Saline nasal irrigation for acute upper respiratory tract infections in infants and children: a systematic review and meta-analysis

Short Title: saline nasal irrigation for upper respiratory tract infections

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Educational Aims:

After reading this paper, the reader will be able to:

- Appreciate that the study did not improve mean days to wellness nor decrease antibiotic usage.
- Understand that saline nasal irrigation (SNI) improves clinical rhinological symptoms.
- Appreciate that the long-term use of SNI led to a decrease in the incidence of acute rhinosinusitis and its complications and appeared to be a safe treatment.

Future research directions:

- Randomized controlled trials (RCTs) of greater power to test SNI vs an intervention deemed less important – such as nose blowing – are required.
- Double blinding is impossible when assessing the efficacy of SNI; therefore it is justifiable to consider a pragmatic approach.
- This approach could be more open, for example using comparative cohorts with modelling to take differences into account, and including healthcare utilization analysis.

Abstract

Purpose

Acute upper respiratory tract infections are the most common infections in infants and children. Saline nasal irrigation (SNI) is widely prescribed and recommended. We conducted a systematic review to assess the efficacy and safety of SNI in infants and children with acute rhinopharyngitis.

Methods

We searched CENTRAL, Medline, Embase and clinicalTrials.gov. Two authors selected randomized control trials (RCTs), including infants ≥ 3 months and children ≤ 12 years, comparing the use of isotonic saline solutions, whatever their mode of administration, with one therapeutic abstention, or a therapy deemed less important for nasal lavage. Trial quality was assessed independently by two authors, who, with a third author, extracted and analysed data. Statistical analysis was conducted using Comprehensive Meta-Analysis software. The standard difference in means (SMD) between groups and its 95% confidence interval were estimated.

Results

Four RCTs (569 participants) were included. The analysis showed a benefit of SNI for certain clinical rhinological symptoms (SMD = –0.29 [–0.45; –0.13]) but no significant improvement of respiratory symptoms (SMD= –0.19 [–0.70; 1.08]) or health status (SMD = –0.30 [–0.68; 0.07]). Its use appeared to limit the prescription of other treatments, whether local or systemic, and particularly antibiotics. Long-term use led to a decrease in the incidence of acute rhinosinusitis and its complications. SNI appeared to be a safe treatment.

Conclusions

SNI is beneficial for rhinological symptoms but not respiratory symptoms. Further research is needed to address the full benefits/risks of this treatment.

Keywords: Child; Infant; Meta-analysis; Review; Saline nasal irrigation; Upper respiratory tract infection

Abbreviations

ARS: acute rhinosinusitis

CENTRAL: Cochrane Central Register of Controlled Trials

CI: confidence interval

ENT: ear, nose and throat

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

RCT: randomized controlled trial

SMD: standard difference in means

SNI: saline nasal irrigation

URTI: upper respiratory tract infection

Introduction

Acute upper respiratory tract infections (URTIs) in children are the leading cause of paediatric consultations in developed countries [1,2]. URTIs, including the common cold, influenza and rhinosinusitis cause rhinorrhoea, nasal obstruction, pharyngeal pain and coughing. The infection is almost exclusively of viral origin [1]. Its resolution is normally spontaneous without treatment and occurs within 15–21 days on average [3]. The main complications are secondary bacterial infections: notably, acute otitis media, acute bacterial sinusitis and conjunctivitis [4].

Professional recommendations for the treatment of URTIs in children include saline nasal irrigation (SNI), and administration of paracetamol in the case of fever and/or pain [4,5,6,7]. The efficacy of antibiotic [8-10], anti-inflammatory [11,12] and antihistamine [13] treatments has not been demonstrated in patients of any age, nor has the effectiveness of different nasal decongestants and antitussives [14,15]. In addition, many studies have shown the risk of toxicity of these drugs, especially in children [16,17]. However, these medications are still frequently used for self-medication or prescribed by health professionals [18].

