Running title: Nasal nebulization and CRS

REVIEW

Clinical efficacy of intranasal drug delivery by nebulization in chronic rhinosinusitis: a systematic review

Gregory Reychler [1,2,3,4], Claire Domachowski [3], Anne-Claire Latiers [4,5], François Jamar [5], Philippe Rombaux [6],

1 Institut de Recherche Expérimentale et Clinique (IREC), Pôle de Pneumologie, ORL & Dermatologie, Université Catholique de Louvain, Brussels, Belgium

2 Service de Pneumologie, Cliniques universitaires Saint-Luc, Brussels, Belgium

3 Haute Ecole Leonard de Vinci – Institut d'Enseignement Supérieur Parnasse-Deux Alice, Brussels, Belgium

4 Service de Médecine Physique et Réadaptation, Cliniques universitaires Saint-Luc, Brussels, Belgium

5 Service de Médecine Nucléaire, Cliniques universitaires Saint-Luc, Brussels, Belgium

6 Service d'Oto-rhino-laryngologie, Cliniques universitaires Saint-Luc, Brussels, Belgium

SUMMARY

Background: Treatment of chronic rhinosinusitis (CRS) aims to treat the underlying inflammation or infection. Although the optimal modality of administration remains controversial, inhalation route is usually preferred. The aim of this systematic review was to summarize the efficacy of intranasal corticoisteroids or antibiotics delivery by nebulization on symptoms, histology, endoscopy scores, nasal obstruction, clinical outcomes and quality of life in CRS.

Method: This systematic review followed the PRISMA guidelines. Randomized controlled, comparative and cohort studies evaluating effects of treatment by nebulization in sinusitis were identified and reviewed from two databases (PubMed and Scopus). Two reviewers independently assessed study quality and reviewed the selected studies.

Results: 600 references were retrieved and 12 studies evaluating 377 patients were included in the systematic review. Different devices were used. Efficacy of nasal delivery by nebulization was systematically observed on symptoms and size of polyps and frequently on inflammatory parameters in all studies. The presence of polyps improved the efficacy of the nebulization. This way of delivery appears not convincing regarding antibiotics. Few side effects were noted in the retrieved studies and only for nebulized antibiotics.

Conclusions: This systematic review highlighted that based on the present literature nebulization is not better than nasal spray to the delivery of corticosteroids due to the positive results on symptoms, endoscopic appearance and histological outcomes. For antibiotics delivery, the nebulization is not of added value.

INTRODUCTION

Rhinosinusitis is one of the most common reasons for visiting a general practitioner(1). Chronic rhinosinusitis (CRS) which is defined by at least 12 weeks of persistent symptoms and signs despite maximal therapy(2), affects 14% of the population at least once in their life and is associated with a reduced quality of life(3).

Treatment of CRS is mainly symptomatic. Medical treatment(4) is usually proposed as first line and aims to treat the underlying inflammation(1). Corticosteroids are the most prescribed drug for treating CRS with or without polyposis(5) with a high level of evidence(2). However, there is a low level of evidence for the efficacy of topical antibacterial therapy(2).

Although the optimal modality of administration (oral, intranasal spray and nasal nebulization) remains controversial for corticosteroids(6), they are usually delivered by inhalation route which offers minimal systemic side-effects(7). This route of administration is supported by level 1A evidence(2). Even if there is no evidence to support one intranasal delivery modality over the others(6), nebulization is frequently proposed and some in vitro data suggest a possible better targeted deposition(8). Even if others drugs were used by nebulization(9), it's anecdotal.

The aim of this systematic review was to summarize the efficacy of intranasal delivery of corticosteroids or antibiotics by nebulization on symptoms, histology, endoscopy scores, clinical outcomes and quality of life in CRS.

METHOD

Protocol

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were consulted during the stages of design, analysis, and reporting of this Systematic Review(10). According to these guidelines, the structured search, study selection, risk-of-bias assessment of individual studies and best-evidence-syntheses for relating risk-of bias to consistency of effect sizes were included in this review. The protocol for this review has been registered in the international prospective register of systematic reviews PROSPERO (Registration No. CRD42017068344).

Eligibility criteria, sources and search strategy

PubMed and Scopus online databases were screened for the primary search strategy from inception to May 2017. Two key terms were combined: « *sinus* » AND « nebuli* » for the patient and intervention category, respectively.

The full search strategy for PubMed was adapted for other databases using terms and Medical Subject Headings (MeSH) combined with Boolean operators. A hand-searching reference lists from the identified articles, citation tracking of included articles, and use of the PubMed related articles option completed the database searches to avoid missing relevant studies.

Study selection and exclusion criteria

After removal of duplicates, abstracts were checked critically and independently for relevance by two independent investigators (C.D. and G.R.). Articles were included if they were research articles about studies evaluating the effects of corticosteroids or antibiotics by nebulization in sinusitis, written in English or French and not classified as case report, review or meta-analysis. Studies about children or animals were excluded (Table 1). The investigators reviewed full-text articles when inclusion or exclusion was unclear based on the title and abstract. Any disagreement about eligibility was resolved by consensus.

Data extraction, study quality appraisal and risk of bias assessment

Study details and data were extracted by two investigators (C.D. and G.R.). Collected data for each study included the design, sample characteristics (including number of participants, age group, disease and severity and inclusion/exclusion criteria of the study), devices and drugs nebulized, clinical outcomes and results, and side effects.

The same two investigators applied the quality Index developed by Downs and Black for assessing the quality of reporting (10 items), the external validity (3 items), the bias and confounding elements (13 items) and the statistical power (1 item) of all the studies(11). This quality index comprises 27 questions with a total maximum score of 28(12). A grade ranging from “poor” (<14 points) to “excellent” (24–28 points) was assigned to each study evaluated by this quality index(12).

Data synthesis

The investigators considered the results of the studies. Descriptive results, mean comparison, side effects and adherence/completion rate were reported when available.

