LITERATURE REVIEW

The efficacy and safety of aerosol therapy in rhinology

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ABSTRACT

Aerosol drug administration has a long history as an important part of the treatment for different respiratory disorders in both adult and paediatric patients. The nebulization process permits the drug delivery directly to the upper and lower airways tracts, allowing increased local effectiveness, and avoids systemic side effects. The aerosol therapy is mainly used in pneumology for lower respiratory tract disorders, a series of drugs having a proven efficacy. Few publications present the efficacy and safety of ENT nebulization, despite its worldwide utilization.

Topical drug delivery to the nasal cavities and paranasal sinuses via aerosols appears to be an interesting, but also a challenging alternative. The transport and deposition of drugs and aerosol particles into the sinuses is debatable due to several factors: sinuses are poorly perfused and virtually non-ventilated cavities; they are protected by the efficient particle filtration function of the nasal cavities. The review evaluates the efficacy and safety of aerosol therapy in rhinologic pathology.

KEYWORDS: aerosol therapy, nebulization, rhinology, rhinitis, sinusitis.

INTRODUCTION

Aerosol drug administration has a long history as an important part of the treatment for different respiratory disorders in both adult and paediatric patients. The nebulization process permits the drug delivery directly to the upper and lower airways tract, allowing increased local effectiveness, and avoids systemic side effects.

Evidence of use of therapeutic aerosols dates from ancient times. The first known reference dates from 1554 BC on a papyrus (the Ebers papyrus) found in Theban necropolis[1,2]. According to it, the Egyptians inhaled the vapours of incinerated herbs (e.g. *Hyoscyamus niger*) for breathing disturbances. Around 1100 BC in China and 1500 BC in South and Central America, opium was smoked for its analgesic and antidiarrheal properties, but with a high toxic effect[1,2]. Charaka and Samhita, two influent Indian physicians back in 600 BC, used aerosols from *Datura stramonium* herbs with anticholinergic properties[1,2].

Evidence of use of aerosol therapy has been found during the days of Hippocrates (460-377 BC), who used the hot vapours for the treatment of several respiratory diseases (breathlessness, cough)[1-3]. Later, in the second century AD, Galen of Pergamon described the efficacy of powder drugs inhalation in relieving nasal and chest symptoms.

The first drawing of a therapeutic inhaler dates from 1654, being developed by the English doctor Christopher Bennet[1]. With the beginning of the Industrial Revolution in 1790, new therapeutic aerosol techniques were developed, such as nebulizers or dry powder inhalers[1]. 1956 represents the beginning of the modern era of pharmacological aerosols, when Medihaler Epi was introduced[1,4] and the development has continued till the present days.

The aerosol therapy is mainly used in pneumology for lower respiratory tract disorders, a series of drugs having a proven efficacy (e.g. bronchodilators, mucolytics, corticosteroids or antibiotics).

Few publications present the efficacy and safety of ENT nebulization, despite its worldwide utilization. The NUAGES survey (2005 in France) evaluated the use and perspectives of

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nebulization in general and specialized medicine and revealed that almost 89% of the interviewed ENT physicians prescribed nebulization therapy to their patients[5,6]. In Romania, there is no official data, but the therapeutic aerosols have a widely spread use in paediatric and adult rhinosinusal and laryngeal inflammatory or infectious pathology.

PHYSICAL CHARACTERISTICS OF AEROSOLS

Aerosols are small, microscopic liquid or solid particles suspended in a gaseous medium. The aerosols used in medicine have a diameter of the order of micrometres. The deposition of the aerosols particles in the airway tract is influenced directly by the size of the particles and varies according to anatomic natural barriers[7,8].

In oral inhalation, which is mainly used and prescribed by pneumologists, the particles with an aerodynamic diameter of 0.5 - 4 μm deposit mainly in the lungs, those between 4 and 5 μm in the bronchi, while those larger than 5 μm accumulate in the oral cavity, the larynx and trachea[5,9]. Particles smaller than 0.5 μm get exhaled.

