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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
RESULTS	6
DISCUSSION	7
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	8
REFERENCES	9
CHARACTERISTICS OF STUDIES	11
APPENDICES	13
CONTRIBUTIONS OF AUTHORS	14
DECLARATIONS OF INTEREST	14
SOURCES OF SUPPORT	14
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	14
INDEX TERMS	14

[Intervention Review]

Interventions for atrophic rhinitis

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ABSTRACT

Background

Atrophic rhinitis is a chronic nasal pathology characterised by the formation of thick dry crusts in a roomy nasal cavity, which has resulted from progressive atrophy of the nasal mucosa and underlying bone. The common symptoms may include foetor, ozaena, crusting/nasal obstruction, epistaxis, anosmia/cacosmia and secondary infection with maggot infestation. Its prevalence varies in different regions of the world and it is common in tropical countries. The condition is predominantly seen in young and middle-aged adults, especially females, with a racial preference amongst Asians, Hispanics and African-Americans. A wide variety of treatment modalities have been described in the literature, however the mainstay of treatment is conservative (for example, nasal irrigation and douches; nose drops (e.g. glucose-glycerine, liquid paraffin); antibiotics and antimicrobials; vasodilators and prostheses). Surgical treatment aims to decrease the size of the nasal cavities, promote regeneration of normal mucosa, increase lubrication of dry nasal mucosa and improve the vascularity of the nasal cavities.

Objectives

To assess the effectiveness of interventions for atrophic rhinitis.

Search methods

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the search was 28 March 2011.

Selection criteria

Randomised controlled trials (RCTs) studying any treatment or combination of treatments in patients with atrophic rhinitis. We excluded studies with follow-up of less than five months following treatment/intervention.

Data collection and analysis

Three review authors abstracted and assessed studies. We tabulated and then compared the responses of the review authors separately for the individual studies.

Main results

No studies met the inclusion criteria for the review. We identified one RCT comparing oral rifampicin plus nasal wash versus nasal submucosal placentrex injection plus nasal wash versus a control group (nasal wash) but had to exclude this study due to inadequate length of follow-up. A further RCT comparing Young's operation with nasal lubrication for primary atrophic rhinitis is underway.

Authors' conclusions

There is no evidence from randomised controlled trials concerning the long-term benefits or risks of different treatment modalities for atrophic rhinitis. Further high-quality research into this chronic disease, with a longer follow-up period, is therefore required to establish this conclusively.

PLAIN LANGUAGE SUMMARY

Interventions for atrophic rhinitis

Atrophic rhinitis is a chronic nasal condition with unknown cause. It is characterised by the formation of thick dry crusts in a roomy nasal cavity, which has resulted from progressive wasting away or decrease in size (atrophy) of the mucous nasal lining (mucosa) and underlying bone. The various symptoms include foetor (strong offensive smell), crusting/nasal obstruction, nosebleeds, anosmia (loss of smell) or cacosmia (hallucination of disagreeable odour), secondary infection, maggot infestation, nasal deformity, pharyngitis, otitis media and even, rarely, extension into the brain and its membranes. Atrophic rhinitis can be classed as primary or, where it is a consequence of another condition or event, secondary. Its prevalence varies in different regions of the world but it is common in tropical countries. A wide variety of treatments have been described in the literature, however treatment is usually conservative (for example, nasal irrigation and douches; nose drops (e.g. glucose-glycerine, liquid paraffin); antibiotics and antimicrobials; vasodilators (drugs that cause dilation of blood vessels) and prostheses). Surgical treatment aims to decrease the size of the nasal cavities, promote regeneration of normal mucosa, increase lubrication of dry nasal mucosa and improve the vascularity (blood flow) of the nasal cavities.

We searched systematically for randomised controlled trials (RCTs) studying any treatment or combination of treatments for atrophic rhinitis in patients with atrophic rhinitis. Despite a comprehensive search we found no RCTs which met our inclusion criteria, although a RCT comparing surgery (Young's operation) with nasal lubrication for primary atrophic rhinitis is underway. Further high-quality research into this chronic disease, with a longer follow-up period, is therefore required to conclusively establish the long-term benefits or risks of different treatment modalities for atrophic rhinitis.

BACKGROUND

Description of the condition

Atrophic rhinitis is a chronic condition with unknown aetiology characterised by the formation of thick dry crusts in a roomy nasal cavity, which has resulted from progressive atrophy of the nasal mucosa and underlying bone. The various symptoms which result from the primary nasal pathology and its sequelae may comprise foetor (strong offensive smell), ozaena (a chronic disease of nose accompanied by a foetid discharge and marked by atrophic changes in nasal structures), crusting/nasal obstruction, epistaxis, anosmia (loss of smell) or cacosmia (hallucination of disagreeable odour), secondary infection, maggot infestation, nasal deformity, pharyngitis, otitis media and even, rarely, intracranial spread (extension into the brain and its membranes). Atrophic rhinitis can be classed as primary or, where it is a consequence of another condition or event, secondary.