RESULTS

Study selection

A total of 600 references were originally retrieved from the different databases (Figure 1). After duplicates removal, 506 articles were identified and screened. At the end of the process, eight RCT were included in the systematic review(13-20).

Characteristics of the studies

The characteristics of the studies are described in Table 2. The majority of the studies are recent (6/8 were published less than 5 years)

Population and inclusion criteria

A total of 263 patients were included from studies including 6 to 60 patients. Age ranged from 18 to 89 years. Five studies included patients with previous endoscopic surgery(13;15;16;18;19). Naso-sinusal polyps were included in 4 studies(13;17;20;21) but only one study evaluated their sizes(20).

Interventions

All the protocols used regarding way of delivery, drugs and devices (settings and properties) were summarized in Table 2. Nebulization was used alone or compared with oral treatment, nasal spray, nasal irrigation or nasal gel. Nebulized antibiotics have been studied as much as nebulized corticosteroids. Only one study combined both drugs(18).

Different devices were found in the studies. Six studies used specific nebulizer to target the sinus(14;15;17;20;22) but only 4 out of them performed the administration with a sonic nebulizers(15;17;20;22). Particle size was determined in 3 studies and the mass median aerodynamic diameter varied from 3.2 to 30 µm(19;23).

The durations of the treatment were heterogeneous, ranging from 7 days to 17 weeks. Regarding the nebulization, the duration of the session was highly variable but often not recorded.

Outcomes

Different outcomes were analyzed in the reviewed studies. Symptoms were evaluated in all studies. Six scales were used: *Visual Analogue Scale* (VAS)(13;16;19), *Disease Specific Symptom Score* (DSSS)(19), *Total Nasal Symptom Score*(15;24), *Lund-Kennedy Score*(18)

and *Sino-Nasal Outcome Test* (SNOT-20)(17). The three last ones are specific to CRS. Olfaction evaluation by the Sniffin' Sticks Test (SST) and the Retro-Nasal Test (RNT) was used as outcome in one study(17).

Nasal secretions were obtained in one study and cultured when any signs of purulence were present(22). Endoscopic evaluations of polyps were performed by the Lund-Mackay score(15), the Kupferberg grades(15) and the Lund-Kennedy Endoscopic scale(18).

Acoustic rhinometry was used in one study to quantify the volume of nasal cavity and the resistance of upper airways(14). The Peak Nasal Inspiratory Flow (PNIF) was also used as a marker of efficacy in the same study(14).

The quality of life was evaluated by one specific (Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) or one generic questionnaire (Short-Form Health Survey 36 (SF-36)).

VAS was used to quantify the symptoms from a predetermined list. The list of symptoms is variable even if nasal congestion/obstruction, pain and rhinorrhea were systematicaly evaluated.

Quality and design of the studies

The quality assessment of the reviewed studies is presented in Table 3. The scores obtained by Downs and Black scale ranged from 14 to 23 and the median score was 19.5/28. All studies were classified as “Fair” or “Good” in the quality appraisal.

Results of the studies

All the results are reviewed in Table 4 and the main results are summarized hereunder by outcome.

<u>Effects on symptoms</u>

Efficacy of nasal delivery by nebulization on symptoms was observed in nearly all studies using this outcome, independently on the nebulized drug.

Nebulized corticosteroids showed a higher decrease of the total score of symptoms than saline solution nebulization even if the difference in change was not always significantly different(14;20). The improvement was similar between corticosteroids nebulized and delivered by nasal spray(15).

Out of the three studies related to the nebulization of antibiotics(13;16;19), symptoms were not improved by the nebulization (13) (16;19).

Both drugs were nebulized concomitantly in two studies from the same team. An improvement was observed at short and long term with the nebulization and it was mainly related to the presence of polyps(18). The effect disappeared 4 weeks after nasal spray delivery(18).

Effects on histology

Corticosteroids reduced some inflammatory parameters but only when they are nebulized(20). The combination of both nebulized drugs in the same treatment sessions demonstrated an effect only in patients with polyps. This effect was not observed with the nasal spray(18).

Effects on endoscopic evaluation

The size of polyps decreased with the delivery of corticosteroids by nebulization(15;20). After treatment with budesonide, an intergroup difference was observed in favor of nebulization compared to the administration by spray(15) or placebo(20).

After tobramycin administration, the endoscopic results improved but they were not different between nebulization and nasal spray(16). In another study, the effect of nebulized aminoglycosides was not different from saline solution nebulization but the patients received oral antibiotics in both groups(19).

The patients without polyps did not demonstrate a benefit of the treatment when corticosteroids and antibiotics were nebulized concomitantly(18).

Effects on nasal obstruction

Only nebulized budesonide resulted in increased PNIF even if the change magnitude was not different compared to saline nebulization(14). However, in the same study, no difference in rhinometry improvement was observed between budesonide and saline nebulization(14).

Saline nebulization was better than tobramycin nebulization on nasal obstruction(16).

Effects on quality of life

The quality of life of these patients was reduced compared to the general population(19).

Quality of life was improved by nebulized corticosteroids but it was not different than saline solution nebulization(14).

No benefit was observed on quality of life after tobramycin nebulization compared to nasal spray delivery or nebulized saline solution(16;19).

Effects on bacteriology

No study evaluated the effects of corticosteroids on bacteriology.

One study evaluated the effect of tobramycin on cultures(13). Efficacy on the initial bacteria was verified with eradication of 47% of strains(13).

Side-effects

Few side effects were noted in the retrieved studies (13;20). The side-effects were always recovered by an adapted treatment.

DISCUSSION

To our knowledge, this is the first systematic review to focus on the effects of nasal corticosteroids or antibiotics delivery by nebulization in CRS. The aim of the systematic review was to summarize the clinical efficacy and the impact on histological parameters, endoscopy scores, nasal obstruction and quality of life related to the nebulized way of delivery. The retrieved studies suggest that nasal nebulization of these drugs which is newly investigated, is an interesting way to treat CRS which is very frequent in the general population(3). Globally, efficacy on symptoms, quality of life and inflammation was verified when nebulization was used as way of delivery.