In nasal inhalation, more frequently recommended by the general practitioners and otorhinolaryngologists, larger particles mainly deposit in the upper airways' mucosa: 10% in the case of 2 μm particles, 50% in those of 5 μm and 90% in 10 μm aerosol particles[5,10,11]. At this level, the particle deposition is also influenced by the local anatomic peculiarities and particle speed. The first filter are the vibrissae found in the nostril, a point where the large particles are allowed to pass. The nasal valve is the site of maximum concentration of aerosol particles. At this point, the airflow passes through a cross-sectional area of 30 mm^2 with 12 - 18 m/s speed[12]. The higher the particles velocity, the higher their concentration level in the upper airways' mucosa[5]. The second deposition location is the inferior turbinate area, with a cross-section of 130 mm^2 which varies over the physiologic nasal cycle. At this point, the airflow velocity decreases at 2 - 3 m/s[12]. Sinuses deposition is controversial, and it seems that particles of 0.7 - 10 μm are optimal.

AEROSOL GENERATORS

For medical use, there are different types of aerosol generators: pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), soft mist inhalers (SMIs) and nebulizers[13,14].

In ENT practice, there are two types of aerosol generators which can be used: sprays and nebulizers. Sprays are ready-to-use portable devices which produce at high-speed large particles (10 - 150 μm); deposition is essentially in the anterior part of the nasal cavity[5,15]. Nebulizers produce, at a lower speed, particles of 1 - 10 μm, with a more distal deposition in the nasal fossae, including the paranasal sinuses[5,16].

There are three types of nebulizers: pneumatic or jet nebulizers (use compressed air; can be used with different liquid substances); ultrasonic nebulizers (use high frequency piezoelectric quartz vibration; do not work properly with substances with high viscosity or in suspension); mesh nebulizers (are silent and small, use the vibration of a microperforated mesh; their functioning is influenced by the device position and the viscosity of the suspensions used). The jet nebulizers are the most used to deliver aerosol therapy, in both ENT adult and paediatric patients[13,14].

DRUG DEPOSITION INTO THE NOSE AND PARANASAL SINUSES

As presented above, the amount of aerosol particles deposit in the nasal cavity is important for nasal symptoms relief and it can be influenced by several important factors. Only 5-20% of particles actually deposit in the nasal cavity. The main controversy is about the amount of aerosol particles that reach the paranasal sinuses. There are several pieces of research which try and succeed in explaining and proving the efficient delivery to the paranasal sinuses by specific types of aerosol generators[16-23].

In 2010, Möller et al.[16] evaluated the level of drug concentration into the sinuses by using pulsation aerosols in five healthy subjects. They found that 6.5% of the nasal drugs administered via pulsating airflow deposited into paranasal sinuses, while the percentage was zero in the case of pump nasal sprays utilization. Also, the drugs clearance kinetics was reduced and the persistent concentration time was high when compared with nasal spray.

In an article published three years later, Möller et al.[17] investigated the delivery efficacy of pulsating aerosols in comparison with a nasal pump spray in two groups – healthy subjects study group (11 patients) and patients with chronic rhinosinusitis (CRS) without nasal polyps before and after sinus surgery (11 patients). Pulsating aerosols were administered to the study group before and after surgery, while the control group received both pulsating aerosols and nasal pump spray. Anterior and lateral planar gamma camera imaging was used to assess the total nasal and sinus (maxillary, sphenoid, frontal) aerosol deposition and lung penetration. Analysing the results, in the control group, it was found a 100% drug deposition in the nasal cavity and no significant deposition in the sinuses (1.8+/-0.2%) and no lung penetration after the use of nasal pump sprays. In the case of pulsating aerosols, there was a 61.3+/-8.6% deposition in the nasal cavities, including the sinuses, with 9.7+/-2.0% in the maxillary and sphenoidal sinuses. The difference between the two administration modalities was statistically significant ($p<0.01$). In the CRS group, the total nasal deposition of pulsating aerosols was 56.7+/-13.3% before sinus surgery and 46.7+/-12.7% after surgery ($p<0.01$). The total maxillary and sphenoidal sinus deposition was 4.8+/-2.4% before surgery and 8.2+/-3.8% after surgery ($p<0.01$). In the frontal sinus, the deposition was not significant in neither of the two groups.

