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

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Abstract

Background: Chronic rhinosinusitis (CRS) treatments aim to alleviate underlying inflammation or infection. Optimal modality of administration remains controversial, however inhalation is usually preferred. This systematic review summarizes the efficacy of delivery by nebulization of intranasal corticoisteroids or antibiotics on symptoms, histology, endoscopy scores, nasal obstruction, clinical outcomes and quality of life in CRS.

Method: Following 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. Different devices were used. Efficacy of nasal delivery by nebulization was systematically observed on symptoms and size of polyps and on inflammatory parameters in all studies. The presence of polyps improved the efficacy of the nebulization. The effectiveness of this form of antibiotics delivery was not convincing. Few side effects were noted and these only applied to nebulized antibiotics.

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

Key words: sinusitis, sinus, nebulization

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 despite maximal therapy[(2)], affects 14% of the population at least once in their life and is associated with reduced quality of life[(3)].
Treatment of CRS is mainly symptomatic. Medical treatment[(4)] is usually proposed as a first line and aims to treat the underlying inflammation[(1)]. Corticosteroids are the most prescribed drug for treating CRS with or without polyposis[(5)] and these have 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 the inhalation route which offers minimal systemic side-effects[(7)]. This route of administration is supported by level 1A evidence[(2)]. Despite the fact there is no evidence to support one intranasal delivery

modality over others[6], nebulization is frequently proposed and some in vitro data suggests a possible better targeted deposition[8]. The evidence for administering other drugs by nebulization[9], is anecdotal at best.

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[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 are 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. Manual searching of the 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.

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 method 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

The same two investigators applied the quality index developed by Downs and Black for assessing quality of reporting (10 items), external validity (3 items), bias and confounding elements (13 items) and 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 based on 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 removal of duplicates, 506 articles were identified and screened. At the end of the process,

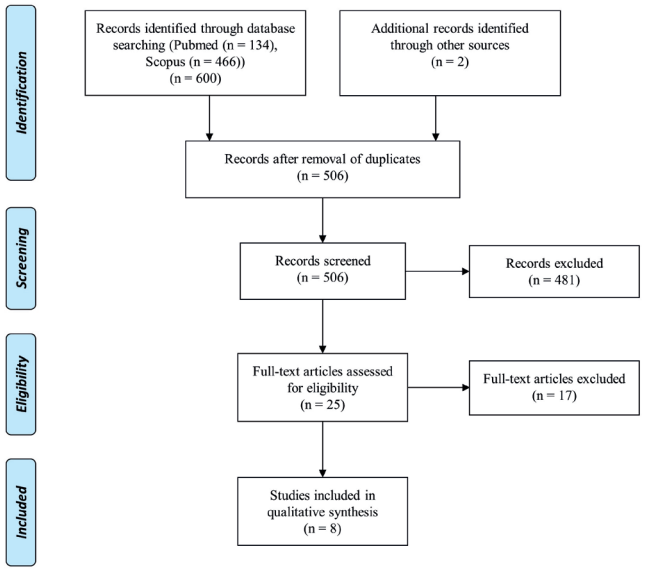

Figure 1. Flow diagram (Prisma Statement).

eight RCTs 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 ago).

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 method of delivery, drugs and devices (settings and properties) are 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 nebulizers to target the sinus[14,15,17,20,22] but only 4 performed the administration with 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 presented as the 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]. Peak Nasal Inspiratory Flow (PNIF) was also used as a marker of efficacy in the same study[14].

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 was 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 using the 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 by outcome herewith.

Effects on symptoms

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

Nebulized corticosteroids showed a bigger decrease in the total number of symptoms than nebulized saline solution, even if the difference in symptom number was not always significant[14,20]. The improvement was similar in nebulized corticosteroids and corticosteroids delivered by nasal spray[15].

In the three studies related to the nebulization of antibiotics[13,16,19], symptoms were not improved by nebulization [13,16,19]. Both drugs were nebulized concomitantly in two studies from the same team. An improvement with nebulization was observed at short and long term follow-up and this 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 were nebulized[20]. The combination of both ne-

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 Method 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 Method 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 Method of delivery: oral Drugs: levofloxacin Dosage: 500 gr Frequency: 2 t/d during 2 w IG Method 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 Method of delivery: nasal nebulization Drug: saline solution Device: RhinoFlow Particle size: 20 to 30 µm Frequency: 2 t/d - 8w Duration: ND Wash-out Method 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

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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 Method 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 Method of delivery: oral + nasal spray Drug: antibiotic based on the culture + mometasone Dosage: ND Frequency: 1t/d - 6w Duration: ND IG + CG Endoscopic cleansing and rinsing (Neilmed Sinus Rinse) 1t/w	1. Lund-Kennedy Symptom Score and 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
Brown et al., 2014	RCT C	IG = 20 CG = 20	IG = 33,3 (18-55) CG = 32,3 (15-52)	IG = 13/7 CG = 9/11	- Surgery: no - Diseases: allergic rhinitis - Polyps: no	IG Method 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 Method 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-Check Peak and 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