Although the protocols and results related to the nebulization are not homogeneous and vary depending on the nebulized drug and the comparator, based on the different studies included in this systematic review, we can conclude that nasal nebulization offers a valuable way of treatment in CRS. Our results justify the place of the nebulization in the treatment of CRS as previously suggested by the European guidelines(2). Moreover, the dose of corticosteroids is lower when nebulized than the administered dose with oral delivery. However, the systemic absorption of corticosteroids when topically delivered by the nose has to be evaluated and taken into account(25) even if the drug delivered by nasal route into the nose is quickly eliminated by mucociliary clearance or through the digestive tract(26).

The efficacy of nebulized antibiotics or corticosteroids on symptoms was or tended to be significant in all studies. Indeed, symptoms decreased systematically after nebulized budesonide(14;15;20). This improvement was similar to the nasal spray delivery which remains the gold standard in CRS. It highlights that the nebulization can be a potential alternative to the nasal spray as a way of administration of corticosteroids even if it is more expensive and more time-consuming. It is also an alternative to oral steroids without the risk of osteoporosis observed with this way of administration(27). Antibiotics were efficient by nasal nebulization (13;16;19) and sometimes associated to side-effects(13). This efficiency of the nebulized antibiotics has been considered as less convincing in the past(28). The nebulized saline alone was also efficient than nebulized tobramycin which confirms this feeling(16)Thus they have been not recommended until now in the guidelines. The presence of polyps seems to play an important role in the response to nebulization(21).A recent systematic review on a similar topic demonstrated also that the results depended on the presence of polyps(29). We hypothesize that it could be explained by the impaction of the nebulized drug on the polyps. Nasal nebulization was demonstrated to deposit better below

the nasal valve as compared to nasal sprays(30-32). However, the improvement related to the nebulized way was not different compared to the delivery by spray(15).

Similar results were found on endoscopic parameters. Nebulized corticosteroids seem even more efficient than all the other treatment. Lund-Kennedy Endoscopic Score improved with nasal nebulization of antibiotics combined to other drugs(18). When patients were refractory to surgical and medical therapies, nebulized tobramycin offers only a small benefit on parameters of sinonasal endoscopy(16) It can be explained by the selected device showing inconsistent delivery into the sinuses(33). By nebulization, budesonide demonstrated also a small but significant benefit on Kupferberg grades as compared to delivery of the same drug by nasal spray with a reduction of edema(15). In this study, the nebulizer was specific to a sinus delivery (34). The PNIF was improved without effect on the nasal volume(14). As this outcome was demonstrated to be an efficient tool to detect nasal patency changes(35;36), it suggests improvement of nasal obstruction.

Surprisingly, the quality of life was evaluated in only a few studies(14;16;19). The benefits were not statistically significant but they were clinically relevant in the study using RQLQ with an improvement higher than the minimal clinically important difference (0.5pts)(37). As far as histological changes, endoscopy scores modification or nasal obstruction are concerned, the results are globally similar for all studies. Inflammatory markers were improved by nebulization of budesonide(20).

This systematic review highlights a great disparity in the tools used between the different studies. A similar observation was mentioned in a previous systematic review on the role of corticosteroids related to surgery(29). Moreover, some non-specific scales were found in the studies, mainly to evaluate symptoms and nasal mucosa appearance. The nebulizers differed also between studies. We found a lot of specific nebulizer in this review. Out of them few nebulizers were delivering pulsatile aerosols. Sonic nebulizers are rarely used in the retrieved studies despite they improve sinusal deposition and delivery by the nasal route as suggested by different studies(34;38). Moreover, the particle size of delivered aerosol varies between studies and could be not optimally adapted to the sinus delivery.

Some limits need to be addressed regarding the results of this systematic review. First, the nebulization could be influenced by a surgery since a study demonstrated a significant lower total nasal deposition after surgery(30). The inclusion criteria in the different studies varied on this point even if the majority of the studies included patients with surgery. The delay between surgery and the experiments and mainly the kind of surgery must also be taken into account. However, it is difficult because this delay varied from 6 weeks to 3 months and the

surgical protocols were poorly or not described in the studies. Secondly, the inclusion of patients with polyps in some studies could also play a role in the results as suggested previously in the discussion. Due to the heterogeneity of the inclusion criteria from the included studies related to the presence of polyps, a sub-analysis comparing CRS with and without polyps is not justified. Thirdly, the sample size is frequently too small to observe an effect. Fourthly, the control group received either saline nebulization or an administration of the same drug by nasal spray. The choice of saline as control in many studies can be questionable since nebulized saline solution improves outcomes in studies on chronic rhinosinusitis(39) and the nasal volume similarly to inhaled steroids(14). Similar benefit than with nasal spray can be considered positive since its efficacy as a way of treatment is largely supported in CRS with or without polyposis (5;40;41). Nasal spray and saline solution were mentioned as a possible treatment in the European guidelines with a high level of evidence(2;39). At least, other modalities were not included in this review. Even if nasal pressurized metered-dose inhalers dominate the market of the devices for nasal drug delivery, other liquids formulations, nasal powder devices exist or are in development. Among these modalities were previously discussed in a paper(42). Mini-invasive options for delivery in the sinus were also investigated(43;44).

In conclusion, this systematic review highlighted that based on the present literature nebulization is not better than nasal spray to the delivery of corticosteroids with positive results observed on symptoms, endoscopic appearance and histological outcomes. For antibiotics, the results are less convincing and the nebulization is not of added value for the nasal delivery. Further large-scale studies are required to clarify the optimal protocol for treating CRS and to perform a cost-effectiveness analysis.

ACKNOWLEDGEMENTS

Gregory Reychler received a grant from the Institut de Recherche Expérimentale et Clinique (Université catholique de Louvain – Brussels – Belgium).