The condition is predominantly seen in young and middle-aged adults, especially females (6:1.5) (Bunnag 1999). Its prevalence varies in different regions of the world. It is a common condition in tropical countries such as India, Pakistan, China, the Philippines and Malaysia, in Saudi Arabia, Egypt, Central Africa, Eastern Europe (Poland), Mediterranean areas and Latin and South America (Lobo 1998; Zohar 1990). Primary atrophic rhinitis has a high prevalence in the arid regions bordering the great deserts of Saudi Arabia (Kameswaran 1991). A racial preference is seen amongst Asians, Hispanics and African-Americans. Prevalence is low in equatorial Africa (Weir 1997). In those countries with a higher prevalence, primary atrophic rhinitis can affect between 0.3% and 1.0% of the population. The majority of publications on atrophic rhinitis are from India, China, Poland and other regions where the condition is common (Dutt 2005). An environmental influence is suggested by its enhanced prevalence in rural areas (69.6%) and amongst industrial workers (43.5%) (Bunnag 1999). It appears to be more common in lower socio-economic classes, poor populations and those living in conditions of poor hygiene (Chaturvedi 1999). In the last four to five decades there has been a notable decline in the incidence of atrophic rhinitis in North America, Britain and some parts of Europe, however such marked decline has not been reported in Asia and Africa.

The exact aetiology of primary atrophic rhinitis is unknown but many factors are implicated. It is seen to have a polygenic inheritance in 15% to 30% of cases, while other studies have revealed either an autosomal dominant (67%) or autosomal recessive penetrance (33%) (Amreliwala 1993). Chronic bacterial infection of the nose or sinus may be one of the causes of primary atrophic rhinitis (Artiles 2000; Zohar 1990). Classically *K. ozaenae* has been implicated (Bunnag 1999), but other infectious agents include *Coccobacillus foetidus ozaenae*, *Bacillus mucosus*, diphtheroids, *Bacillus pertussis*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and proteus species. It is still not clear whether these bacteria cause the disease or are merely secondary invaders. It may be possible that superinfection with mixed flora causes ciliostasis leading to epithelial destruction and progressive mucosal changes. A developmental aetiology has been suggested, which considers the disease to be associated with poor pneumatization of the maxillary sinuses, congenitally spacious nasal cavities, excessively patent nasal cavities in relation to shape and type of the skull and platyrrhinia (Chaturvedi 1999; Hagrass 1992; Zohar 1990). Nutritional deficiency, especially of iron, fat

soluble vitamins and proteins, has also been suggested (Bernat 1968; Chaturvedi 1999; Zakrzewski 1993). Phospholipid deficiency (Sayed 2000), autonomic dysfunction leading to excessive vasoconstriction (Ruskin 1932) or reflex sympathetic dystrophic syndrome (Ghosh 1987), endocrinal imbalances resulting in oestrogen deficiency (Barbary 1970; Zohar 1990), allergy (Bunnag 1999), immune disorders (Makowska 1979; Medina 2003) and biofilm formation have also been implicated in the aetiology of primary atrophic rhinitis.

Secondary atrophic rhinitis, however, is known to occur as a consequence of many factors. These include local injury involving extensive accidental maxillofacial and nasal trauma/surgery (notably turbinate surgery (Moore 2001)), recurrent acute and chronic suppurative infections of the nose/paranasal sinuses (PNS), viral exanthems in children, chronic granulomatous disorders of nose (tuberculosis, lupus vulgaris, syphilis, leprosy, rhinoscleroma, yaws, pinta (Carducci 1965; Mehta 1981), typhoid fever (Singh 1992) and AIDS (Xu 1999). Radiation-induced atrophic rhinitis is well reported, especially in those receiving chemotherapeutic agents and decongestants (Chen 2003). Uncommon causes include occupational exposure to phosphorite and apatite dusts (Mickiewicz 1993), anhydrotic ectodermal dysplasia (Sinha 2003), osteochondroplastic trachobronchopathy (Wiatr 1993) and ichthyosis vulgaris (Reisser 1992).

A diagnosis of atrophic rhinitis is essentially clinical and based on a triad of characteristics: foetor, greenish crusts and roomy nasal cavities. Such a full-blown clinical picture is usually seen during later stages and the early course of disease may consist of cacosmia only, with the presence of thick nasal crusts. In the latter situation the turbinates may look normal. Two histopathological variants of atrophic rhinitis were described by Taylor and Young in 1961, depending upon the vascular involvement (Taylor 1961). Type I is more common (50% to 80%) and is characterised by endarteritis obliterans, periarteritis and periarterial fibrosis of terminal arterioles as a result of chronic infection with round cell and plasma cell infiltration. In contrast, type II is less common (20% to 50%) and shows capillary vasodilation with active bone resorption. While the former variety is likely to improve with the vasodilator effects of oestrogen, the latter variety is not amenable to such therapy. It is important to exclude primary chronic sinus suppuration, suppurating adenoidal disease in adolescents, and neglected foreign body/rhinoliths in unilateral cases before diagnosing primary atrophic rhinitis. Similarly, general and systemic examination should thoroughly evaluate the possibilities of atrophic rhinitis secondary to tuberculosis, leprosy, scleroma and syphilis. Investigations, including haematological work-up, radiological assessments and biopsy (Chaturvedi 1999; Weir 1997), mainly aim to exclude secondary causes of atrophic rhinitis and other granulomatous conditions. Apart from haemoglobin estimation (anaemia), total leucocyte count (TLC)/differential leucocyte count (DLC) and general blood picture (GBP) may show leucocytosis (infection) or a microcytic hypochromic picture (iron deficiency anaemia), raised erythrocyte sedimentation rate (ESR) (tuberculosis and granulomatous infection) and blood sugar (diabetes), which are important considerations in diagnosis. Serum protein and plasma vitamin level estimations are necessary to exclude malnutrition. In selected suspicious cases, autoimmune assays for immunological study, radiology of paranasal sinuses for assessment of bony framework, venereal disease research laboratory (VDRL) test (for syphilis), chest X-ray and Mantoux test/

