 s	510 s	540 s	570 s	600 s
8	103 s	136 s	171 s	205 s	240 s	274 s	309 s	343 s	376 s	411 s	445 s	480 s	514 s	549 s	583 s	616 s	651 s	685 s
9	115 s	154 s	193 s	231 s	270 s	309 s	346 s	385 s	424 s	463 s	501 s	540 s	534 s	616 s	655 s	694 s	733 s	771 s
10	129 s	171 s	214 s	256 s	300 s	343 s	385 s	429 s	471 s	514 s	556 s	600 s	639 s	685 s	729 s	771 s	814 s	856 s
11	141 s	189 s	235 s	283 s	330 s	376 s	424 s	471 s	519 s	565 s	613 s	660 s	706 s	754 s	801 s	849 s	895 s	943 s
12	154 s	205 s	256 s	309 s	360 s	411 s	463 s	514 s	565 s	616 s	669 s	720 s	771 s	823 s	874 s	925 s	976 s	1029 s
13	166 s	223 s	279 s	334 s	390 s	445 s	501 s	556 s	612 s	669 s	724 s	780 s	835 s	891 s	946 s	1003 s	1057 s	1114 s
14	180 s	240 s	300 s	360 s	420 s	480 s	540 s	600 s	660 s	720 s	780 s	840 s	900 s	960 s	1020 s	1080 s	1140 s	1200 s
15	193 s	256 s	321 s	385 s	450 s	514 s	579 s	643 s	706 s	771 s	835 s	900 s	964 s	1029 s	1093 s	1156 s	1221 s	1285 s

Table 3. Treatment time (6J/cm^2 and 9 J/cm^2)

DISCUSSION

5.1. **Efficacy and tolerability of mUV/VIS in nasal polyposis**

CRSwNP is a chronic disease, which has a major impact on quality of life and daily activity. The prevalence of CRSwNP in the population is 1-4%, often present with concomitant allergic rhinitis, asthma and other pulmonary diseases like cystic fibrosis, primary ciliary dyskinesia or aspirin intolerance. CRSwNP can be clinically characterized by oedema formations extending into the nasal cavity causing nasal obstruction, rhinorrhea, reduction/loss of the sense of smell, and/or facial/headache (10,11). In the pathogenesis, terminally differentiated eosinophils migrate and accumulate in the tissues where they release various cytokines and chemokines, such as IL-5, IL-3, GM-CSF, or RANTES. These factors can further enhance the inflammatory process by contributing to stromal fibrosis, epithelial damage, increased oedema and increased extracellular matrix protein production. Thus, eosinophils potentially damaged cells and their prolonged survival are the key factors in the pathogenesis (10,13). Apoptotic cell death is determining in the regulation of eosinophil's removal. Delayed apoptosis has been reported as an important mechanism for tissue eosinophilia in several diseases, including nasal polyps. IL-5 is one of the principle cytokines which promotes eosinophil maturation, activation and survival. CD4+ T cells are considered to be the main source of IL-5, but other cell types including mast cells and eosinophils also release this cytokine (1,2,10,11). Regarding to the role of surface epithelial cells in the process of nasal polyp formation, is not neglectable since they have a capacity to produce eotaxins, GM-CSF and RANTES activating eosinophils, and SCF attracting mast cells, respectively. (46) In addition, the proliferation capacity of surface epithelial cells is related to recurrance rate of polyp similarly to degree of eosinophil density (47). These facts make the surface epithelials cells considerably targeted by rhinophototherapy.

During the initial research, photosensitizing drugs (psoralen) and phototherapy were combined (PUVA psoralen and ultraviolet A). Csoma et al proved that intranasal PUVA therapy significantly reduced the symptoms of patients suffering from allergic rhinitis. Our research group showed that in CRS, both the number of eosinophils and the level of IL-5 decreased after intranasal PUVA phototherapy, accompanied by a decreasing trend of the level of ECP, a cytotoxic mediator which participates in tissue damage. We proved that

intranasal PUVA phototherapy had an anti-inflammatory effect in nasal polyposis without Samter's triad (asthma, aspirin sensitivity and nasal polyps) (26).