AUTHORSHIP CONTRIBUTION

GR: guarantor of the paper, design and recording of the review, study selection, review and analysis, study details extraction and data interpretation, manuscript writing

CD: study selection, review and analysis, study details extraction and data interpretation, manuscript drafting

ACL: design of the review, data interpretation, manuscript drafting

FJ: design of the review, data interpretation, manuscript drafting

PR: design of the review, data interpretation, manuscript drafting

CONFLICT OF INTEREST

Gregory Reychler, no conflict of interest

Claire Domachowski, no conflict of interest

Anne-Claire Latiers, no conflict of interest

François Jamar, no conflict of interest

Philippe Rombaux, no conflict of interest

CORRESPONDING AUTHOR
Gregory Reychler
Pneumology Unit
Cliniques Universitaires St-Luc (UCL)
Avenue Hippocrate 10
1200 Brussels, Belgium
E-mail: gregory.reychler@uclouvain.be

Reference List

(1) Thomas M, Yawn BP, Price D, Lund V, Mullol J, Fokkens W. EPOS Primary Care Guidelines: European Position Paper on the Primary Care Diagnosis and Management of Rhinosinusitis and Nasal Polyps 2. Prim Care Respir J 2008;17(2):79-89.

(2) Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl 2012;(23):3-298.

(3) Lange B, Holst R, Thilsing T, Baelum J, Kjeldsen A. Quality of life and associated factors in persons with Chronic Rhinosinusitis in the general population. Clin Otolaryngol 2013;38(6):474-80.

(4) Smith TL, Kern R, Palmer JN, et al. Medical therapy vs surgery for chronic rhinosinusitis: a prospective, multi-institutional study with 1-year follow-up. Int Forum Allergy Rhinol 2013;3(1):4-9.

(5) Alobid I, Mullol J. Role of medical therapy in the management of nasal polyps. Curr Allergy Asthma Rep 2012;12(2):144-53.

(6) Ah-See KL, MacKenzie J, Ah-See KW. Management of chronic rhinosinusitis. BMJ 2012;345:e7054.

(7) Petty DA, Blaiss MS. Intranasal corticosteroids topical characteristics: side effects, formulation, and volume. Am J Rhinol Allergy 2013;27(6):510-3.

(8) Moller W, Schuschnig U, Meyer G, Mentzel H, Keller M. Ventilation and drug delivery to the paranasal sinuses: studies in a nasal cast using pulsating airflow. Rhinology 2008;46(3):213-20.

(9) Casale M, Sabatino L, Frari V, et al. The potential role of hyaluronan in minimizing symptoms and preventing exacerbations of chronic rhinosinusitis. Am J Rhinol Allergy 2014;28(4):345-8.

(10) Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.

(11) Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52(6):377-84.

(12) O'Connor SR, Tully MA, Ryan B, Bradley JM, Baxter GD, McDonough SM. Failure of a numerical quality assessment scale to identify potential risk of bias in a systematic review: a comparison study. BMC Res Notes 2015;8:224.

(13) Bonfils P, Escabasse V, Coste A, et al. Efficacy of tobramycin aerosol in nasal polyposis. Eur Ann Otorhinolaryngol Head Neck Dis 2015;132(3):119-23.

(14) Brown K, Lane J, Silva MP, DeTineo M, Naclerio RM, Baroody FM. A pilot study of the effects of intranasal budesonide delivered by NasoNeb(R) on patients with perennial allergic rhinitis. Int Forum Allergy Rhinol 2014;4(1):43-8.

(15) Dai Q, Duan C, Liu Q, Yu H. Effect of nebulized budesonide on decreasing the recurrence of allergic fungal rhinosinusitis. Am J Otolaryngol 2017.

(16) Desrosiers MY, Salas-Prato M. Treatment of chronic rhinosinusitis refractory to other treatments with topical antibiotic therapy delivered by means of a large-particle nebulizer: results of a controlled trial. Otolaryngol Head Neck Surg 2001;125(3):265-9.

(17) Reychler G, Colbrant C, Huart C, et al. Effect of three-drug delivery modalities on olfactory function in chronic sinusitis. Laryngoscope 2015;125(3):549-55.

(18) Shikani AH, Kourelis K, Alqudah MA, et al. Multimodality topical therapy for refractory chronic rhinosinusitis: our experience in thirteen patients with and twelve patients without nasal polyps. Clin Otolaryngol 2013;38(3):254-8.

(19) Videler WJ, van Drunen CM, Reitsma JB, Fokkens WJ. Nebulized bacitracin/colimycin: a treatment option in recalcitrant chronic rhinosinusitis with Staphylococcus aureus? A double-blind, randomized, placebo-controlled, cross-over pilot study. Rhinology 2008;46(2):92-8.

(20) Wang C, Lou H, Wang X, et al. Effect of budesonide transnasal nebulization in patients with eosinophilic chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 2015;135(4):922-9.

(21) Shikani AH, Kourelis K, Rohayem Z, Basaraba RJ, Leid JG. Topical gel therapy for sinonasal polyposis in Samter's triad: preliminary report. Ann Otol Rhinol Laryngol 2012;121(11):719-24.

(22) Bonfils P. [Nebulization aerosol therapy in otorhinolaryngology. Review of the literature]. Ann Otolaryngol Chir Cervicofac 1997;114(5):147-56.

(23) Macchi A, Terranova P, Digilio E, Castelnuovo P. Hyaluronan plus saline nasal washes in the treatment of rhino-sinusal symptoms in patients undergoing functional endoscopic sinus surgery for rhino-sinusal remodeling. Int J Immunopathol Pharmacol 2013;26(1):137-45.

(24) Wang C, Lou H, Lou W, Zhang L. [The efficacy and safety of a short course of budesonide inhalation suspension via transnasal nebulization in chronic rhinosinusitis with nasal polyps]. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2012;26(8):347-50.

(25) Lipworth BJ, Seckl JR. Measures for detecting systemic bioactivity with inhaled and intranasal corticosteroids. Thorax 1997;52(5):476-82.

(26) Vecellio L, De Gersem R., Le Guellec S., et al. Deposition of aerosols delivered by nasal route with jet and mesh nebulizers. Int J Pharm 2011;407(1-2):87-94.