SNI is generally described as a safe symptomatic treatment that is suitable for children [19-21]. This treatment is often prescribed by general practitioners and paediatricians. Its efficacy is proven for chronic upper respiratory tract diseases (infectious, inflammatory or allergenic) [22]. SNI is recommended for the treatment of URTI in children [4,6,7] and is a reference against which other local treatments are compared in most studies on nasal irrigation. However, few studies have been performed to evaluate SNI's efficacy for treating URTIs. Some work has focused on a qualitative approach, often in small, limited study populations of unequal quality [23,24]. In their meta-analysis of 2015, King *et al.*[25] focused on the use of saline solution for nasal cleansing to treat URTIs in children and adults, without distinguishing and stratifying the two populations. The study did not demonstrate real efficacy

in children, with regard to mean days to wellness and antibiotic usage. Furthermore, they did not focus on clinical rhinological and respiratory symptoms, which are important clinical outcomes for children.

Infants, pre-school and school-age children up to 12 years are a specific sub-population, more likely to be exposed to URTIs, and in whom the risks of complications are higher, owing to the immaturity of their anatomical structures and immune systems.

Using a systematic review of the literature and meta-analysis, we aimed to answer the following questions: Does clearing the nasopharyngeal passages with saline solution in infants, pre-school and school-age children up to 12 years reduce symptoms, rapidly resolve the infection, reduce the occurrence of complications and reduce the use of other treatments judged inefficacious and harmful?

Methods

Research strategy

The authors followed the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses.(PRISMA) [26] (Appendix 1) and the Cochrane Handbook [27]. The literature search focused on randomized controlled trials (RCTs), without any language restriction, to evaluate local treatment by rhinopharyngeal cleansing using isotonic saline solution to treat URTIs in children. All elements likely to be included in viral and post-viral URTI were sought, for example laryngitis and influenza syndromes. We searched for all published data and documents produced outside commercial publishing circuits and on the margins of bibliographic control systems (grey literature).

The literature search was performed from February to December 2018. The keywords used for the search were: ‘common cold’, ‘upper respiratory tract infection’,

‘nasopharyngitis’, ‘rhinosinusitis’, ‘sodium chloride’, ‘(hypertonic or isotonic) saline solution’, ‘nasal irrigation’ and ‘nasal lavage’, ‘infant’, ‘child’. The detailed search strategy is presented in Appendix 2. The following electronic databases and publishers were queried: Medline via PubMed, CENTRAL via the Cochrane Library, Embase, Google Scholar, Google and the International Register of Trials in Progress. The following were consulted for grey literature: Open Grey, Grey Literature Report, pharmaceutical laboratories marketing saline solutions for nasal lavage, the programmes of international congresses and reference paediatric ear, nose and throat (ENT) websites. The references of the articles obtained were also analysed. The initial research method was implemented independently on PubMed by one of the authors (MR) and by an information specialist in the University Library of the Medical Faculty of Clermont University, then together, with conciliation in the case of disagreement [28].

Selection of trials

Two authors (MR and PV) independently read the titles and abstracts of all publications obtained from the search engines. Studies selected by both authors independently as eligible for inclusion in the meta-analysis were included; studies excluded by both authors independently were excluded. Studies on which the two authors disagreed were discussed until consensus was reached.

Inclusion and exclusion criteria

All trials satisfying the quality of an RCT were selected: trials comparing the use of isotonic and hypertonic saline solutions, regardless of their mode of administration, with one therapeutic abstention, or a therapy deemed less important for nasal lavage. The ages of the children had to be between 3 months and 12 years. Acute (occurrence at less than 12 weeks of

age) rhinopharyngeal and sinus infection had to be assumed to be viral or post-viral. Trials involving patients with chronic, complex, allergic symptoms or bronchiolitis and those comparing local decongestant solutions and systemic treatments were excluded. Articles whose quality did not satisfy the criteria of an RCT but which did satisfy the inclusion criteria were selected and discussed according to a qualitative approach.

Assessment criteria

The main criteria were: an improvement in the effects of nasal infection (obstruction, discharge, purulence, coughing and/or sneezing), effects on respiration and effects on health status and activity (e.g. eating, drinking, sleeping and playing). The secondary criteria were the time to resolution of the symptoms, recurrence and complications, the use of other systemic treatments including antibiotics or topical treatments and the safety of the treatment.