Interventions for atrophic rhinitis (Review)

enzyme linked immunosorbent assay (ELISA) (for tuberculosis), and ear lobe puncture/smear and nasal biopsy (for leprosy - morphological and bacteriological indices) may be needed. Nasal biopsies may be performed for Young and Taylor classification and for secondary atrophic rhinitis related to nasal granuloma such as lupus, leprosy, scleroma and gumma.

Description of the intervention

A wide variety of treatment modalities have been described in the literature. The mainstay of treatment is conservative and includes the following.

1. Nasal irrigation and douches
2. Glucose-glycerine nose drops
3. Liquid paraffin nose drops
4. Estradiol in arachis oil
5. Kemicetine anti-ozaena solution
6. Chloramphenicol/streptomycin drops
7. Placental extract
8. Acetylcholine with or without pilocarpine
9. Antibiotics and antimicrobials
10. Iron, zinc, protein and vitamin (A and D) supplements
11. Vasodilators
12. Prostheses
13. Vaccines

Surgical treatment aims to:

1. decrease the size of nasal cavities by submucosal injection and insertion of various substances and implants (type A);
2. promote regeneration of normal mucosa by classical Young's operation and its modifications (Gadre 1973; Ghosh 1987; El Kholly 1998; Sinha 1977) (type B);
3. increase lubrication of dry nasal mucosa (Raghav Sharan's operation) (type C); and
4. improve the vascularity of the nasal cavities by stellate ganglion block, cervical sympathectomy, pterygopalatine fossa block and juxta-nasal sympathectomy (type D).

Why it is important to do this review

More than 15 types of conservative treatment and over 25 types of surgery have been described in the literature; most of these interventions have been tried in only a very small number of patients. It is likely that the literature therefore reflects a large number of case reports and few randomised controlled trials. The mainstay of surgical management has been the Young's operation, while conservative management has mainly focused on lubrication of the nasal mucosa and removal of crusts. There is a distinct advantage of conservative treatment in terms of the cost involved, especially in the developing world where this disease is prevalent. However, proponents of surgery claim to be able to reduce the time to onset of recovery in such patients.

Direct comparison of medical versus surgical management, as well as evaluation of the most commonly used conservative methods (liquid paraffin and kemicetine anti-ozaena nose drops) and surgical technique (Young's operation) would be worthwhile. One randomised controlled trial from India was published in 2008 (Jaswal 2008). A Cochrane Review of interventions for atrophic

rhinitis is therefore warranted and, in the event of an absence of sufficient randomised controlled trials, serves to highlight important gaps in the evidence base for management of this disease.

OBJECTIVES

To assess the effectiveness of interventions for atrophic rhinitis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

We considered patients with atrophic rhinitis diagnosed on the basis of atrophic/roomy nasal cavity, unilateral or bilateral formation of thick crusts and foetid odour with or without atrophic/roomy nasal cavity. We excluded studies with follow-up of less than five months following treatment/intervention.

Types of interventions

We included trials studying any treatment or combination of treatments for atrophic rhinitis (primary or secondary) and documented the types of treatment(s) (unilateral or bilateral). Comparisons included:

- medical versus surgical;
- medical plus surgical versus medical alone;
- medical plus surgical versus surgical alone;
- medical versus medical;
- surgical versus surgical.

Types of outcome measures

Primary outcomes

- Proportion of patients with subjective improvement in symptoms (disappearance of odour, dryness sensation, headache, nasal obstruction, improved responses to nasal disease specific questionnaire) according to validated symptom scales.

Secondary outcomes

- Radiographic modalities including computed tomography (CT) scanning/magnetic resonance imaging (MRI).
- Bacterial cultures (including growth of *K. ozaenae*).
- Saccharine test time.
- Endoscopic evaluation of transitional changes of nasal mucosa from dry to moist texture or appearance of free mucus in nasal cavity (post-Young's operation). Improvement in the consistency of free mucus (reduced viscosity) was also considered.
- Histological mucosal (ultrastructural) changes with either recovery of cylindrical epithelium or deterioration to squamous epithelium. The classical normal respiratory lining is pseudostratified ciliated columnar epithelium with goblet cells that change to cuboidal or stratified squamous epithelium (metaplasia) in atrophic rhinitis, along with atrophy of cilia and

mucosal and submucosal glands. Reverse changes are seen with recovery and are an important objective parameter.