(27) Winblad L, Larsen CG, Hakansson K, Abrahamsen B, von BC. The risk of osteoporosis in oral steroid treatment for nasal polyposis: a systematic review. Rhinology 2017;55(3):195-201.

(28) Goh YH, Goode RL. Current status of topical nasal antimicrobial agents.

Laryngoscope 2000;110(6):875-80.

(29) Pundir V, Pundir J, Lancaster G, et al. Role of corticosteroids in Functional Endoscopic Sinus Surgery--a systematic review and meta-analysis. Rhinology 2016;54(1):3-19.

(30) Moller W, Schuschnig U, Celik G, et al. Topical drug delivery in chronic rhinosinusitis patients before and after sinus surgery using pulsating aerosols. PLoS One 2013;8(9):e74991.

(31) Suman JD, Laube BL, Dalby R. Comparison of nasal deposition and clearance of aerosol generated by nebulizer and an aqueous spray pump. Pharm Res 1999;16(10):1648-52.

(32) Miller TR, Muntz HR, Gilbert ME, Orlandi RR. Comparison of topical medication delivery systems after sinus surgery. Laryngoscope 2004;114(2):201-4.

(33) Negley JE, Krause H, Pawar S, Reeves-Hoche MK. RinoFlow nasal wash and sinus system as a mechanism to deliver medications to the paranasal sinuses: results of a radiolabeled pilot study. Ear Nose Throat J 1999;78(8):550-4.

(34) Moller W, Schuschnig U, Khadem SG, et al. Pulsating aerosols for drug delivery to the sinuses in healthy volunteers. Otolaryngol Head Neck Surg 2010;142(3):382-8.

(35) Teixeira RU, Zappelini CE, Alves FS, da Costa EA. Peak nasal inspiratory flow evaluation as an objective method of measuring nasal airflow. Braz J Otorhinolaryngol 2011;77(4):473-80.

(36) Wilson AM, Sims EJ, Robb F, Cockburn W, Lipworth BJ. Peak inspiratory flow rate is more sensitive than acoustic rhinometry or rhinomanometry in detecting corticosteroid response with nasal histamine challenge. Rhinology 2003;41(1):16-20.

(37) Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. J Allergy Clin Immunol 1996;98(4):843-5.

(38) Durand M, Le Guellec S., Pourchez J, et al. Sonic aerosol therapy to target maxillary sinuses. Eur Ann Otorhinolaryngol Head Neck Dis 2012;129(5):244-50.

(39) Majima Y, Sakakura Y, Matsubara T, Murai S, Miyoshi Y. Mucociliary clearance in chronic sinusitis: related human nasal clearance and in vitro bullfrog palate clearance. Biorheology 1983;20(2):251-62.

(40) Kemp JP, Berkowitz RB, Miller SD, Murray JJ, Nolop K, Harrison JE. Mometasone furoate administered once daily is as effective as twice-daily administration for treatment of mild-to-moderate persistent asthma. J Allergy Clin Immunol 2000;106(3):485-92.

(41) Penagos M, Compalati E, Tarantini F, Baena-Cagnani CE, Passalacqua G, Canonica GW. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis. Meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. Allergy 2008;63(10):1280-91.

(42) Djupesland PG. Nasal drug delivery devices: characteristics and performance in a clinical perspective-a review. Drug Deliv Transl Res 2013;3(1):42-62.

(43) Rizan C, Elhassan HA. Post-sinus surgery insertion of steroid-eluting bioabsorbable intranasal devices: A systematic review. Laryngoscope 2016;126(1):86-92.

(44) Taulu R, Bizaki AJ, Numminen J, Rautiainen M. A prospective, randomized clinical study comparing drug eluting stent therapy and intranasal corticoid steroid therapy in the treatment of patients with chronic rhinosinusitis. Rhinology 2017;55(3):218-26.

Figure Legend:

Figure 1: Flow diagram (Prisma Statement)

Table 1: Selection criteria

	Inclusion criteria	Exclusion criteria
Patients	– Human – Adults – Sinusitis	– Animals – Children – Healthy subjects – Nasal cast – Cystic fibrosis
Interventions	– In vivo studies – Intranasal delivery of corticosteroids or antibiotics by nebulization	– In vitro studies
Comparator	– Another way of administration – Placebo – No treatment – Intranasal delivery of another drug by nebulization	
Outcomes	– Quality of life – All clinical symptoms – Endoscopic evaluation (Kupferberg grades, Lund Mackay score…) – Rhinometry – Nasal pick inspiratory flow – Cytology of the nasal cavity	– Deposition studies
Design	– Randomized controlled trial – Controlled study – Cross-over study	– Systematic review – Meta-analysis – Case report – Descritpive study – Cohort study – Pilot study

