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Inspiratory muscle training and exercise versus exercise alone for asthma (Protocol)

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[Intervention Protocol]

Inspiratory muscle training and exercise versus exercise alone for asthma

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness of inspiratory muscle training plus exercise versus exercise alone in people with asthma.

BACKGROUND

Description of the condition

An estimated 300 million people are affected by asthma worldwide and the prevalence ranges from 1% to 18% of the population depending on the country (GINA 2014). Asthma is a chronic inflammatory respiratory disease characterised by airway hyperresponsiveness causing a reduction of airways' diameter due to smooth muscle contraction and inflammation, resulting in airflow limitation and increased inspiratory muscle work. Asthma leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing (Ramnath 2007). These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that resolves either spontaneously or with treatment (GINA 2014). Acute asthma events cause participants to attend the emergency room or hospital with a consequent increase in healthcare cost of the disease. Asthma is a major cause of absence from work in many countries (Masoli 2004). A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough and chest tightness (GINA 2014)

The treatment of asthma consists of both pharmacological and non-pharmacological therapy. Current pharmacological therapy includes bronchodilators and anti-inflammatory agents. Personalised action plans help individuals prevent acute asthma episodes and carry out activities of daily living and work, and consequently improve health-related quality of life (HRQoL) (GINA 2014). Non-pharmacological therapy consists of asthma self-management education and respiratory physiotherapy, including whole-body exercise training, inspiratory muscle training (IMT) and breathing retraining techniques (Bruurs 2013).

Evidence of the effectiveness of exercise training to improve exer-

cise capacity and break the vicious cycle of dyspnoea, sedentarism and impaired exercise capacity encountered in asthma is emerging (Bruurs 2013; Eijkemans 2012; Mendes 2010; Wanrooij 2013). However there is debate regarding the role of inspiratory muscle training in this population. A previous Cochrane systematic review demonstrated there was no conclusive evidence to support or refute inspiratory muscle training for asthma (Silva 2013). However inspiratory muscle strength in combination with whole-body exercise training may improve exercise capacity and reduce the risk for exacerbations more than exercise training or IMT implemented in isolation.

Description of the intervention

In some parts of the world, IMT and exercise training are commonly used in people with asthma in addition to pharmacological treatment. IMT and ET can be implemented alone or in combination.

IMT comprises inhaling against an external resistive device to produce increments in muscle strength and endurance. The aim of IMT is to improve tolerance to the increased workload that occurs during asthma attacks and exercise efforts (Silva 2013; Turner 2011; Weiner 2000). The resistive device is typically adjusted with a range of resistance from 15% to 80% of maximal inspiratory pressure (MIP, PImax) measurement. IMT is often prescribed twice a day, five times per week for a duration which can vary from weeks to months (Silva 2013; Turner 2011; Weiner 2002).

Exercise training constitutes an evidence-based treatment for people with chronic obstructive lung conditions. The exercise training programmes are individually designed for each patient according to their exercise capacity, determined via clinical exercise tests such as the incremental shuttle walk test, six-minute walk test (6MWT) or maximal inspiratory pressure test (to assess respiratory muscle capacity). Training intensities can range from low- to high-intensity loads; however structured, individualised exercise programmes using moderate- to high-intensity aerobic and strength exercises have been shown to improve exercise capacity in people with asthma (Bruurs 2013; Carson 2013). Exercise programmes can be implemented in the hospital or outpatient setting, with a frequency of twice to three times per week. These programmes are generally conducted for a group of participants under the supervision of a physiotherapist. Recently, community-based programmes have been implemented in sport centres or at participants' homes. The training programmes could be directly supervised by a health-care professional; or indirectly supervised, by making use of a diary where participants collect data concerning the exercise programme. The duration of programmes can range from short (6 weeks) to longer programmes (20 months) at a frequency of one to seven session-days per week.