Our previous publication revealed that mixed ultraviolet light/visible light (mUV/VIS) intranasal phototherapy was safe and effective in intermittent allergic rhinitis (28). In persistent allergic rhinitis, mUV/VIS improved significantly all nasal symptom scores and nasal inspiratory peak flow results (33). The results proved that mUV/VIS treatment was safe and effective in persistent allergic rhinitis. Mixed UV/VIS phototherapy induced a dose-dependent increase of eosinophil and T-cell apoptosis. Several data suggests that persistence of tissue eosinophilia is very important in the pathogenesis of CRSwNP as well, the aim of this study was to evaluate the capacity of mUV/VIS light in suppressing the clinical symptoms of patients with eosinophilic polyposis and to compare the efficacy of a treatment based only on the regular use of intranasal steroids with a unique combination therapy of mUV/VIS phototherapy and intranasal steroids in vivo. During the 12-week treatment period, the subjects received the total dosage of phototherapy in lower energy prolated over time. This kind of treatment protocol fits in the safety research methods. The treatment was delivered under endoscopic visualization, in a targeted, highly controlled way, to affect only the pathological mucosa and to save the normal mucosa from direct ultraviolet light strain. In the control group, intranasal steroid therapy, the gold standard basic therapy in nasal polyposis was applied. Due to medical-ethical reasons, the placebo controlled study design was not preferred (48).

Different subjective and objective methods were used to assess the efficacy of phototherapy. A major problem in the nasal area is that objective measures of nasal resistance do not correlate with subjective sense of obstruction. The nasal valve region primarily determines nasal resistance, whereas the sensation of nasal obstruction may be related to congestion in other areas, like the ethmoid region (49).

The quality of life of patients with CRSwNP is determined by the nasal congestion, discharge, headache and lose of the sense of smell. Subjects scored these symptoms on a visual analog scale during the study. The results were compared to endoscopic findings during visits. All of this data showed significant improvement in the group that received phototherapy and these good results could be observed even 3 months after finishing phototherapy.

The disturbance of olfaction has an effect on everyday life, because it is closely involved in the regulation of visceral function and emotional expression. The olfactory receptor area is localized to a small region of the cribriform plate, adjacent to nasal septum

and superior turbinate. Phototherapy induced shrinking of the nasal polyps cause airflow increase into this superior nasal area, improving the olfaction of the patient. The results showed significant increase in the smell threshold in the phototherapy group.

The Lund Mackay scoring system of the nasal endoscopic findings is the only system regarding mucosal thickening. As polyposis is present, nasal endoscopy scoring is very useful in treatment evaluation, despite the discrepancy between objective and subjective findings (39,49). We performed endoscopy as an objective measurement to evaluate the efficacy of phototherapy. Significant improvement in the stage and grade of the polyps in the phototherapy group was observed, and these findings were present in the 3-month follow up.

Several authors studied acoustic rhinometry (ARM) and nasal inspiratory peak flow (NIPF) in CRSwNP. Proimos et al found both methods promising for objective evaluation and monitoring of nasal obstruction in CRS. NIPF correlated strongly with nasal obstruction visual analog scale (VAS), ARM correlated moderately with VAS scaling (50). According to Spronsen et al subjective nasal obstruction correlates better with objective functional measurements of nasal airflow resistance, like NIPF, than with measurements of nasal cavity width, like ARM, despite the fact that they are used in many studies as an outcome of treatment effects (51). Nathan et al found 5 to 10 % of reproducibility by acoustic rhinometry in allergic rhinitis (49). The main basis for poor repeatability can arise from technical factors (nosepiece fits) and both the nasal cycle and diurnal variations in nasal airway caliber. In the present study, a significant improvement was observed in NIPF one month after the end of phototherapy, and a tendency of improvement at the end of phototherapy. In ARM, the results showed moderate, non-significant improvement at the end of phototherapy.

