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Bronchial thermoplasty for moderate or severe persistent asthma in adults (Protocol)

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[Intervention Protocol]

Bronchial thermoplasty for moderate or severe persistent asthma in adults

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the efficacy and safety of bronchial thermoplasty in adult patients with bronchial asthma, in terms of improvement of symptoms, quality of life and functional parameters, as well as the reduction in the use of conventional medication, the severity of exacerbations in this population and incidence of side effects.

BACKGROUND

Description of the condition

Bronchial smooth muscle plays a central role in bronchial obstruction in patients with asthma. In fact, the first treatment step in such patients, and particularly when they are symptomatic, is the use of bronchodilators (beta$_2$-adrenergic agonists) to relax bronchial smooth muscle (GINA 2007). Over the past 20 years, there have been significant advances in the understanding of the pathophysiology of bronchial smooth muscle, as well as in the development of treatments such as inhaled corticosteroids and long-acting bronchodilators. Both treatments have short term effects, requiring daily maintenance doses. The application of these advances, in combination with adherence to diagnostic and treatment guidelines, has had a positive impact on morbidity, mortality and quality of life in people with asthma (Rodriguez-Trigo 2008).

Despite these efforts, however, even in compliant patients asthma remains a poorly controlled disease in a small but important minority of patients, and as such, is still a common reason for emergency room visits. Furthermore, between three and six per cent of patients with asthma respond poorly to treatment (Torrego 2010), including oral corticosteroid therapy, and continue to experience symptoms and a diminished quality of life. The care for patients with more severe disease is a major public health burden, which makes it clear that new treatments are required to improve the prognosis of this group of patients (Moore 2006).

Description of the intervention

Bronchial thermoplasty is an innovative procedure that consists of the delivery of controlled radiofrequency-generated heat via a catheter inserted in the bronchial tree through a flexible bronchoscope. Once the bronchoscope has been placed in the airway, the catheter is advanced to a bronchial segment and expanded so that it is in contact with bronchial mucosa (Mayse 2007). Then radiofrequency energy is applied through the catheter, across the contact points. Treatments are applied consecutively so that the entire bronchopulmonary segment is treated. Three separate bronchoscopic treatment sessions are required to treat all of the airways (except for the right middle lobe).

How the intervention might work

The mechanism of action of bronchial thermoplasty is not definitively established, but experimental evidence in animal models (Brown 2005; Danek 2004) suggests that it might work by reducing airway smooth muscle, thereby reducing the ability of the smooth muscle to bronchoconstrict.

As a consequence of this mechanism of action, this treatment could then reduce asthma symptoms and exacerbations, resulting in improved asthma control and quality of life.

Why it is important to do this review

Although several recent reviews have discussed the efficacy of bronchial thermoplasty (Cayetano 2011; Wahidi 2012), this review will provide a rigorous summary of the available evidence regarding the efficacy of this intervention, focusing on its trade-off between relevant patient outcomes and safety, in the short and long term (Thomson 2011).

OBJECTIVES

To determine the efficacy and safety of bronchial thermoplasty in adult patients with bronchial asthma, in terms of improvement of symptoms, quality of life and functional parameters, as well as the reduction in the use of conventional medication, the severity of exacerbations in this population and incidence of side effects.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled clinical trials that compare bronchial thermoplasty versus conventional treatment, with or without the use of a placebo, as treatment for adult patients with moderate or severe persistent asthma.

Types of participants

We will include adult patients with moderate or severe persistent asthma according to the Global Initiative for Asthma (GINA) criteria (GINA 2007).

Types of interventions

We will include trials assessing bronchoscopically-delivered thermoplasty adjuvant to conventional treatment for patients with moderate to severe persistent asthma.

Elegible trials will include a control group of patients with moderate to severe persistent asthma, receiving only conventional treatment, or with the addition of a sham bronchoscopy.

Types of outcome measures

Primary outcomes

1. Health-related quality of life (HRQOL) evaluated through asthma-specific or generic questionnaires.
   a. Asthma-specific: Asthma Quality of Life Questionnaire (AQLQ); considering a change in the score of 0.5 points the threshold of clinical relevance (Juniper 1994).
   b. Asthma-specific: St. George's Respiratory Questionnaire; considering a change in the score of 4 points the threshold of clinical relevance (Jones 2002).
   c. Generic: SF-36 questionnaire on health status; Nottingham Health Profile (NHP); World Health Organization's (WHO's) instrument on health-related quality of life (WHOQOL-100).
2. Number of exacerbations, defined as any of the following.
   a. Exacerbations requiring hospital or intensive care unit admissions.
   b. Exacerbations requiring emergency departments visits or unscheduled health care visits.
   c. Exacerbations resulting in the use of a course of oral or systemic corticosteroids, or an increase in the regular required doses.
3. Serious adverse events, defined as any of the following.
   a. Fatal events.
   b. Hospital admission.
   c. Risk of death at the time of event.
   d. A permanent or significant disability.