- Tissue and haematological profiles to observe cellular predominance (specially lymphocytic) and cytokine profiles to estimate vaccine effectiveness and characterise inflammation.
- Functional changes of nasal mucosa (including surface temperature of conchal mucosa, acid-base scale of nasal secretions and volume of nasal secretions).

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The authors contacted a couple of original authors for clarification and no translations of papers were deemed necessary for further clarification of data. The date of the search was 28 March 2011.

Electronic searches

We conducted electronic searches of various bibliographic databases including the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 1); PubMed; EMBASE; CINAHL; AMED; ISI Web of Science; BIOSIS Previews; CAB Abstracts; LILACS; KoreaMed; IndMed; PakMediNet; ICTRP; Clinicaltrials.gov; ISRCTN and Google.

We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. ([Handbook 2011](#))). Search strategies for major databases including CENTRAL are provided in [Appendix 1](#).

Searching other resources

We scanned the reference lists of identified studies for further trials. We decided beforehand to contact authors of published trials and other experts in the field either in person or by post. We searched PubMed, TRIPdatabase, NHS Evidence - ENT & Audiology and Google to retrieve existing systematic reviews and meta-analyses possibly relevant to this systematic review, in order to search their reference lists for additional trials. We searched reference lists from the available pertinent articles and books, conference proceedings and personal communications. We also handsearched older non-indexed Indian journals for relevant studies in our 100-year old academic institution.

Data collection and analysis

Selection of studies

The systematic review was carried out as per the methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Handbook 2011](#)). All three review authors worked independently to search for and assess trials for inclusion and methodological quality. We undertook a pilot testing on a sample of reports to redefine and clarify the eligibility criteria and thereby train the authors to come up with a consistent opinion. Subsequently all the authors compiled the search results using reference manager software and later merged their work. We examined the titles and abstracts of the studies to determine

the studies satisfying the inclusion criteria. We retrieved the full text of potentially relevant studies to decide compliance of the studies with eligibility criteria and resolved any differences throughout review by consensus. We calculated a Kappa statistic for measuring agreement between two authors making simple inclusion/exclusion decisions. We contacted a couple of original authors/investigators to provide more references. All the three authors collectively prepared a list of excluded studies amongst the short-listed ones.

Data extraction and management

We reviewed trials that were short-listed to record the following information.

- Date of study
- Study ID
- Citation/contact details
- Source of funding
- Patient recruitment details (including number of patients, study setting, age, sex, country, co-morbidities, ethnicity, socio-economic status, education)
- Inclusion and exclusion criteria
- Study design
- Randomisation and allocation
- Concealment methods
- Number of participants randomised
- Confounders
- Blinding (masking) of participants, care givers and outcome assessors
- Total number of intervention groups
- Type of therapy (intervention)
- Duration of intervention
- Co-interventions
- Number of patients lost to follow-up
- Reasons for withdrawal from protocol (side effects, refusal etc.)
- Details on side effects of intervention
- Whether intention-to-treat analysis was possible from the data

We recorded the outcome measures as discussed earlier where feasible. We noted the key conclusions and important comments from study authors. We independently recorded the miscellaneous comments of the review authors. We undertook a pilot entry of a preliminary data collection form for a couple of studies to counter the initial problems and facilitate necessary modifications to create the final version. We resolved any differences in data extraction by consensus at multiple meetings.

Assessment of risk of bias in included studies

We were to assess the quality of the included studies according to six major components, as per the 'Risk of bias' tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Handbook 2011](#)) as follows:

1. Sequence generation: trials were to be scored as Grade A = adequate sequence generation, Grade B = unclear; Grade C = no sequence generation (Grade A = low risk of bias, i.e. high quality).
2. Allocation concealment: trials were to be scored as Grade A = adequate allocation concealment; Grade B = unclear; Grade C =

clearly inadequate allocation concealment (Grade A = low risk for bias or high quality).

3. Blinding: trials were to be scored as Grade A = participants, care givers and outcome assessors blinded; Grade B = outcome assessors blinded; Grade C = unclear; Grade D = no blinding of outcome assessors (Grade A and B = low risk for bias, i.e. high quality).
4. Incomplete outcome data: trials were to be scored as Grade A = no missing data or irrelevant missing data unlikely to be related to the true outcome; Grade B = unclear; Grade C = clearly missing data likely to be related to true outcome (Grade A = low risk for bias, i.e. high quality).
5. Selective outcome reporting: trials were to be scored as Grade A = all the pre-specified primary and secondary outcomes have been reported; Grade B = all the pre-specified primary outcomes have been reported; Grade C = unclear; Grade D = clearly incomplete reporting of pre-specified primary outcomes (Grade A and B = low risk for bias, i.e. high quality).
6. Other sources of bias were to be noted for either judgement of (a) low risk of bias when the study appeared to be free of other sources of bias; or (b) high risk of bias when there is at least one important risk factor (such as a potential source of bias related to the specific study design used; or study was claimed to have been fraudulent; or with some other problem) or (c) unclear risk of bias when there may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias. For follow-up of randomised patients, trials were to be scored as Grade A = outcomes measured in greater than 90%; Grade B = outcomes measured in 80% to 90%; Grade C = unclear; Grade D = outcomes measured in less than 80% (Grade A = low risk for bias, i.e. high quality).