Analysis of the methodological quality of the trials

The methodological quality of the trials was analysed using the grid of the Cochrane Collaboration's risk of bias tool for quality assessment of RCTs [29], by two authors (AC and MR). In cases of disagreement, the problem was discussed with a third author (PV) and a biostatistician (BP) to obtain consensus using the Cochrane Collaboration's tool for assessing risk of bias [30].

Data extraction

The data were extracted independently by two authors (MR and BP). These data were the years in which the trials were performed, their location, the type of population and ages of the patients, the type of treatment administered with the necessary details on the method used, the results according to the assessment criteria, and the possible secondary effects.

Statistical considerations

Statistical analysis was conducted using Comprehensive Meta-Analysis (version 2; Biostat Corporation, Englewood, NJ, USA) [31] and Stata (version 13; StataCorp LP, College Station, TX, USA) software. Type I error was fixed at $\alpha = 0.05$. The standard difference in means between groups (SMD; the difference between means divided by the pooled standard deviation, with a correction for small sample bias) and 95% confidence interval were estimated using DerSimonian and Laird random-effects models (assuming that the true effect estimates varied between studies) [32]. The analyses were performed by considering that a study could be reported several times in the same meta-analysis. Although this approach overestimated the statistical power, it seemed more appropriate to limit the bias induced by the choice of only one criterion used to describe a multifactorial symptom. Statistical heterogeneity between the results was assessed by examining forest plots, confidence intervals and using I^2, which is the most common and easily interpretable metric for measuring the magnitude of between-study heterogeneity. I^2 values range between 0% and 100% and are typically considered low at <25%, modest at 25–50%, and high at >50%. This statistical method generally assumes heterogeneity when the p-value of the I^2 test is <0.05.

Results

We identified 214 trials, of which four met the inclusion criteria. The RCTs were Bollag *et al.* [33], Šlapak *et al.* [34], Wang *et al.*[35] and Köksal *et al.* [36], involved 544 children and permitted analysis of the results from 489 patients: 334 in the saline solution group and 155 in the placebo group. Two prospective, non-controlled, non-randomized trials were excluded (see Appendix 3: Qualitative analysis of excluded trials) [37, 38].

Research and trial selection

The following trials were selected using the search strategy: 115 articles from Medline, 26 from CENTRAL, 60 from Embase and 18 articles found by manual searching on Google and Google Scholar, the analysis of clinical trial registers and databases of grey literature and exchanges with pharmaceutical laboratories (Figure 1).

Trials included

Four double-blind RCTs met the inclusion criteria: Bollag *et al*. (1984) [33], Šlapak *et al*. (2008) [34], Wang *et al*. (2009) [35] and Köksal *et al*. (2016) [36]. Quantitative analysis was used to survey the four RCTs for the primary endpoint (rhinological score), two for the secondary endpoint (respiratory score) and four for the third endpoint (health status score). Only one RCT permitted evaluation of scores of reports of illness and complications. See Table 1, Characteristics of included studies.

Risk of study bias

The trials were considered to pose an unknown or high risk for the items of sequence generation, allocation concealment, blinding of participants and personnel or blinding of outcome assessment, and selective outcome reporting. Risk assessment of bias is presented in Table 2 and Appendix 4.

Effects of interventions

Main assessment criterion

We performed a meta-analysis of the four trials included as a function of the main assessment criterion: improvement of clinical symptoms of URTI. Three types of symptoms were defined: rhinological, respiratory and health-status-related. The results are presented in forest-