Exhaled nitric oxide (NO) measurement is a simple and non-invasive method for monitoring airway inflammation. The major part of nitric oxide is produced by the ciliary epithelia cells in the paranasal sinuses. Its level may be low even in the presence of normal activity if the sinus ostia are blocked because of nasal polyps. Successful treatment results in higher nasal NO (nNO) by opening the maxillary sinus ostium. An increase in inflammation could also show a rise in concentrations, therefore, a nasal endoscopy is needed to distinguish between these possibilities (43-45). Jeong et al found lower nNO in CRSwNP, than in CRSwNP combined with allergic rhinitis (AR). The healthy control group's nNO levels were the highest (52). They found a significant inverse relation between nNO and severity of nasal obstruction. We performed nNO level measurement with an electrochemical analyzer in 30 subjects: a non-significant difference was found, phototherapy group nNO level increased, however, in intranasal steroid group, it decreased.

5.2. Efficacy of mUV/VIS in the prevention of recurrence of nasal polyps

In our previous study we proved, that mUV/VIS phototherapy reduced the symptoms of patient with CRSwNP. During phototherapy mUV/VIS targeted directly the surface of the polyps. In this study we wanted to examine the efficacy of mUV/VIS on reducing the tissue eosinophilia and inflammation in the mucosa. There is no international literature or guideline regarding the use of mUV/VIS phototherapy after functional endoscopic surgery. Our study was the first to evaluate the efficacy and tolerability of postoperative phototherapy.

Regarding the high recurrence rate of CRSwNP several observations were made. Batra et al's cross sectional study's objective was to construct the clinical profile of patients with chronic rhinosinusitis (CRS) with/without polyposis undergoing revision sinus surgery and to evaluate the relationship of polyposis, asthma, acetylsalicylic acid (aspirin) (ASA) sensitivity, inhalant allergies, and previous sinus surgery on disease severity. 225 patients data were analyzed. They found that patients with CRS with polyposis had a statistically significant increase in presence of asthma, inhalant allergy and ASA sensitivity. The number of previous surgeries had a statistically significant correlation with endoscopy and CT scores. The group of recalcitrant CRS patient undergoing revision sinus surgery has a high prevalence of polyposis, asthma, inhalant allergy, ASA sensitivity, and elevated disease. The polyp phenotype signifies statistically higher prevalence of associated comorbidities and greater objective disease severity. The presence of asthma, inhalant allergy, and ASA sensitivity also predicts statistically higher disease burden (53).

McMains et al reported objective and subjective outcomes after revision sinus surgery (RESS) for chronic rhinosinusitis (CRS). They performed a retrospective analysis of prospectively collected data in 125 patients requiring revision functional endoscopic sinus surgery after failing both maximum medical therapy and prior sinus surgery for CRS. Computed tomography (CT) scans were graded as per Lund-MacKay and patient symptom scores were recorded using the Sinonasal Outcome Test 20 (SNOT-20) instrument. Individual rhinosinusitis symptoms were evaluated on a visual analog scale (0-10) before and after surgery, with a minimum 2-year follow-up. They found that patients with asthma and polyposis had higher CT scores. At 12-month follow-up, each individual symptom score decreased significantly. Overall, 10 patients failed revision sinus surgery and required additional surgical intervention, all of them had nasal polyposis (54).

Wynn et al. aim was to provide reference information for recurrence rates and need for revision surgery in patients with severe nasal polyposis. One hundred and eighteen records were reviewed. Fifty percent of patients had asthma, and 79% had documented allergy. All patients required extensive bilateral nasal polypectomy, complete anterior and posterior ethmoidectomy, and maxillary sinusotomy, 85% also had frontal or sphenoid sinusotomy. Follow-up ranged from 12 to 168 months. 60% developed recurrent polyposis, from which 47% were advised to undergo revision surgery, and 27% underwent surgery. History of previous sinus surgery or asthma predicted higher recurrence and revision surgery. History of allergy also predicted recurrence and need for revision. In their study, patients with asthma are at higher risk of recurrence (55).