All the above assessments were to be included in the 'Risk of bias' tables. The inter-reviewer reliability for the identification of the high-quality studies for each component was to be measured using a Kappa statistic.

Data synthesis

For the dichotomous outcome variables of each individual study (comparison of intervention arms), we were to calculate proportional and absolute risk reductions using a modified intention-to-treat analysis. An initial qualitative comparison of all the individually analysed studies (intervention arms) would have determined whether pooling of results (meta-analysis) would have been reasonable. This would have taken into account differences in study population, intervention, outcome assessment and estimated effect size.

The results from all the studies that met the inclusion criteria and reported any of the outcomes of interest were to be included in the subsequent meta-analysis. We intended to calculate a summary statistic for each study and subsequently would have calculated a summary (pooled) treatment effect estimate as a weighted average of the various treatment effects estimated in the individual studies. Depending upon the data we planned a random-effects or a fixed-effect meta-analysis. Hence, we would have calculated a summary weighted risk ratio and 95% confidence interval using the inverse variance approach of each study result for weighting (using the Cochrane statistical package RevMan 5.1 (RevMan 2011)).

Subgroup analysis and investigation of heterogeneity

We planned in the protocol to compare various treatment modalities from various RCTs such as medical versus surgical; medical plus surgical versus medical alone; medical plus surgical versus surgical alone; medical versus medical; and surgical versus surgical. However, in the absence of any RCTs this was not undertaken. In addition, if feasible, we planned to use variables such as time to clinical cure and clinical improvement as being normally distributed continuous variables, so that the mean difference in outcomes could have been estimated. We would have tested any heterogeneity between the studies for statistical significance using a Chi² test ($P < 0.1$). We would have calculated the 95% confidence interval, estimated using a random-effects model, wherever statistical heterogeneity was present.

Sensitivity analysis

In the absence of RCTs the sensitivity analysis was not performed.

RESULTS

Description of studies

Results of the search

Searches in February 2010 and March 2011 retrieved a total of 68 reports. We discarded 39 as not relevant and considered 29 references for the review. We discarded 13 animal studies. We initially excluded seven studies on the basis of title and abstract and retrieved the full text of a further nine for further assessment (Borgstein 1993; Fang 1998; Jaswal 2008; Johnsen 2001; Kehrl 1998; Klemi 1980; Nielsen 1995; Shehata 1996; Stoll 1958). Following full-text assessment, none of the studies met the inclusion criteria for this review.

Included studies

We identified no studies which met the inclusion criteria for the review.

Excluded studies

We excluded a total of 16 studies (see [Characteristics of excluded studies](#)). To date only a single randomised controlled trial of treatment for atrophic rhinitis has been published (Jaswal 2008), however it did not fulfil our inclusion criteria in terms of long-term outcome measurement. In this study 30 patients with primary atrophic rhinitis were randomised into three groups: oral rifampicin plus nasal wash; nasal submucosal placentrex injection plus nasal wash; and a control group (nasal wash). Oral rifampicin showed the most promising results regarding objective, subjective and histopathological improvement with maximum disease-free interval on regular follow-up as compared to submucosal placentrex injections, while both performed better than the control group.

Borgstein 1993 was a clinical controlled trial with 50 patients in two groups (22 versus 28) that compared oral rifampicin plus cotrimoxazole plus nasal wash with oral ciprofloxacin plus nasal wash for the outcomes of nasal crusting, nasal obstruction, purulent secretions, olfactory changes, dysphonia, cough and malaise. We excluded the study as it was not a true RCT, both comparable groups were not totally similar and the study had insufficient information available.

Fang 1998 was a 20-patient series: endoscopic sinus surgery (ESS) was performed (Stammberger's technique along with middle turbinectomy) in 14 while another six underwent treatment with antibiotics (not indicated). Patients were evaluated using clinical symptoms, radiological sinus images, saccharine time tests, bacterial cultures and mucosal ultrastructures, before and after ESS. The duration of follow-up was two years. The study revealed the various clinical characteristics of the disease that were associated with favourable outcome.

Johnsen 2001 was a non-randomised cross-over study in 79 patients with nasal mucosa dryness (not necessarily atrophic rhinitis). In Arm 1, half the subjects received pure sesame oil for 14 days followed by ISCS (isotonic sodium chloride solution) for 14 days. In Arm 2 the other half received ISCS for 14 days followed by pure sesame oil for 14 days. Nasal mucosa dryness, stuffiness and crusts were scored every evening with a visual analogue scale. Nasal mucosa dryness improved significantly when pure sesame oil was used compared with ISCS ($P < 0.001$). The improvement in nasal stuffiness was also better with pure sesame oil ($P < 0.001$) as was improvement in nasal crusts ($P < 0.001$). Eight of 10 patients reported that their nasal symptoms had improved with pure sesame oil compared with 3 of 10 for ISCS ($P < 0.001$). The trial authors concluded that when nasal mucosa dryness due to a dry winter climate was treated, pure sesame oil was shown statistically to be significantly more effective than ISCS.