plot form for rhinological scores (Figure 2), for respiratory scores (Figure 3), and for health status scores (Figure 4), making it possible to present the data from each study in terms of the effect size and associated 95% confidence interval. For the four tests taken together, we observed a statistically significant benefit of SNI for rhinological symptoms (SMD = –0.29 [–0.45; –0.13], I^2= 75%). For respiratory symptoms, a non-significant benefit was evident in the trials of Šlapak *et al.* [34] and Wang *et al.* [35]: SMD= –0.19 [–0.70; 1.08], I^2=83%. Regarding health status and activity, there was no significant improvement in the intervention group (SMD = –0.30 [–0.68; 0.07], I^2=85%). A beneficial but non-significant trend was observed in the meta-analysis of SNI in the trials of Šlapak *et al.* [34] and Wang *et al*. [35]. The study by Wang *et al*. [35] measured nasal peak expiratory flow rate, expressed as the variation in the percentage of the baseline measurement (–20.28% for the control group and –16.97% for the saline group). These results were added to those of Figure 3 relating to the respiratory scores described by Bollag *et al.* [33] and Šlapak *et al*. [34].

Secondary assessment criteria

The secondary assessment scores were: time until resolution of URTI; occurrence of complications, recurrence and relapse; and recourse to other treatments. Only the trial by Šlapak *et al.* [34] reported results for these criteria (Table 3).

Tolerance and safety

The tolerance and safety of SNI in children in the intervention groups were presented in the four RCTs analysed. They were reported qualitatively in the RCTs of Bollag *et al*. [34] and Wang *et al*. [35]. In the trial by Šlapak *et al*. [34], a score on a qualitative scale was used to measure tolerance, ranging from 1, ‘very pleasant’, to 5, ‘very unpleasant’ (the assessment of tolerance took place 5 minutes before performing the intervention). Children using the fine

spray reported higher comfort during and after application than the medium jet users. Overall, saline nasal wash was well tolerated; most complaints appeared in the medium jet group and were associated with the stronger flow of the wash. The number of complaints was too low (8.7% of the participants at the start of the study and 2.4% of participants at its end) for statistical analysis to be performed. Therefore, the assessment of safety of use was performed qualitatively. In the RCT of Wang *et al*. [36] the compliance rate was undefined.

No serious adverse events were reported in the intervention groups treated with SNI. There were some episodes of nasal bleeding in the trials by Šlapak *et al*. [34] and Köksal *et al* [36] and no adverse event in the trials of Bollag *et al*. [33] and Wang *et al*. [35].

Discussion

Our review is the first to focus on the efficacy of SNI in children only, using clinical criteria. Statistical analysis of the four RCTs allowed us to form a conclusion on the efficacy of nasal irrigation with isotonic saline solution in treating URTIs in children aged 3 months to 12 years. Although the assessment criteria differed, the results generally tended towards improvement. In the trials by Šlapak *et al*. [34] and Köksal *et al.* [36], benefits were observed for rhinological symptoms: sore throat, nasal secretion (rhinorrhoea) and loss of smell/taste in the trial by Šlapak *et al*. [34] and cough in the trial by Köksal *et al*. [36]. The improvement was not significant for other symptoms assessed in this trial (dry cough, productive cough, itching and sneezing) and for all rhinological symptoms assessed in the trial by Wang *et al*. [35]. No benefit was observed for SNI in the trial by Bollag *et al*. [33].

It was possible to evaluate the secondary assessment criteria only in the trial by Šlapak *et al*. [34], which demonstrated a significant benefit of SNI in the acute phase on the time to resolution of URTI. In the acute and preventive phases, there was a reduction in the

occurrence of complications, relapse, and the consumption of additional medication, especially antibiotics.

The method of delivering nasal irrigation differed in the four trials. As confirmed by the study of Jeffe *et al* [39], tolerance of SNI appears good. In the trial by Šlapak *et al*. [34], the use of a fine spray seemed more comfortable, which is essential for compliance of topical treatment in children, and was equally effective as a medium jet. The nasal solution used in the Bollag *et al*. [33], Wang *et al*. [35] and Köksal *et al*. [36] trials was 0.9% saline solution; Šlapak *et al*. [34] used a commercial isotonic seawater product containing mineral elements including zinc or selenium. These differences limit the possibility of data comparison.