Table 2: Characteristics of the studies, populations, interventions and outcomes

Author	Type and studied drug	Population				Interventions	Outcomes
		n (included)	Age (mean)	Gender (M/F)	Inclusion criteria		
Desrosiers et al., 2001	RCT A	IG = 10 CG = 9	23 to 89 y.o. (49 y.o.)	8/12	- **Surgery:** yes - **Disease:** refractory CRS - **Polyps:** ND	**IG** **Way of delivery:** nasal nebulization **Drug:** trobamycin **Dosage:** 4 mL - 20mg/mL **Device:** RinoFlow Nasal + Sinus Wash System **Particle size:** ND **Duration:** ND **Frequency:** 3t/dJ durant 4 semaines **CG** **Way of delivery:** nasal nebulization **Drug:** solution saline + 1mg/mLde quinine **Device:** RinoFlow Nasal et Sinus Wash System **Dosage:** (0,9% NaCl) **Particle size and duration:** ND **Frequency:** 3t/d - 4 w	**1. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)** - Before w2, w4, After (w8) **2. VAS:** - Symptoms: secretion, congestion, pain - Before, w2, w4, After (w8) **3. Sino-nasale endoscopy** - Secretions + oedema - Scale 0 to 4 - Before, w2, w4, After (w8)
Videler et al., 2008	RCT, crossoever A	IG = 6 CG = 8	33 to 87 y.o (52 y.o.)	6/8	- **Surgery:** yes (4/patient) - **Disease:** CRS + S. aureus.	**Gr IG + CG: oral antibiotic** - **Way of delivery:** oral - **Drugs:** levofloxacin - **Dosage:** 500 gr - **Frequency:** 2 t/d during 2 w **IG** **Way of delivery:** nasal nebulization **Drug:** bacitracin/colimycin **Dosage:** 8mL > 830/640 µg/ml **Device:** RhinoFlow **Particle size:** 20 to 30 µm **Frequency:** 2 t/d - 8w **Duration:** ND **CG** - **Way of delivery:** nasal nebulization - **Drug:** saline solution - **Device:** RhinoFlow - **Particle size:** 20 to 30 µm - **Frequency:** 2 t/d - 8w - **Duration:** ND **Wash-out** - **Way of delivery:** nasal nebulization - **Drug:** saline solution	**1. VAS:** - Symptoms: nasal obstruction, rhinorrhea, postnasal drip, crusts, headache, facial pain, smell disturbance, nasal pain, nose bleeds, fever, malaise, fatigue - Before and after **2. Disease-Specific Symptom Score** - Before and after **3. SF-36 questionnaire** - Before and after **4. Sino-nasale endoscopy** - Nasal obstruction, rhinorrhea, crusts, polyps, color of mucosa and postnasal drip - Scale with 3 points (no – mild – severe) - Before discharge
Shikani et al., 2013	RCT Comb	IG = 25 CG = 10	> 18 y.o. (48 y.o.)	ND	- **Surgery**: yes - **Diseases**: **IG:** 13 CRS + polyps and 12 CRS **CG:** 5 CRS + polyps and 5CRS - **Polyps**: ND	**IG: Multimodality topical regimen** - **Way of delivery:** nasal nebulization + hydroxyl-ethylcellulose by gel (1 t/w) - **Drug:** mometasone + antibiotic based on the culture - **Dosage:** ND - **Device:** ASL Pharmacy - **Particle size:** ND - **Frequency:** 1t/d - 6w - **Duration:** ND **CG: Oral therapy** - **Way of delivery:** oral + nasal spray - **Drug:** antibiotic based on the culture + mometasone - **Dosage:** ND - **Frequency:** 1t/d - 6w	**1. Lund-Kennedy Symptom Score & Endoscopic Score** - Before, w3, w6 and 4w post treatment **2. Histological response** - Inflammation, edema, epithelial attenuation, epithelial hyperplasia, squamous metaplasia, fibrosis, and goblet cell hyperplasia - Score from 0 to 5 (5 the most severe) - Before and after

Author	Type and studied drug	Population				Interventions	Outcomes
		n (included)	Age (mean)	Gender (M/F)	Inclusion criteria		
						- **Duration:** ND **IG + CG** - Endoscopic cleansing and rinsing (Neilmed Sinus Rinse) 1t/w	
Brown et al., 2014	RCT C	IG = 20 CG = 20	IG = 33,3 (18-55)CG = 32,3 (15-52)	IG = 13/7CG = 9/11	- **Surgery:** no - **Diseases:** allergic rhinitis - **Polyps:** no	**IG** **Way of delivery:** nasal nebulization **Drug:** budesonide (Pulmicort Respules) **Dosage:** 0.25 mg **Device:** NasoNeb **Frequency:** 1 t/d - 2w **Particle size:** ND **Duration :** ND **CG** **Way of delivery:** nasal nebulization **Drug:** saline solution (placebo) **Dosage:** 2mL **Device:** NasoNeb **Frequency:** 1 t/d - 2w **Particle size:** ND **Duration :** ND	**1. Symptoms** - sneezing, runny nose, nasal congestion, and itchy nose - Score from 0 to 3 by item (0 = none, 1 = mild, 2 = moderate, and 3 = severe) and total score is the sum of morning and evening evaluation - Every 12h **2. Nasal peak inspiratory flow (NPIF)** - In-Ckeck Peak & Inspiratory Flow Meter - Every 12h **3. Acoustic rhinometry** - ECCOVISION acoustic rhinometer (Hood Laboratories, Pembroke, MA) - Nasal volume between 2 and 8 cm from the nasal vestibule - At baseline, after 2w and at the end **4. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)** - 28 items - At baseline, after 2w and at the end
Reychler et al., 2014	RCT C	OG = 10 SpG = 10 NebG = 10	OG = 51,2 (10,1) SPG = 48,5 (16,7) NebG = 42,5 (7,5)	OG: 4/6 SPG: 5/5 NebG: 6/4	- **Surgery:** yes - **Disease:** CRS with or without NP - **Polyps**: ND	**OG** **Way of delivery:** per os **Drug:** methylprednisone (Medrol) **Dosage:** 32 mg/8d, 16 mg/4d, 8 mg/4d **SpG** **Way of delivery:** nasal spray **Drug:** budesonide **Dosage:** 2 × 64 µg/nostril **Device:** Rhinocort **Particle size:** ND **Frequency:** 2 t/d – 16d **NebG** **Way of delivery:** nasal sonic nebulization **Drug:** budesonide (Pulmicort) **Dosage:** 1 mg/4mL **Device:** sonic nebulizer NL11SN (Diffusion Technique Française) **Particle size:** ND **Frequency:** 2 t/d – 16d **Duration:** 10min	**1. Orthonasal Psychophysical Olfactory Test** - Olfactory threshold, odor discrimination, odor identification - Before and after **2. Retronasal Psychophysical Olfactory Test** - Before and after