Kehrl 1998 was a randomised comparison of parallel groups (not a RCT) and comprised 48 outpatients diagnosed with rhinitis sicca anterior (not classical atrophic rhinitis). In Arm 1, 24 patients were treated with a nasal spray: dexpanthenol in physiologic saline solution (Nasicur). In Arm 2, the control group of 29 patients received a placebo. The assessment of nasal breathing resistance and the extent of crust formation according to scores were defined as target parameters. The superiority of the dexpanthenol nasal spray in comparison to the placebo medication was demonstrated for both target parameters as clinically relevant and statistically significant. Dexpanthenol nasal spray showed no statistically significant difference in comparison to placebo. The trial authors concluded that the result of the controlled clinical study confirms that the dexpanthenol nasal spray is an effective medicinal treatment of rhinitis sicca anterior and is more effective than common medications.

Klemi 1980 was a double-blind study of 37 patients with allergic rhinitis, not atrophic rhinitis.

Nielsen 1995 was a case series revealing clinical response in 10 patients with ozaena. Patients received ciprofloxacin in a daily dose of 500 to 750 mg twice daily for one to three months. The patients were followed regularly for up to 26 to 74 months after treatment. All the patients registered permanent disappearance of odour, crusting and growth of *Klebsiella ozaena*.

Shehata 1996 was a review article, not a clinical experimental/observational study.

Stoll 1958 was possibly a case series evaluating a single agent (inplacen) response in a series of patients. The study is very old, in the German language and incomplete information is available to conclude exclusion.

We excluded the other studies on the grounds of either (1) not satisfying our disease inclusion criteria, (2) not fulfilling the required study design criteria or (3) lack of clearcut time-linked outcome measures.

Risk of bias in included studies

We found no eligible studies comparing treatment modalities in atrophic rhinitis that met the criteria for inclusion in this review.

Effects of interventions

We found no eligible studies comparing treatment modalities in atrophic rhinitis that met the criteria for inclusion in this review.

DISCUSSION

Although our search identified a single randomised controlled trial (RCT) it did not fulfil our inclusion criteria in terms of follow-up duration (**Jaswal 2008**). Hence this systematic review has overall failed to determine the best amongst the various interventions (medical and surgical) for atrophic rhinitis as described in the literature to date.

Based on the evidence discussed earlier, the mainstay of surgical management for atrophic rhinitis has been Young's operation, while conservative management has mainly focused on lubrication of the nasal mucosa and removal of crusts. However, it is to be noted that there are methodological deficiencies in these earlier studies that either limit the validity of the findings or lead to reservations in arriving at definitive conclusions.

Some interesting observations can be made regarding the single RCT (**Jaswal 2008**) in the light of the established literature. This is the first RCT reported to date and is also from the Indian subcontinent. It compared oral rifampicin with submucosal injection of placentex. This RCT included three groups (I: alkaline nasal douche or control group; II: submucosal placentex injection group; III: oral rifampicin group) with histological, endoscopic and subjective (as per established questionnaire) outcomes measured for a 12-week follow-up period. They described that the group III patients remained asymptomatic until the end of six months after completion of therapy, however this assessment was not based on a validated subjective questionnaire as had been used at the end of the 12-week follow-up period. None of the secondary outcomes were reported subsequent to that 12-week follow-up analysis. The best outcome was seen in group III followed by group II (the average disease-free interval being 2.7 months); while the control group I had the lowest disease cure rate with all the patients having a moderate degree of crusting at the end of 12-week therapy. The authors mention that this control group showed the least consistent result on follow-up with "almost all symptoms" recurring within two weeks of discontinuation of therapy. It is not clear from the loose statement "almost all symptoms" which were the specific symptoms that recurred and what their severity was. Furthermore, it was interesting to note that, with respect to histological criteria only, there was a significant difference in the outcomes of group III versus group I or group II, while no significant difference was seen in outcomes between group II and group I. In terms of endoscopic objective outcomes, the behaviour of these groups was somewhat different. The effectiveness of improving endoscopic signs was significantly increased in patients in group II and group III as compared to group I. However, on the contrary the subjective improvement scores at 12 weeks in comparison with

the 2nd week showed statistically significant improvement in all three groups. Thereafter the sustained improvement was reported only in the subjective outcomes. At this point it is to be stressed again that these improvements in histological and endoscopic criteria along with subjective improvement based on the specific questionnaire were reported only until the end of the 12-week follow-up period. The sustained subjective improvement involving "almost all symptoms" was based more on overall subjective reporting of the patients rather than on the established symptom scoring.