No adverse effect was reported in the trials and the occurrence of benign secondary effects was rare. The safety of the use of SNI must be compared with that of other treatments, including those available on the market, that are responsible for potentially serious secondary effects [40,41]. The benefit/risk advantage of SNI provides an argument for recommending this treatment for URTIs in children. However, publication bias cannot be excluded in this study, despite our aim of performing exhaustive documentary research, with an approach that included unpublished literature.

The main difficulty with this type of RCT is that it is impossible to conduct a double blinded trial. It is also difficult to find a placebo, both for the intervention itself and for the product assessed. However, if blinding is impossible for the patient, it is still possible for a research team member to perform a blind evaluation of the assessment criterion. However, it is difficult to evaluate variable symptomatology on an inter-individual level according to quantitative criteria, despite the validation of scores such as those used by Wang *et al*. [35].

In the trials performed by Bollag *et al*. [33] and Wang *et al*. [35], some of the results – relating to health status, the intensity of symptoms and the occurrence of complications – were reported by the parents of the patients, either during follow-up consultations (Bollag *et*

al. [33], Köksal *et al*. [36]) or by way of a logbook (Wang *et al.* [35]). This increased the subjectivity of the assessment. In addition, a therapeutic trial performed in one location and at one time favours contamination bias, which probably applied to all three trials.

Despite the frequency of this infection in children and its cost, few RCTs have been performed on this topic. Our review of the literature found only four RCTs and two comparative non-randomized trials with a low number of participants. This lack of statistical power does not allow demonstration of a strong association, even if it exists. These observations do not call into doubt the pertinence and precision of the question raised but reveal the necessity of performing other studies with greater power and homogeneity.

All four RCTs used the same clinical assessment criteria: the improvement of nasal, respiratory and general symptoms. However, there were differences in these criteria among the trials and they were measured using different scales. The time units also differed as a function of the trial (2 days for Köksal *et al*. [36], 2 days for Bollag *et al.* [33], 1 week for Wang *et al.* [35] and 1–3 weeks for Šlapak *et al.* [34]). This heterogeneity made the meta-analysis difficult to perform. Although the analysis is theoretically possible, it is necessary to take into account this methodological flaw when interpreting the results. The use of reference scores or parameters measurable at given times is necessary.

This meta-analysis was subject to another bias: the details of the scores in the trial by Bollag *et al*. [33] were not given because only the total score was reported, in contrast to the RCTs of Šlapak *et al.* [34] and Wang *et al*. [35] The results of the RCT by Bollag *et al*. [33] regarding rhinological symptoms therefore had less impact on the final result.

In contrast to the meta-analyses reported by Kassel [42] and King [25], our study was interested only in children. We felt that this was important, given the frequency of nasopharyngeal infection in this age group. Furthermore, as described previously, our review gives more details of the evaluation of outcomes related to rhinological and respiratory

symptoms and health status. Therefore, by focusing on children and considering endpoints clinically relevant, the conclusions we have presented in this work differ considerably from those proposed by previous studies.

In combination with other studies focusing on (acute and chronic) rhinosinusitis, we can assert that SNI is a safe treatment that permits a reduction in the use of other treatments judged ineffective and/or harmful [23,24,42]. The improvements in symptoms, especially in children with allergic disease, the reduction of the use of other treatments and the safety of the use of SNI have been also identified in several other literature reviews. However, the recommendations of learned societies are based on these studies of low statistical power while awaiting stronger levels of proof.

Conclusion

This systematic review responded to research questions concerning the efficacy and safety of SNI for the treatment of URTIs in children. Quantitative analysis of the trials showed that SNI is beneficial in the treatment of certain rhinological symptoms. It appears to reduce the incidence of URTI and its complications in the acute phase and in the long term. This intervention also permits a reduction in the use of other treatments such as topical therapies – including those available on the market – and systemic drugs such as antibiotics. This study of RCTs and prospective studies demonstrates the safety of SNI.