How the intervention might work

In asthma, lung hyperinflation is a common consequence after asthma attacks (Burgel 2009). With the increase in lung volume, the chest wall geometry is modified, shortening the inspiratory muscles and leaving them at a sub-optimal position in the length-tension relationship (Clanton 2009). The reduction of strength generated by the inspiratory muscles produces an increase in respiratory drive (McConell 2005). The resistance imposed during inspiratory muscle training has an effect on the recruitment of muscle units during every inspiration conducted against the load. In people with chronic obstructive pulmonary disease (COPD), this type of training induces redistribution of muscle fibre type, with an increment of fibre type I with respect to type II fibres, and increments in cross-sectional area of the muscle fibre and number of capillaries per fibre (Ramirez-Sarmiento 2002). Furthermore, in respiratory patients the increase of the maximal inspiratory pressure (PImax) resulting from the IMT may significantly reduce the inspiratory motor drive (Huang 2003), with consequent reduction in the sensation of dyspnoea. Those changes lead to improvements in strength, endurance and oxidative capacity of the respiratory muscles (Levine 2003; Levine 1997; Orozco-Levi 1999).

Young, and adolescent, people with asthma present with lower aerobic capacity and monitored aerobic capacity compared with healthy controls (Lochte 2008). However, some studies observed a preserved limb muscle force and modestly impaired inspiratory muscle strength related to a slightly increased thickness of the diaphragm (de Bruin 1997). Furthermore, in people with persistent asthma, an inspiratory muscle adaptation was observed because of the overload effect on these muscles that must work against an increased respiratory resistance (Diaz Ledo 2010). However, there is some evidence pointing to a reduction in muscle function in people with asthma (Perez 1996). People with asthma have a increased thickness of the diaphragm compared to people without asthma (de Bruin 1997). These differences may indicate different mechanisms responsible for respiratory muscle dysfunction in people with asthma in comparison to COPD. However, there is a lack of knowledge about the respiratory muscle structure in people with asthma.

In the case of COPD, exercise training has a direct effect on cardiovascular and peripheral muscle adaptations to exercise by improving oxygen transport and muscle oxidative capacity (Nici 2006). The latter is related to changes in the peripheral muscle structure, namely improvements in fibre type redistribution, mitochondrial density, number of capillaries and activity of oxidative enzymes (Whittom 1998). These changes may result in a reduced respiratory stimulus and ventilatory demand for a certain workload, contributing to a more efficient breathing pattern and reduced perception of dyspnoea by people with asthma and COPD (O'Donnell 1998; Wanrooij 2013). Exercise training has a positive impact on exercise capacity and health-related quality of life in people with asthma (Carson 2013). Recently a meta-analysis, including 17 studies, confirms that exercise training produces a reduction in

bronchial hyperresponsiveness and exercise-induced bronchoconstriction in addition to an increase of exercise capacity, quality of life and pulmonary function (Eichenberger 2013). For all these positive effects, exercise training must be implemented in standard asthma treatment. IMT and exercise training in combination could improve beneficial physiologic effects.

Why it is important to do this review

The role of IMT in asthma management is a matter of some debate, although it is frequently used in clinical practice in some parts of the world despite inconclusive evidence (Silva 2013). The benefit that IMT may add to exercise training in this population is even less clear. This systematic review will help to better understand the additional value of IMT when added to exercise training in people with asthma to provide further recommendations for its application in clinical practice.

OBJECTIVES

To assess the effectiveness of inspiratory muscle training plus exercise versus exercise alone in people with asthma.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will include studies reported as full-text, those published as abstract only, and unpublished data. We will exclude studies that present healthy subjects as a control group.

Types of participants

We will include both adults and children with a diagnosis of asthma (any severity). We will exclude participants with the following comorbidities/characteristics:

1. Other chronic respiratory disease.
2. Other disease that may produce any ventilatory limitation or respiratory muscle dysfunction.

Types of interventions

We will include trials comparing inspiratory muscle training combined with exercise training with exercise training alone. We will use the following comparisons:

1. IMT and exercise training versus exercise training alone.
2. IMT and exercise training versus sham IMT and exercise training.

We will exclude trials that consider:

1. Other type of exercise intervention such us Tai Chi, Yoga, etc. not related to aerobic training.
2. Short-term interventions (interventions shorter than 1 week).