The limitations of this RCT were multifold. Firstly the sample size was small and the follow-up period did not satisfy our inclusion criteria amongst all groups (2.7 months in group II and two weeks in group I, with no long-term consequences). Secondly a loose criteria of subjective improvement was used after the 12-week follow-up period in group III without using a validated symptom scoring. Thirdly the potential for bias was reflected by inadequate sequence generation, inadequate allocation concealment and no blinding being considered in the study. However, despite the above limitations the authors of this RCT should be given credit for importantly comparing the disease prognosis, albeit in the short-term, based on the modalities used. Oral rifampicin showed the most promising results with regards to objective, subjective and histopathological improvement with maximum disease-free interval on regular follow-up, as compared to submucosal placentrex injection.

Apart from the various treatment modalities mentioned in the [Background](#) section many other authors have suggested the use of rifampicin, co-trimoxazole and ciprofloxacin ([Borgstein 1993](#); [Nielsen 1995](#)) in this disease, while the use of sesame oil to combat nasal dryness has been suggested by [Johnsen 2001](#). None of the studies have helped in establishing the ideal management protocol but have suggested a definite role of combating nasal dryness by either using lubricants or reducing evaporation from the mucosal surface. It may be possible that this disease, which has a multifactorial aetiology, may or may not respond to a particular modality of treatment targeting one specific aetiology, thereby resulting in variable responses across studies.

Contrary to the popular belief that extensive surgery results in iatrogenic secondary atrophy, [Fang 1998](#) reported a definite improvement with endoscopic sinus surgery in a subpopulation of atrophic rhinitis, pointing towards its infectious origin.

At our 100-year old university hospital we have been using liquid paraffin-based lubricants for decades without a single incidence of paraffin granuloma being reported. In extremely severe cases with complications we traditionally opt for Young's operation. Antibiotics are considered for a longer duration only in the presence of documented chronic infection. Unfortunately, despite having a rich clinical experience, no RCTs have yet been undertaken at our institute but currently we are pursuing a RCT comparing Young's operation and nasal lubrication ([Mishra 2011](#)).

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from randomised controlled trials to suggest a standard modality of treatment for atrophic rhinitis to be effective in the long term.

Implications for research

There is no evidence from randomised controlled trials concerning the long-term benefits or risks of different treatment modalities for atrophic rhinitis. Further high-quality research into this chronic disease, with a longer follow-up period, is therefore required to conclusively establish the same. The incidence and severity of atrophic rhinitis has shown a decreasing trend in the last few decades as evidenced by the clinical presentation/morbidity compared to earlier reports. Hence it may be possible that the current trends of treatment response may be different to those reported earlier. Considering the difficulties in the practical use of placentrex, along with the cost involved, further studies need to focus upon the more practical/affordable surgical modalities such as Young's operation or alternative, less expensive, medical modalities in clinical testing. Finally, the multifactorial aetiology may suggest that trials of different subsets of atrophic rhinitis should be undertaken, with different modalities of treatment focusing upon the specific aetiology. One randomised controlled trial comparing Young's operation with nasal lubrication for primary atrophic rhinitis is underway ([Mishra 2011](#)).

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES
Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Baroody 2001	ALLOCATION Randomised controlled trial PARTICIPANTS Patients with perennial allergic rhinitis (not atrophic rhinitis)
Borgstein 1993	ALLOCATION Not a true RCT, compared groups were not totally similar and the study had insufficient information available
Fang 1998	ALLOCATION Clinical controlled trial (not a RCT)
Jaswal 2008	ALLOCATION Randomised controlled trial PARTICIPANTS 30 patients with primary atrophic rhinitis INTERVENTIONS Oral rifampicin plus nasal wash versus nasal submucosal placentrex injection plus nasal wash and a control group (nasal wash) OUTCOMES Excluded on the basis of insufficient duration of follow-up. Oral rifampicin showed most promising results regarding objective, subjective and histopathological improvement with maximum disease-free interval on regular follow-up as compared to submucosal placentrex injections, while both performed better than control group.
Johnsen 2001	ALLOCATION Randomised cross-over study PARTICIPANTS

Study	Reason for exclusion
	Non-specific nasal dryness (not atrophic rhinitis)
Kehrl 1998	ALLOCATION Randomised, double-blind study PARTICIPANTS Rhinitis sicca anterior (not atrophic rhinitis)
Klemi 1980	ALLOCATION: Non-randomised double-blind study (patients with allergic rhinitis)
Klossek 2001	ALLOCATION Not randomised
Laliberte 2000	ALLOCATION Not randomised
Mehrotra 2005	ALLOCATION Not randomised
Nemeth 2002	ALLOCATION Not randomised
Nielsen 1995	ALLOCATION: Case series revealing clinical response in 10 patients with ozaena
Schwartz 2007	ALLOCATION Not randomised
Shehata 1996	ALLOCATION A review article with no treatment arm
Stoll 1958	ALLOCATION Possibly a case series of a single agent (inplacen) response in a series of patients. The study is very old, in the German language and incomplete information information is available to conclude exclusion
Stoor 1999	ALLOCATION Not randomised

RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

[Mishra 2011](#)

Trial name or title	Effect of surgical vs. non-surgical management on olfactory status in primary atrophic rhinitis
Methods	Prospective randomised controlled trial
Participants	96 patients with atrophic rhinitis allocated to 2 treatment groups

Interventions for atrophic rhinitis (Review)

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Mishra 2011 (Continued)

Interventions	Medical arm (nasal douche and lubrication) versus surgical arm (Young's operation)
Outcomes	Clinical, microbiological and histopathological outcomes along with olfactory status change
Starting date	June 2009
Contact information	Anupam Mishra, Professor of Otolaryngology, CSMMU, Lucknow, India anupampenn@yahoo.com
Notes	Sponsored by Indian Council of Medical Research (ICMR). Project No. 5/8/10-1(oto)/07-NCD-I

APPENDICES
Appendix 1. Search strategies

CENTRAL	PubMed	EMBASE (Ovid)	CINAHL (EBSCO)	CAB Abstracts (Ovid)
#1 MeSH descriptor Rhinitis, Atrophic explode all trees	#1 "Rhinitis, Atrophic" [Mesh] OR ozena* OR ozaena	1 exp atrophic rhinitis/	S1 (MH "Rhinitis, Atrophic")	1 exp atrophic rhinitis/
#2 ozena* OR ozaena*		2 (ozena* or ozaena*).tw.	S2 ozena* OR ozaena*	2 (ozena* or ozaena*).tw.
#3 (#1 OR #2)	#2 ("Rhinitis" [Mesh] OR "nose" [Mesh] OR rhinit* OR nose [ti] OR nasal [ti])	3 1 or 2	S3 S1 or S2	3 1 or 2
#4 MeSH descriptor Rhinitis explode all trees	AND ("atrophy" [Mesh] OR atroph* OR crust* OR fetor OR foetor OR foul OR halitosis OR maggot* OR miasis OR myiasis)	4 exp *rhinitis/	S4 (MH "Rhinitis+")	4 exp *rhinitis/
#5 MeSH descriptor Nose explode all trees		5 exp *nose/	S5 (MH "Nose+")	5 exp *nose/
#6 (rhinit*:ti OR nose:ti OR nasal:ti)	#3 #1 OR #2	6 (rhinit* or nose or nasal).ti.	S6 rhinit* OR nose OR nasal	6 (rhinit* or nose or nasal).ti.
#7 (#4 OR #5 OR #6)		7 4 or 5 or 6	S7 S4 or S5 or S6	7 4 or 5 or 6
#8 MeSH descriptor Atrophy explode all trees		8 exp atrophy/	S8 (MH "Atrophy+")	8 exp atrophy/
#9 (atroph* OR crust* OR fetor OR foetor OR foul OR halitosis OR maggot* OR miasis OR myiasis)		9 (atroph* or crust* or fetor or foetor or foul or halitosis or maggot* or miasis or myiasis).tw.	S9 atroph* OR crust* OR fetor OR foetor OR foul OR halitosis OR maggot* OR miasis OR myiasis	9 (atroph* or crust* or fetor or foetor or foul or halitosis or maggot* or miasis or myiasis).tw.
#10 (#8 OR #9)		10 8 or 9	S10 S8 or S9	10 8 or 9
#11 (#7 AND #10)		11 7 and 10	S11 S7 and S10	11 7 and 10
#12 (#3 OR #11)		12 3 or 11	S12 S3 OR S11	12 3 or 11
Cochrane ENT Disorders Group Trials Register (ProCite database)	Web of Science/BIOSIS Previews (Web of Knowledge)	LILACS	ICTRP	

(Continued)

(ozena* OR ozaena* OR atroph* OR crust* OR fetor OR foetor OR foul OR halitosis OR maggot* OR miasis OR myiasis)	#1 TI=(rhinit* OR nose OR nasal) #2 TS=(atroph* OR crust* OR fetor OR foetor OR foul OR halitosis OR maggot* OR miasis OR myiasis) #3 TS=(ozena* OR ozaena*) #4 #2 AND #1 #5 #4 OR #3	(rhin\$ or nose or nasal) and (atroph\$ or crust\$ or fetor or foetor or foul or halitosis or maggot\$ or miasis or myiasis or ozena\$ or ozaena\$)	ozena OR ozaena OR rhinitis AND atroph* OR rhinitis AND crust*
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CONTRIBUTIONS OF AUTHORS

All the authors searched the studies independently and reviewed those that were short-listed while the write-up was primarily prepared by the principal author in full consensus with the other two co-authors.

Anupam Mishra: lead author, study selection, data extraction, risk of bias assessment, data analysis, drafting the review.

Rahul Kawatra: study selection, data extraction, risk of bias assessment, data analysis, checking the draft.

Manoj Gola: study selection, data extraction, risk of bias assessment, data analysis, checking the draft.

DECLARATIONS OF INTEREST

None known.

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol was duly followed with no deviation.

INDEX TERMS

Medical Subject Headings (MeSH)

Rhinitis, Atrophic [*therapy]

MeSH check words

Humans