This treatment can therefore be recommended while other studies on the subject are ongoing. RCTs of greater power are required that compare SNI to an intervention deemed less important, such as nose blowing. Studies evaluating the long-term use of SNI are likely to confirm its preventive effect. Given that double blinding is impossible when assessing the efficacy of SNI, it is justifiable to consider a pragmatic approach, without the rationale of determining the benefit: risk ratio. The approach could be more open, for example, using

comparative cohorts with modelling to take differences into account, or a medico-economic analysis.

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Conflict of Interest: None

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Figure 1: Flowchart of study selection

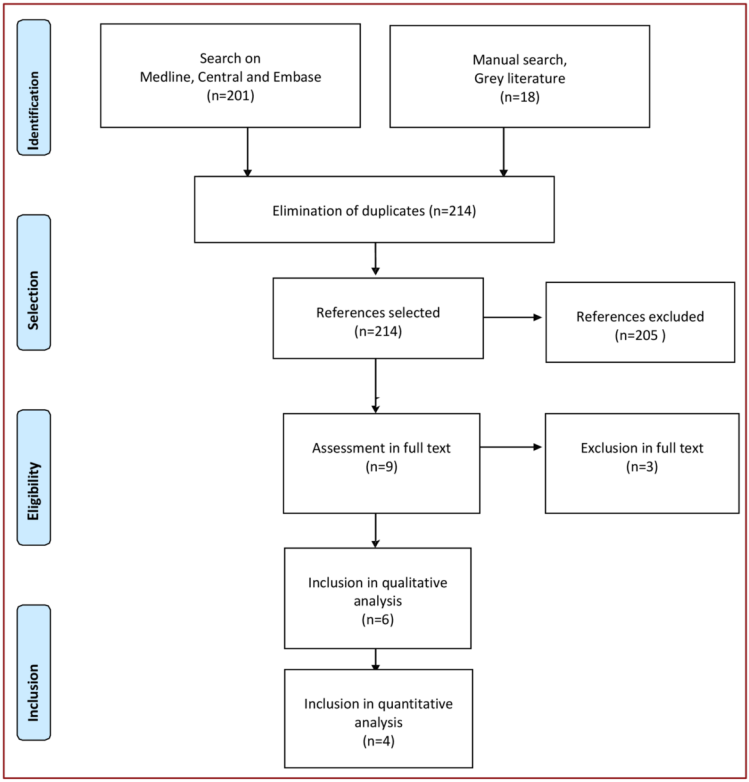

Figure 2: Forest plot of rhinological scores

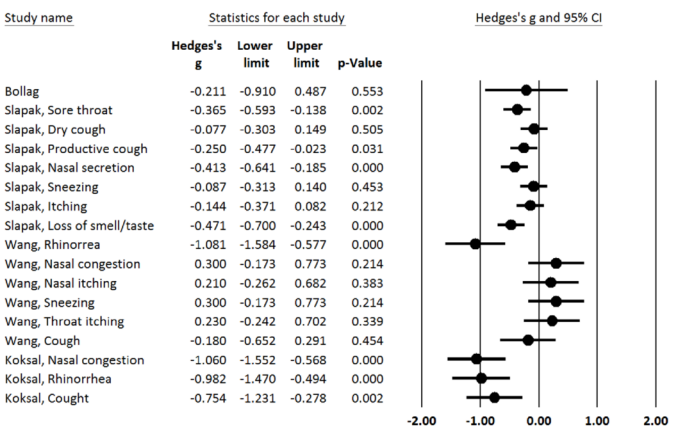

Figure 3: Respiratory scores

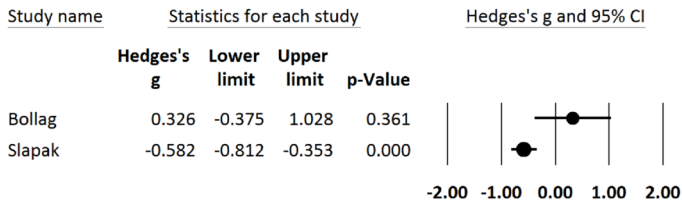

Figure 4: Forest Plot of health status scores

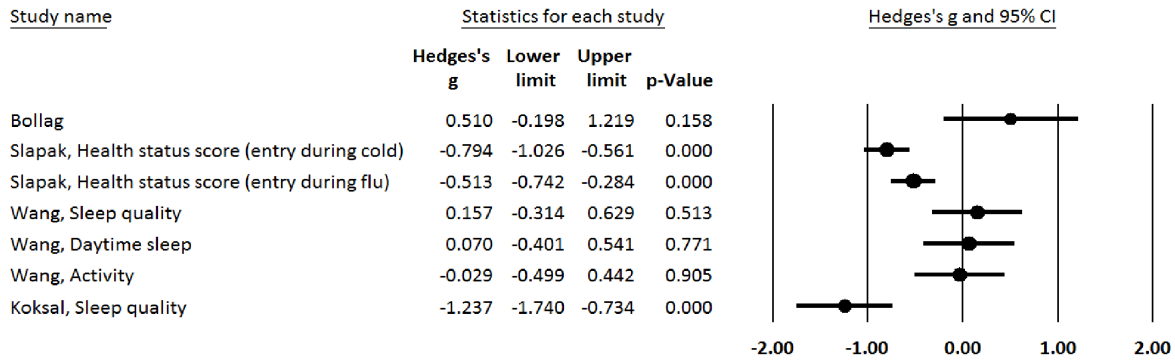

Table 1. main characteristics of the included studies

Authors	No. of patients	Age	Doses and duration of therapy	Primary outcome	Concomitant treatment	Side effects