Durand et al.[19] in 2011 and Durand et al.[20] in 2012 demonstrated that the sonic nebulization (nebulization coupled to a 100Hz sound) increased the drug deposition into the maxillary sinus and the importance of a functional middle meatus.

Starting from the involvement of a normal functioning middle meatus, and from the statement that a normal intrasinus particle delivery depends on the status of this anatomical region, Pourmehran et al.[21] evaluated the aerosol deposition and transport pattern on a computational fluid dynamics (CFD) model. The authors demonstrated that the drug delivery to the proximity of the maxillary ostium in the middle meatus can be increased with at least 45% if the nozzle diameter of the nebuliser decreases. This can be a starting point for creating new and advanced nebulizers.

Leclerc et al.[22] in 2023, assessing various types of nasal aerosol delivery techniques and medical devices, concluded that an important factor in improving the intrasinusal drug deposition is the aerosol delivery technique (the soft palate position during the process) associated with the type of aerosol device (frequency and amplitude of the acoustic aerosol).

AEROSOL THERAPY IN PATIENTS WITH INFLAMMATORY OR INFECTIOUS PATHOLOGY OF THE NOSE AND SINUSES

Topical drug delivery to the nasal cavities and paranasal sinuses via aerosols appears to be an interesting, but also a challenging alternative. The transport and deposition of drugs and aerosol particles into the sinuses is debatable due to several factors: sinuses are poorly perfused and virtually non-ventilated cavities; they are protected by the efficient particle filtration function of the nasal cavities.

Searching the Web of Science, PubMed, ScienceDirect and Scopus databases, between 1990 and 2024, on inhaled topical aerosol therapy in upper airway diseases, especially the use of therapeutic aerosols in inflammatory and infectious pathology of the nose and paranasal sinuses, one can conclude that this subject is insufficiently covered and even neglected when compared to their use in pulmonary pathology[5,24-39].

In 2008, Liam et al.[24] performed a systematic review about the use of topical antimicrobials in the management of chronic rhinosinusitis between 1949 and 2007. Of the 14 articles included in the review, five evaluated the effect of nebulized antimicrobials[25-29]. Of these five, four studies presented the positive effects with a level of evidence IIb[25] and III[26-28]. Vaughan et al.[25] studied the microbiological impact of three types of antibiotic administration in 42 patients undergoing endoscopic sinus surgery for chronic rhinosinusitis and acute infection: standard oral, intravenous, nebulization. The authors evaluated the symptoms of the patients according to the visual analogue scale and performed cultures from sinus endoscopy samples at the end of the treatment. Improvement was seen in facial/pressure pain, postnasal discharge and emotional consequences when comparing pre-nebulization with post-nebulization statements. Also, it was seen than the nebulized antibiotic aerosol therapy resolved the infection in 76% of cases.