Types of outcome measures

Primary outcomes

1. Exercise capacity: 6MWT distance or maximal exercise capacity or endurance time or combinations thereof.
2. Maximal inspiratory pressure (PImax).
3. Exacerbation/asthma attacks (number and days to clinical resolution).
4. Health-Related Quality of Life: Asthma Quality of Life Questionnaire (AQLQ), Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ).

Secondary outcomes

1. Use of rescue medication (type and dose).
2. Asthma control and severity: Asthma Control Questionnaire (ACQ).
3. Lung function: PEF, FEV_1, FVC, MVV.
4. Adverse events/side effects.

Search methods for identification of studies

Electronic searches

We will identify trials from the Cochrane Airways Group's Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through 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 using the search strategy in Appendix 2. We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). 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 search relevant manufacturers' websites for trial information.

We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two teams of review authors (EGS and JV, GF and RTC) will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publication and two review authors (EGS and JV, GF and RTC) will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (RR). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review.

Two review authors (EGS, RTC, JV and GF) will independently extract the following study characteristics from included studies.

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (EGS, RTC, JV and GF) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. Disagreements will be resolved by consensus or by involving a third person (RR). One review author (RTC) will transfer data into the Review Manager 5 (RevMan 2014) file; and data will be double-checked against the original study reports. A second review author (EGS) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (EGS and JV) 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 disagreements by discussion or by involving another author (RR). We will assess the risk of bias according to the following domains:

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarise the risk of bias judgments across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios and continuous data as mean difference or standardised mean difference. We will enter data presented as a scale with a consistent direction of effect. We will only undertake meta-analyses where this is meaningful (i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense).

We will narratively describe skewed data reported as medians and interquartile ranges.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

Unit of analysis issues

The unit of analysis will be the individual.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis**.**

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity we will report it and explore possible causes by pre-specified subgroup analysis. The possible sources of heterogeneity could be caused by different study lengths, training regimes and asthma severities, among others.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study and publication biases.

Data synthesis

Because of the probable heterogeneity of the trials, we will perform a random-effects meta-analysis and use fixed effect as a sensitivity analysis. If meta-analysis is not possible because of paucity of data or reasons militating against pooling (clinical or statistical), we will provide a narrative synthesis of the available data.

Summary of findings table

We will create a 'Summary of findings' table using the following outcomes: exacerbation/asthma attacks, health-related quality of life, use of rescue medication, asthma control and severity, and other adverse events. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software. We will justify all decisions to downgrade or upgrade the quality of studies using footnotes and we will make comments to aid readers' understanding of the review, where necessary.

Subgroup analysis and investigation of heterogeneity

If adequate data exists from included studies (Higgins 2011), we plan to run separate analyses to explore differences between the following subgroups:

1. Different age group (younger than 18 years versus 18 years and older).
2. Exercise intensity (low versus high intensity).
3. Duration of exercise intervention (less than eight weeks versus eight weeks or more).

We will use the formal test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We will perform a sensitivity analysis to investigate the effect of trial quality ('high' risk of bias on any item versus no 'high' risk on any item) on review findings.

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Christian Osadnik was the Editor for this protocol and commented critically on the protocol.

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* *Indicates the major publication for the study*

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*The Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly

(*Continued*)

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

Asthma 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

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.

Appendix 2. Search strategy for Cochrane Airways Group Register

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 ((inspiratory* or ventilat* or respiratory*) and (muscle*) and (strength* or train* or endur*))
#6 IMT or RMT
#7 resist* NEAR (train* or breath*)
#8 threshold* NEAR (load* or device*)
#9 MeSH DESCRIPTOR Breathing Exercises
#10 MeSH DESCRIPTOR Respiratory Muscles
#11 #5 or #6 or #7 or #8 or #9 or #10
#12 #4 and #11

[Note: in search line #1, MISC1 denotes the field in the record where the reference has been coded for condition, in this case, asthma)

CONTRIBUTIONS OF AUTHORS

Elena Gimeno-Santos and Jordi Vilaró wrote the first draft of the protocol. Guilherme AF Fregonezi, Rodrigo Torres-Castro and Roberto Rabinovich performed a critical revision of the protocol for important intellectual content. All authors agreed on the content of the protocol.

DECLARATIONS OF INTEREST

There are no known conflicts of interest.

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External sources

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