Bollag *et al.* (1984)	74 children	3 weeks to 2 years	0.9% saline solution (four drops in each nostril every 2 hours as needed) during 3 days. 3 groups: nasal saline irrigation, phenylephrine hypochloride 1.4% and a control group	Nasal symptoms Respiratory symptom Activity sign measured at J2	None	No significant side effects
Šlapak *et al.* (2008)	401 children	6 -10 years	0.9% saline solution, (6 times per day) , 4 groups : 3 intervention (Group 1, medium jet flow; Group 2, fine spray; Group 3, eye and nose wash with a fine spray) and a control group.	Nasal symptoms Respiratory score Health status score Additional treatment required	Antipyretics Nasal decongestants Mucolytics Systemic antibiotics	Nose bleeding. Some associated with the stronger flow of the wash. burning and bitter taste.
Wang *et al*. (2009)	69 children	3 – 12 years	0.9% saline solution, 15–20 ml, 1-3 times daily, administered using a disposable syringe during 3 weeks.	Nasal symptoms Paediatric Rhinoconjunctivitis Quality of Life Score Nasal peak expiratory flow rate	Standard treatment (including systemic antibiotics, mucolytics and nasal decongestants)	No significant side effects
Köksal *et al.* (2016)	109 children	< 2 years	Tree groups : 36 children using 0.9% saline solution, 36 using 2.3% hypertonic saline solution and 35 in the control group (no intervention) during 7 days.	Nasal symptoms Sleep quality	None	Nasal bleeding, without difference between groups