Reychler et al.[30] evaluated the scores of olfactory functions (orthonasal threshold, discrimination and identification test – TDI, retronasal olfactory tests – RNT) in patients with chronic rhinosinusitis before and after 16 days of corticotherapy: oral administration (prednisolone), nasal sonic aerosol therapy (budesonide), nasal spray (budesonide). At baseline, TDI and RNT scores were similar between the three groups. At the end of the treatment, TDI scores improved for oral, sonic nebulization and nasal spray groups by 5.8±4.1, -1.1±3.3 and 5.5±7.5 respectively, the improvement being clinically relevant for aerosol sonic therapy and oral administration (p=0.010). RNT improved equally for the three study groups (1.1±6.6, 0.7±2.4, 4.2±4.7) (p=0.231). In contrast, Poletti et al.[39] found no significant difference in olfactory function improvement after 2 weeks of treatment with topical steroid therapy as nasal spray and aerosols in chronic rhinosinusitis patients. In a prospective randomized study published in 2019, Velepič et al.[33] studied the efficacy of topical nasal corticosteroid spray and saline nasal irrigation versus inhalation aerosol therapy by nebulization (essential oils, saline, dexamethasone, gentamicin) evaluating the Lund-Kennedy score and the Glasgow Health Status Inventory (GHSI). The results showed a significant improvement in Lund-Kennedy scores in both study groups (p<0.001), with no difference when comparing them directly (p=0.11). From the subjective point of view, GHSI scores were significantly lower in the second group (p=0.037) and were almost unchanged in the first study group (p=0.29). Evaluating the benefit of the medical intervention by the Glasgow Benefit Inventory, the improvement of the patients' quality of life after treatment was much better in those patients who performed aerosol therapy (p=0.002).

There are studies that show a positive effect of transnasal nebulization treatment not only on symptoms but also at histopathologic and immunologic level. Wang et al.[31] evaluated the immunologic and remodelling effect of budesonide nebulization therapy in patients with eosinophilic chronic rhinosinusitis with nasal polyps. After 14 days treatment, both clinical and immunological improvement was observed: improved symptoms, decrease in polyps' size, reduction in eosinophil infiltration, decrease in remodelling indices (albumin, matrix metalloproteinases – MMP-2, MMP-7, MMP-8, MMP-9) and increase in collagen deposition and tissue inhibitors of metalloproteinases (TIMP-1, TIMP-2, TIMP-4).

The clinical usefulness of nebulizer therapy in 245 paediatric children with chronic rhinosinusitis was investigated by Watanabe et al.[35]. The treatment consisted in anti-inflammatory drugs, nasal saline irrigation and aerosols. After the 3-month evaluation period, there was a clinical improvement in 64.9% of patients and on X-ray in 49.8%. The authors also reported a positive correlation between the response rate and

the frequency of nebulizer therapy ($p<0.01$).

Different types of drugs can be used in aerosol therapy: saline, corticosteroids, mucolytics, antibiotics, even essential oils. Precaution should be taken when mixing nebulized medication, because there are certain mixtures which are incompatible due to different characteristics (e.g. changes in particle size).

The use of corticosteroids is controversial and insufficiently studied. Thus, there are studies which evaluate and demonstrate their efficiency in reducing the local nasal inflammation[30,31,33]. A certain caution should be taken when recommending corticosteroid nebulized therapy in paediatric patients, due to its potential adverse events. Even if there are clinical trials showing that inhaled corticosteroids safety profile is higher than the systemic administration[40], the systemic adverse events are a matter of concern in children and adolescents. Evidence-based guidelines and consensus recommend the use of inhaled corticosteroids (nebulized, nasal sprays) in asthma, laryngitis, chronic rhinitis, rhinosinusitis, adenoids hypertrophy[40-42]. It improves nasal obstruction symptoms, reduces local inflammation. The strong recommendation is to use the lowest proper dose of corticosteroids, for the shortest efficient time frame (no more than 10 minutes per session) and regularly monitor the cases with prolonged treatment[40,41,43,44].

Aerosol transnasal delivery of antibiotics permits the accumulation of high doses at the level of nasal and sinus mucosa, thus having a potential better benefit than the nasal sprays. Studies show their efficacy in managing the symptoms in chronic rhinosinusitis refractory to medical and surgical treatment[5,25,26,28,29,33,37,45].

Essential oils, such as menthol or eucalyptus, induce ciliary beat frequency, have antibacterial, antifungal and antiviral activity[33].

Whatever the drugs used in aerosol therapy, attention should be on the possible side-effects: local nasal intolerance (itching, sneezing, nasal bleeding), sore throat, cough, laryngeal bronchospasm, fungi colonization of the upper airways.