Author	Type and studied drug	Population				Interventions	Outcomes
		n (included)	Age (mean)	Gender (M/F)	Inclusion criteria		
Wang et al., 2014	RCT C	IG = 30 CG = 30	IG = 48.23 (29-68) CG = 44.03 (19-76)	IG : 12/18 CG: 17/13	- **Surgery:** No - **Disease:** CRS with polyps - **Polyps :** CG = 4.72cm (0,67) - IG = 4.85cm (0,69)	**IG** **Way of delivery:** nasal nebulization **Drug:** budesonide **Dosage:** 1 mg **Device:** Pari Sinus + Pari Master Compressor (PARI GmbH) **Particle size:** ND **Frequency:** 2 t/d - 14d **Duration:** NA **CG** **Way of delivery:** nasal nebulization **Drug:** saline solution **Dosage:** ND **Device:** Pari Sinus + Pari Master Compressor (PARI GmbH) **Particle size:** ND **Frequency:** 2 t/d - 14d **Duration:** NA	**1. The total nasal symptom score (TNSS)** - nasal obstruction, nasal discharge, loss of smell, and headache/facial pain - Visual analogue scale - Sum of scores for 4 symptoms - Before and after **2. Inflammatory markers** - Before and after **3. Nasal remodeling** - Before and after
Bonfils et al., 2015	RCT A	IG = 32 CG = 23	IG : 46 (22-70) CG: 53 (29-70)	IG = 17/15 CG = 10/13	- **Surgery:** yes - **Disease:** Nasal polyposis - **Polyps:** ND but not extending beyond the roof of the maxillary sinus	**IG** **Way of delivery:** nasal nebulization **Drug:** trobamycin **Dosage:** 150 mg/3mL **Device:** Easynose **Particle size:** ND **Frequency:** 2t/d – 7d **Duration:** 10 min **CG** **Way of delivery:** nasal nebulization **Drug:** saline solution **Dosage:** 0,9% NaCl - 3mL **Device:** Easynose **Particle size:** ND **Frequency:** 2t/d – 7d **Duration:** 9min 50s	**1. Bacteriology** - d0 and d10 **2. Symptoms** - nasal congestion, anterior and posterior rhinorrhea,facial pain and heaviness and olfactory impairment - VAS - d0, d10 and d30 **3. Compliance and adverse events** - d1 and d7
Dai et al., 2017	RCT C	IG = 15 CG = 15	IG: 43,27 ± 12,57 CG: 42,4 ± 15,7	IG: 9/6 CG: 8/7	- **Surgery**: yes - **Disease**: allergic fungal rhinosinusitis	**IG** **Way of delivery:** nasal nebulization **Drug:** budesonide (Pulmicort respules) **Dosage:** 1 mg **Device:** Pari Sinus + Pari Master Compressor (PARI GmbH) **Particle size:** ND **Frequency:** 2t/d for 2w; 1t/d for 2w; 1t/2d for 4w; 2t/w for 8w; 1t/ w **Duration:** NA **CG** **Way of delivery:** nasal spray **Drug:** budesonide **Dosage:** ND **Device:** Rhinocort **Particle size:** ND **Frequency:** 2t/d for 2w; 1t/d for 2w; 1t/2d for 4w; 2t/w for 8w; 1t/ w **Duration:** NA	**1. Kupferberg grades after endoscopy** - Before and after surgery, w4, w12, w24 **2. Lund-Mackay radiologic scoring system** - CT scan - Right and left sides (maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinuses, ostiomeatal complex) - Score ranging from 0 to 2: 0 (no abnormality), 1 (partial opacification) or 2 (total opacification) - Before and after surgery, w4, w12, w24 **3. The total nasal symptom score (TNSS)** - nasal obstruction, nasal discharge, loss of smell and headache/facial pain - Visual analogue scale - Sum of scores for 4 symptoms - Before and after surgery, w4, w12, w24

Author	Type and studied drug	Population				Interventions	Outcomes
		n (included)	Age (mean)	Gender (M/F)	Inclusion criteria		

Legend : A = antibiotics / C = corticosteroids / Comb = treatment combining antibiotics and corticosteroids / y.o. = years old / ND = Non defined / CRS = chronic rhinosinusitis / RSOM-31 = Rhinosinusitis Outcome Measure / RQLQ: Rhinoconjunctivitis Quality of Life / RCT = Randomized controlled trial / w = week/ d = day / m = month / IL = interleukin/ SF-36 = The Short Form (36) Health Survey / VAS = visual analogue scale/IG = intervention group / CG = control group/RQLQ: Rhinoconjunctivitis Quality of Life / AFRS = Allergic fungal rhinosinusitis/ OG = oral treatment / SPG = spray nasal group / NebG = nasal nebulization group

Table 3: Quality assessment of the reviewed studies by Downs and Black scale

	Items	Desrosiers et al., 2001	Videler et al., 2008	Shikani et al., 2013	Brown et al., 2014	Reychler et al., 2014	Wang et al., 2014	Bonfils et al., 2015	Dai et al., 2017
Reporting	1	1	1	1	0	1	1	1	1
	2	1	1	1	1	1	1	1	1
	3	1	1	0	1	1	1	1	0
	4	1	1	1	1	1	1	1	1
	5	0	0	0	2	2	0	2	2
	6	0	1	1	1	1	1	1	1
	7	1	0	0	1	1	1	0	1
	8	1	0	0	1	0	0	1	0
	9	1	1	0	1	0	1	1	1
	10	0	1	1	1	1	1	1	1
	Subtotal	**7**	**7**	**5**	**10**	**9**	**8**	**10**	**9**
External validity	11	0	0	0	0	0	1	0	1
	12	0	0	0	0	0	0	0	1
	13	1	1	1	1	1	1	1	1
	Subtotal	**1**	**1**	**1**	**1**	**1**	**2**	**1**	**3**
Internal validity	14	1	1	0	1	0	1	1	0
	15	1	1	1	1	0	1	1	1
	16	1	1	1	1	1	1	1	0
	17	1	1	1	1	1	1	1	1
	18	0	1	0	0	1	0	1	1
	19	1	1	1	1	1	0	1	0
	20	1	1	1	1	1	1	1	1
	21	0	0	0	0	0	1	0	1
	22	1	0	0	1	0	1	0	1
	23	1	1	1	1	1	1	1	1
	24	0	0	1	0	1	0	1	0
	25	0	0	0	0	1	0	1	1
	26	1	0	0	1	0	0	1	1
	Subtotal	**9**	**8**	**7**	**9**	**8**	**8**	**11**	**9**
Statistical power	27	1	0	1	1	1	1	1	1
	Total	**18**	**16**	**14**	**21**	**19**	**19**	**23**	**22**
	Quality level	**F**	**F**	**F**	**G**	**G**	**G**	**G**	**G**