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			Age (mean)	Gender (M/F)	Inclusion criteria		
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 Method of delivery: per os Drug: methylprednisone (Medrol) Dosage: 32 mg/8d, 16 mg/4d, 8 mg/4d SpG Method of delivery: nasal spray Drug: budesonide Dosage: 2 × 64 µg/nostril Device: Rhinocort Particle size: ND Frequency: 2 t/d – 16d NebG Method 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
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 Method 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 Method 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. 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

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Author	Type and studied drug	n (included)	Population			Interventions	Outcomes
			Age (mean)	Gender (M/F)	Inclusion criteria		
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 Method of delivery: nasal nebulization Drug: trobamycin Dosage: 150 mg/3mL Device: Easynose Particle size: ND Frequency: 2t/d – 7d Duration: 10 min CG Method 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 Method 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 Method 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. 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

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 selected studies using 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

bulized 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 administration by spray[15] or placebo[20].

After tobramycin administration the endoscopic results improved, but there was no difference 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].

Patients without polyps did not demonstrate benefit from 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 performed better than tobramycin nebulization in 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 to 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 resolved 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 method of delivery. The retrieved studies suggest that nasal nebulization of these drugs is an

Table 4. Results and side-effects in the selected 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 Improvement after treatment in IG and in CG No difference between groups 3. SF-36 questionnaire Before: lower than normal for all items After: no improvement 4. Endoscopy No difference after treatment between modalities Color of secretions improved in IG (p<0.0001)	No side effect
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 Improvement 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: Bigger 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
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

Authors	Results	Side-effects
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

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 / AFRS = Allergic fungal rhinosinusitis/ OG = oral treatment/ SPG = spray nasal group / NebG = nasal nebulization group.

interesting way to treat CRS, which is a common condition in the general population[3]. Globally, efficacy on symptoms, inflammation and quality of life was verified when nebulization was used as way of delivery.

Although the protocols and results related to 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 form of treatment in CRS. Our results justify the role of nebulization in the treatment of CRS as previously suggested by 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 that of nasal spray delivery which remains the gold standard in CRS. It highlights that nebulization can be a potential alternative to nasal spray as a way of administering corticosteroids, even if it is more expensive and time-consuming. It is also an alternative to oral steroids without the risk of osteoporosis observed with this method of administration[27]. Antibiotics administered by nasal nebulization were efficient [13,16,19] although sometimes associated with side-effects[13]. The efficiency of nebulized antibiotics has been considered as unconvincing in the past[28]. Nebulized saline alone was as efficient as nebulized tobramycin which confirms this view[16]. Nebulized antibiotics has therefore not been recommended in the guidelines until now. The presence of polyps seems to play an important role in the response to nebulization[21]. A recent systematic review on a similar topic also demonstrated that results depended on the presence of polyps[29]. We hypothesize that this could be explained by the impaction of the nebulized drug on the polyps. Nasal nebulization was demonstrated to deposit better below the nasal valve compared to nasal sprays[30-32]. However, the improvement related to nebulization was not different compared to delivery by spray[15].

Similar results were found regarding endoscopic parameters. Nebulized corticosteroids seem to be more efficient than all other treatments. Lund-Kennedy Endoscopic Score improved with nasal nebulization of antibiotics combined with other drugs[18]. When patients were refractory to surgical and medical therapies, nebulized tobramycin offered a small benefit in terms of sinonasal endoscopy parameters[16]. This can be explained by the selected device showing inconsistent delivery into the sinuses[33]. Nebulization of budesonide also demonstrated a small but significant improvement in Kupferberg grades compared to delivery of the same drug by nasal spray, with a reduction of edema[15]. In this study, the nebulizer was specific to sinus delivery[34]. PNIF improved without effect on 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, 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 greater 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 in 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 also differed between studies. We found a large number of specific nebulizers, few of which were delivering pulsatile aerosols. Sonic nebulizers were rarely used in the retrieved studies despite the fact that 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 sinus delivery.

Some limits need to be addressed regarding the results of this systematic review. First, that nebulization could be influenced by surgery, as one study demonstrated a significant lower total nasal deposition after surgery[30]. Inclusion criteria in the different studies varied on this point, although the majority of the studies did include patients with surgery. The delay between surgery and the experiments and the kind of surgery must also be taken into account. This is difficult because the delay varied from 6 weeks to 3 months and the surgical protocols were described poorly or not at all 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 inclusion criteria related to the presence of polyps in the selected studies, 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], as well as nasal volume similarly to inhaled steroids[14]. Similar benefit than with nasal spray can be considered positive since its efficacy as a method 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]. Other treatment modalities were not included in this review. Although nasal pressurized metered-dose inhalers dominate the market of devices for nasal drug delivery, other liquid formulations and nasal powder devices exist or are in development, and these have been the subject of previous research[42]. Mini-invasive options for delivery in the sinus have also been investigated elsewhere[43,44].

Conclusions

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

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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

No conflict of interest.

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