INDICATIONS FOR SUCCESS IN AEROSOL THERAPY

In 2014, the French Society of ORL elaborated a consensus document for nebulization prescription in rhinology[5] (Table 1). Taking into consideration the available clinical data, studies results, information about aerosol deposition, aerosol generators, the working group concluded that, in rhinology, the aerosol therapy can be recommended in: acute and subacute rhinosinusitis, exacerbations of chronic rhinosinusitis and postoperative sinonasal suppurations.

From the point of view of the Romanian Rhinologic Society, the aerosol intranasal therapy can be indicated in: acute infections of the nasopharynx, acute rhinosinusitis (nebulization used after saline nasal irrigation and nasal decongestion for a proper middle meatus targeting), chronic rhinosinusitis without nasal polyps and in laryngeal pathology (acute laryngitis in both adults and children, as adjuvant therapy in vocal

Table 1. French Society of ORL guidelines for nebulization treatment in rhinology[5].

Guidelines	Level of agreement
Nebulization should enable deposition over the entire nasal cavity mucosa, including the middle meatus.	Strong agreement
Sonic nebulizers are recommended in rhinosinus pathology. Ultrasonic aerosols are suitable for bronchopulmonary pathology.	Strong agreement
Nasal plugs are to be preferred in rhinology. Mouth end-pieces are reserved to lower airway applications.	Strong agreement
Oro-nasal masks cause deposition on the face and within the oral cavity and should be reserved to patients unable to use a nasal plug.	Strong agreement
Active substances should not be diluted for last-generation nebulizers, as residual volume is slight.	Relative agreement
Nebulization time depends on drug volume; it should not exceed 10 minutes.	Strong agreement
In the absence of studies of sinonasal pathology, the work group recommends nebulization of drugs with market authorization in bronchopulmonary pathology: budesonide, beclomethasone, tobramycin, colomycin.	Relative agreement
In the absence of clinical efficacy studies of drug associations in aerosol sinonasal pathology, the work group advises against nebulizing associations in a given session.	Disagreement
The work group advises against nebulizing oily preparations (risk of lipid pneumonia) or those containing sulphites (risk of bronchospasm) or other empiric preparations.	Relative agreement
The work group recommends nasal cavity lavage ahead of nebulization.	Relative agreement
Nebulization is recommended in purulent edematous rhinosinusitis, subacute rhinosinusitis and exacerbated chronic rhinosinusitis.	Relative agreement
Nebulization is recommended in persistent postoperative rhinosinus suppuration (> 1 month).	Strong agreement
Two nebulizations per day should be prescribed for at least seven days.	Relative agreement
Audiometric monitoring is recommended in iterative rhinologic aminoside nebulization.	Relative agreement

Table 2. Romanian Rhinologic Society recommendation for aerosol therapy.

Aerosol therapy recommendations
• Proper indication for aerosol treatment according to the pathology – selected cases
• Proper choose of the device and the particle dimensions
• Proper combination of the substances (usually corticosteroid, mucolytic, antibiotics, saline)
• Proper preparation of the nasal cavity to allow the nebulisation flow to pass to the larynx or enter the sinuses
• Treatment frequency and duration – usually once a day, 10-15 minutes, 10 days.

fold edematous or inflammatory conditions). The efficiency and safety of aerosol therapy is influenced by several factors such as indication, aerosol device, medication, treatment time, as presented in Table 2.

CONCLUSIONS

Aerosol therapy is a very popular method in the treatment of a variety of upper and lower airways pathologies all over the world. Mainly used in bronchopulmonary conditions, therapeutic nebulization has its well-defined indications in rhinology, even if the literature does not have a good coverage of this specific subject.

There is a wide variety of devices used for aerosol therapy, so proper choose of the nebulizer is essential for the efficiency and safety of the treatment. In rhinologic pathology, jet nebulizers are efficient with nasal plugs.

Only a small number of substances proved to have a proper sinus cavities penetration, mainly the maxillary and sphenoid sinuses.

Caution in your paediatric patients and in patients with known respiratory hyperreactivity!

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