Secondary outcomes

1. Respiratory function tests:
   a. bronchial hyperactivity evaluated through non-specific (direct muscle contraction) bronchial stimulation tests;
   b. peak expiratory flow (PEF); and
   c. forced expiratory flow during the first second (FEV_1).
2. Doses of regular medication for asthma control with inhaled corticosteroids +/- long-acting $beta_2$-agonist, according to recommendations in international guidelines (GINA 2009).
3. Use of rescue medication with:
   a. the addition of a short-acting $beta_2$-agonist to the combination of long-acting $beta_2$-agonist and inhaled corticosteroids; or
   b. the use of a combined budesonide plus formoterol.

4. Asthma symptom-free days.

5. Lost days from work or school.

Search methods for identification of studies

Electronic searches

We will identify trials from the Cochrane Airways Group's Specialised Register of Trials (CAGR), which is derived from systematic searches of bibliographic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We will search all records in the CAGR coded as asthma, using the following terms:

thermoplast or bronchoscop* or ((surger* or surgical) and bronchi*) or thermal* or catheter or Alair or Asthmatx*

We will also conduct a search of ClinicalTrials.gov. We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will contact authors of identified trials and ask them to identify other published and unpublished studies. We will also contact manufacturers and experts in the field.

Data collection and analysis

Selection of studies

Two independent evaluators (JJYN and AT) will screen the titles and abstracts identified through the electronic searches to identify the studies to include in the review. We will discuss any disagreements and consult with a third reviewer (VP or IS). If additional information or any clarification are needed from any article, we will contact the trial authors.

Data extraction and management

Two independent evaluators (JJYN and AT) will read all reports in detail and will summarise the pertinent details in a standard data extraction sheet (which will include the kind of study; methodology; number and description of participants; type, drug doses, and duration of intervention; type, timing, and method of outcome measurement; as well as evaluation of methodology). We will discuss disagreements and reach agreement by consensus with a third reviewer (VP or IS).

Assessment of risk of bias in included studies

Two review authors (IS and MR) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion, or by involving a third assessor. We will assess risk of bias according to the following domains.

Sequence generation (selection bias): For each included study, we will describe in detail the methodology used to generate the allocation sequence and we will evaluate the methodology to determine if it can produce comparable groups. We will assess sequence generation as: low risk of bias (any truly random process, e.g. random number table, computer random number generator); high risk of bias (any non-random process, e.g. odd or even date of birth, hospital or clinic record number); or unclear risk of bias.

Allocation concealment (selection bias): For each included study, we will describe in detail the methodology used to conceal the allocation sequence and we will evaluate the methodology to determine whether intervention allocation could have been foreseen in advance, during recruitment, or changed after assignment. We will evaluate allocation concealment as: low risk of bias (e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes); high risk of bias (open random allocation, unsealed or non-opaque envelopes, alternation, date of birth); or unclear risk of bias.

Blinding (performance bias): For each included study, we will describe the methodology used, if any, to blind study participants and personnel from knowing the intervention that a participant received. We will also provide information on whether the intended blinding was effective. Where blinding is not possible, we will assess whether the lack of blinding was likely to have introduced bias. We will assess blinding separately for different outcomes or classes of outcomes. We will evaluate blinding as: low risk of bias, high risk of bias, or unclear risk of bias for participants; and low risk of bias, high risk of bias, or unclear risk of bias for outcome evaluators.

Incomplete outcome data (attrition bias through withdrawals, dropouts, or protocol deviations): For each included study and for each outcome or class of outcomes, we will include a description of the completeness of data, including attrition and exclusions from the analysis, as well as an assessment of the reasons of attrition or data exclusion (if available). We will record the number of attrition and exclusions, as well as the number of patients included in the analysis at each stage (compared with the total randomised participants).

Selective outcome reporting: We will assess selective outcome reporting for each included study. We will evaluate selective outcome reporting as: low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported); high risk of bias (where not all of the study's prespecified outcomes have been reported, one or more reported primary outcome(s) were not prespecified, outcomes of interest are reported incompletely and so cannot be

used, study fails to include results of a key outcome that would have been expected to have been reported); or unclear risk of bias.