Table 2. Summary of the risks of bias for each trial

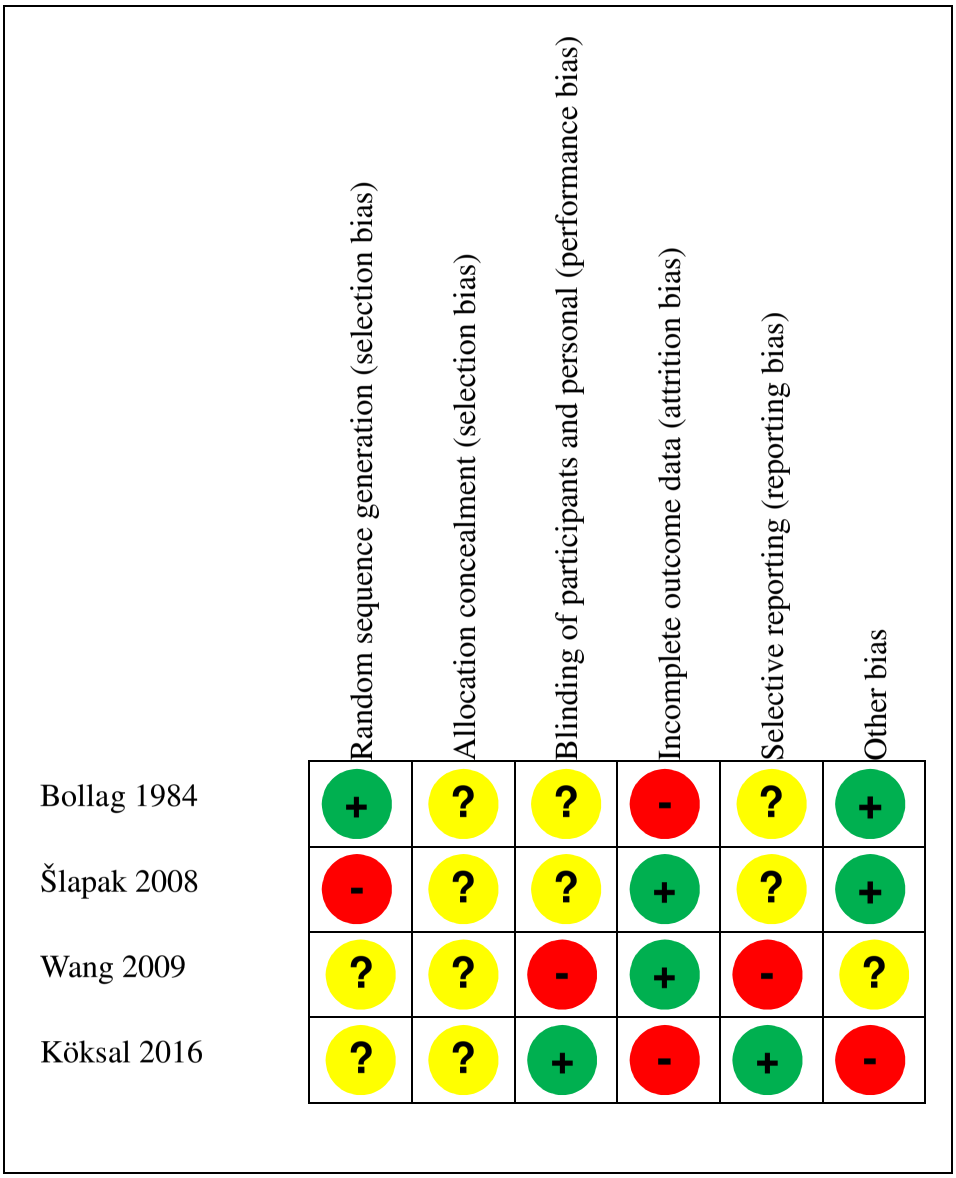

Table 3. Scores of reports of illness and complications - Slapak RCT

		Control (n=101)		Saline irrigation (n=289)	
		n	%	n	%
	Illness and complications				
VISIT 3	**Reported illness**	76	75.2	89	30.9*
	Reported school absence	35	34.7	49	17*
	Complications	32	31.7	24	8.3*
VISIT 4	**Reported illness**	53	52.5	64	22.2*
	Reported school absence	25	24.8	25	8.7*
	Complications	14	13.9	12	4.2*
	Additive medication				
VISIT 2	**Antipyretics**	13	12.9	22	7.6
	Nasal decongestant	36	35.6	46	15.9*
	Mucolytics	32	31.7	50	17.3*
	Systemic antibiotics	9	8.9	16	5.5
VISIT 3	**Antipyretics**	33	32.7	27	9.4*
	Nasal decongestant	47	46.5	15	5.2*
	Mucolytics	37	36.6	28	9.7*
	Systemic antibiotics	21	20.8	16	5.6*
VISIT 4	**Antipyretics**	20	19.8	19	6.6*
	Nasal decongestant	43	42.6	11	3.8*
	Mucolytics	24	23.8	14	4.9*
	Systemic antibiotics	9	8.9	12	4.2

* $P < 0.05$