DeConde et al performed a prospective multicenter cohort study of patients undergoing ESS for medically recalcitrant CRSwNP. The objective was to evaluate the prevalence of nasal polyp recurrence up to 18 months after endoscopic sinus surgery (ESS) with congruent continuing medical management. All patients received baseline nasal endoscopy quantified using Lund-Kennedy grading. All patients included for final analysis provided at least 6 months of postoperative endoscopy examinations. 363 CRSwNP patients were enrolled. Surgery plus postoperative medical management significantly improved endoscopy total scores at 6 months. The recurrence of nasal polyposis 6 months after endoscopic sinus surgery was 35% and 40% after 18 months. They targeted on the fact both surgical and medical management strategies are warranted to improve upon the observed prevalence of recurrence (56).

Veloso-Teles et al investigations objective was to evaluate endoscopic sinus surgery efficacy in CRSwNP treatment and to establish prognostic factors for disease recurrence. They tried to find independent variables that can predict surgical outcomes in patients with CRSwNP. Eighty-five patients with CRSwNP submitted to endoscopic sinus surgery, and a minimum follow-up of 9 months were selected. Patient demographics, occupational organic exposure (e.g., cotton, fuel gas, wood dust) and inorganic dust exposure (e.g., bleach, metals, cement), comorbidities, previous nasal surgeries, pre- and postoperative symptoms, ear, nose and throat examination findings, computed tomography results, and medical and surgical treatment information were collected from medical records. All rhinologic symptoms improved after surgery, in a statistically significant way, with the best recovery rate for nasal obstruction and the worst for hyposmia. Disease recurrence occurred in 31% of the patient, but only 7% required surgical reintervention. Their analysis identified occupational dust

exposure and non-immunoglobulin E mediated asthma as independent predictive variables in CRSwNP recurrence (57).

International guidelines recommend conservative treatment after surgery in case of chronic rhinosinusitis with nasal polyps, to reduce the number of recurrences (10). Our previous studies proved the positive effect of mUV/VIS phototherapy in CRSwNP. The aim of this study was to answer the question; whether mUV/VIS phototherapy can reduce the rate of recurrence in nasal polyps after surgery. Our thought was that irradiating the mucosa locally, in predilective areas as soon as possible after endoscopic sinus surgery might have an additive role in the treatment of this chronic disease. Our results showed that it might have a supportive role in the treatment of recurrent CRSwNP cases.

6. NEW RESULTS

6.1. **Efficacy of intranasal mUV/VIS phototherapy in nasal polyposis**

Our data show that mixed ultraviolet/visible light phototherapy led to improvement in chronic rhinosinusitis with nasal polyps. The improvement in nasal symptoms, sense of smell and reduced nasal obstruction could be observed even 3 months after finishing intranasal phototherapy, which has an outstanding importance in this chronic disease.

Mixed ultraviolet and visible light (UV/VIS) phototherapy was well tolerated. No severe side-effects were found. Few patients reported mild dryness of the nasal mucosa, which disappeared in a few days with the use of Coldastop® nasal drops. No systemic rescue treatment was necessary.

6.2. **Efficacy of postoperative intranasal mUV/VIS phototherapy in the prevention of recurrence of nasal polyposis**

Mixed UV/VIS therapy significantly reduced the recurrence of nasal polyps, and a significant improvement in Total Nasal Score (TNS: nasal discharge, sneezing, smell ability, nasal obstruction), and Nasal Obstruction Score Evaluation (NOSE) was observed. Rhinophototherapy with standard nasal steroid may have a supportive role in the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP).

No severe side effects were observed, no systemic rescue treatment was necessary. Three patients reported nasal dryness of the nasal mucosa, which was treated with Coldastop® nasal drops.

6.3. **Development of a new handler, a measurement device and an armrest for intranasal phototherapy under endoscopic supervision**

We have developed and successfully used the handler device, the new measurement method and the armrest. It made the treatment of the patients easier and more precise under endoscopic supervision.

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