F : fair quality level

G : good quality level

Table 4: Results and side-effects of the retrieved studies

Authors	Results	Side-effects
Desrosiers et al., 2001	IG vs CG: pain(w2) and nasal congestion(w2, w4, w8) were higher , no difference for QoL or endoscopy IG + CG: QoL, symptoms and endoscopy improved at w2, w4 and w8	ND
Videler et al., 2008	**1. VAS** Crusts and facial pain decreased significantly in IG and CG No difference in symptom severity reduction between groups: nasal obstruction (p=0.38), rhinorrhea(p=0.84), postnasal drip(p=0.22), crusts(p=0.64), headache(p=0.90), facial pain(p=0.53), smell disturbance(p=0.72), nasal pain(p=0.50), nose bleeds(p=0.36), fever(p=0.25), malaise(p=0.07), fatigue(p=0.42) **2. Disease-Specific Symptom Score** Imporvement after treatment in IG and in CG No difference between groups **3. SF-36 questionnaire** Before: lower than normal for all items After: no imporvement **4. Endoscopy** No difference after treatment between modalities Color of secretions imporved in IG (p<0.0001)	No
Shikani et al., 2013	**1. Lund-Kennedy Symptom Score** IG vs CG: NA in CRS without polyps but significant difference at w6 (p<0.001) and w10 (p = 0.003) in CRS with polyps Improvement in IG at w3 and after for CRS without polyps (p=0.003) but no difference after 10w in CG Imporvement at w3 in both groups for CRS with polyps but no difference in CG **2. Endoscopic Score** Improvement in IG for CRS with and without polyps **3. Histological response** Improvement only for CRS with polyps in IG	ND
Brown et al., 2014	**1. Symptoms** IG vs CG: Higher decrease in IG (-3.3 vs -2.0) than in CG but non significantly Decrease after 2 and 4 days in IG and CG respectively **2. Nasal peak inspiratory flow** No difference in change between groups (+36L/min vs +18L/min; p=0.09) Increase only in IG (p=0.03) **3. Acoustic rhinometry** No difference between groups at visit 2 and visit 3 **4. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)** No difference between groups (w2: p = 0.33 and w4: p = 0.41) Improvement for IG and CG at w2 and w4(p<0.001)	ND
Reychler et al., 2014	**1. Orthonasal Psychophysical Olfactory Test** Greater improvement for total score and odor discrimination in OG and NebG vs SpG (p<0.05) **2. Retronasal Psychophysical Olfactory Test** No difference between groups (p=0.231) **3. Adherence** 100% for all groups	ND

Authors	Results	Side-effects
Wang et al., 2014	**1. Symptoms** IG vs CG: TNSS (p=0.001), polyps size (p=0.01), nasal congestion (p=0.001), rhinorrhea (p=0.001), loss of smell (p=0.001), headache (p=0.001) **2. Inflammatory markers** IG vs CG:?????????????????? IG: improvement of eotaxin, IL-5, IL-10 and TGFbeta (p<0.05) but no difference for IL-17 and IFN-g; eosinophil numbers decreased; TH2, TH1, TH17, TR1 and nTreg cells improved CG: no alteration of the level of any cytokines, eosinophil numbers and cells types **3. Nasal remodeling** Affected in IG but not in CG **4. Adherence** IG: 2 CG: 1	No side effect Nasal dryness in 5 patients from IG
Bonfils et al., 2015	**1. Bacteriology** - Eradiaction of 47% of strains by d10 in IG vs 17% in CG (p = 0.02) - Less positive culture in IG (p=0.02) **2. Symptoms** - No significant differences in symptoms between D0 vs D10 or D30 **3. Compliance and adverse events** Excellent (98.9% in CG and 97% in IG) Similar duration per application	- 5 failures to take tobramycin - 27 adverse events (none serious) (asthma attack, cough, bronchitis, otalgia, otitis, diarrhea, nausea and erythematous skin lesions) - No difference between groups (p=0.58)
Dai et al., 2017	**1. Kupferberg grades after endoscopy** - Difference: 0.13 ± 0.35, 0.00 ± 0.00 and 0.00 ± 0.00 vs 0.40 ± 0.63, 0.13 ± 0.35 and 0.07 ± 0.26 in Gr A and in Gr B, respectively - Significant between-group differences at w4 in favor of Gr A (p=0.041) but no difference at w12 and w24 (p>0.05) **2. Lund-Mackay radiologic scoring system** - Significant differences at w24 (p=0.036) **3. TNSS** - Differences in TNSS: 7.73 ± 3.79, 6.40 ± 1.80 and 5.67 ± 1.05 vs 9.07 ± 4.68, 6.67 ± 2.35 and 6.00 ± 1.92 in Gr A and in Gr B, respectively - No between-group differences (p=0.05) **4. Recurrence** - 27% in Gr B vs 0% in Gr A (p=0.032)	NR

Legend : CG = control group / ND = Non defined NA = non available / CRS = chronic rhinosinusitis / RSOM-31 = Rhinosinusitis Outcome Measure/ RQLQ: Rhinoconjunctivitis Quality of Life / w = week/ d = day/ m = month/ IL = interleukin/ SF-36 = The Short Form (36) Health Survey / VAS = visual analogue scale / IG = intervention group / CG = control group/RQLQ: Rhinoconjunctivitis Quality of Life/ AFRS = Allergic fungal rhinosinusitis/ OG = oral treatment/ SPG = spray nasal group/NebG = nasal nebulization group