Overall risk of bias: We will classify all studies according to the following criteria: low risk of bias (all individual items were at "low risk of bias"); moderate risk of bias (one or more individual item(s) was at "unclear risk of bias" while the remaining were at "low risk of bias"); or high risk of bias (one or more individual item(s) was at "high risk of bias").

Measures of treatment effect

We will assess treatment effect through mean differences (MDs) or standardised mean differences (SMDs) for continuous outcomes, and risk ratios (RRs) for dichotomous outcomes. We will present all measures with 95% confidence intervals (CIs). We will run all statistical analyses with Review manager 5.1 (RevMan 2011).

Unit of analysis issues

The unit of analysis will be the patient, i.e. for dichotomous outcomes such as exacerbations, we will use the number of patients experiencing one or more event(s) to avoid double counting of patients who exacerbate frequently.

Dealing with missing data

The main analysis will be an available data analysis in each of the papers. If a paper presents both intention-to-treat and per protocol data, we will use the former in the analyses.

Assessment of heterogeneity

We will assess clinical heterogeneity by examining the trials in terms of patient characteristics, interventions, controls and definition of results. We will then evaluate statistical heterogeneity through the I^2 statistic. We will use a cut-off point of $I^2 > 50\%$ to indicate relevant statistical heterogeneity. We will determine causes of heterogeneity through sensitivity analyses and analysis of subgroups.

Assessment of reporting biases

We will explore publication bias by means of a funnel plot (Egger test; Egger 1997), if ten or more studies are available (Higgins 2011).

Data synthesis

We will perform meta-analyses using a random-effects model and using the inverse variance method. We will present forest plots for each result where we are able to extract data.

Subgroup analysis and investigation of heterogeneity

We will carry out a subgroup analysis according to the severity of the participants, classified as having severe asthma versus moderate asthma. We will use the classification reported in the included trials, and when possible, we will try to classify severity on the basis of the intensity of treatment required to achieve good asthma control (GINA 2011; Taylor 2008).

Sensitivity analysis

We will carry out sensitivity analyses to determine the effect of the following parameters on the treatment effect estimates.

- Risk of bias: including only low risk of bias studies.
- Meta-analysis model: applying a fixed-effect model compared to a random-effects model.

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APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group's Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
CENTRAL (The Cochrane Library)	Quarterly (4 issues per year)
psycINFO (Ovid)	Monthly
CINAHL (Ebsco)	Monthly
AMED (Ebsco)	Monthly

Hand-searches: Core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE Search strategy used to identify trials for the CAGR

Condition search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.

8. (bronch$ adj3 spasm$).mp.

9. bronchoconstrict$.mp.

10. exp Bronchoconstriction/

11. (bronch$ adj3 constrict$).mp.

12. Bronchial Hyperreactivity/

13. Respiratory Hypersensitivity/

14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.

15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.

16. or/1-15

17. exp Aspergillosis, Allergic Bronchopulmonary/

18. lung diseases, fungal/

19. aspergillosis/

20. 18 and 19

21. (bronchopulmonar$ adj3 aspergillosis).mp.

22. 17 or 20 or 21

23. 16 or 22

24. Lung Diseases, Obstructive/

25. exp Pulmonary Disease, Chronic Obstructive/

26. emphysema$.mp.

27. (chronic$ adj3 bronchiti$).mp.

28. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

29. COPD.mp.

30. COAD.mp.

31. COBD.mp.

32. AECB.mp.

33. or/24-32

34. exp Bronchiectasis/

35. bronchiect$.mp.

36. bronchoect$.mp.

37. kartagener$.mp.

38. (ciliary adj3 dyskinesia).mp.

39. (bronchial$ adj3 dilat$).mp.

40. or/34-39

41. exp Sleep Apnea Syndromes/

42. (sleep$ adj3 (apnea$ or apnoea$)).mp.

43. (hypopnea$ or hypopnoea$).mp.

44. OSA.mp.

45. SHS.mp.

46. OSAHS.mp.

47. or/41-46

48. Lung Diseases, Interstitial/

49. Pulmonary Fibrosis/

50. Sarcoidosis, Pulmonary/

51. (interstitial$ adj3 (lung$ or disease$ or pneumon$)).mp.

52. ((pulmonary$ or lung$ or alveoli$) adj3 (fibros$ or fibrot$)).mp.

53. ((pulmonary$ or lung$) adj3 (sarcoid$ or granulom$)).mp.

54. or/48-53

55. 23 or 33 or 40 or 47 or 54

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

CONTRIBUTIONS OF AUTHORS

All of the authors have contributed to the conception, development and drafting of this protocol.

DECLARATIONS OF INTEREST

None.

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