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Bronchial Thermoplasty in Severe Asthma

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Asthma is a major public health problem currently affecting 25.9 million adults in the USA [1] and approximately 300 million people in the world [2]. The number of disability adjusted life years currently lost due to asthma worldwide has been estimated to be about 15 million per year (similar to diabetes, cirrhosis of the liver, and schizophrenia). In 2008, asthma accounted for an estimated 14.2 million days of lost work in adults. The annual direct health care cost of asthma is approximately 50.1 billion dollars. Indirect costs (e.g. lost productivity) add another $5.9 billion for a total of $56.0 billion dollars [1].

The pathophysiology of asthma is complex and involves airway inflammation, intermittent airflow obstruction, and bronchial hyper responsiveness. The mechanism of inflammation in asthma may be acute, subacute, or chronic. The presence of airway edema and mucus secretion also contributes to airflow obstruction and bronchial reactivity. This is associated with varying degrees of mononuclear cell and eosinophil infiltration, mucus hypersecretion, desquamation of the epithelium, smooth muscle hyperplasia, and airway remodeling.

Most patients with intermittent, mild, moderate, or severe persistent asthma are managed with inhaled bronchodilators and inhaled or systemic anti-inflammatory medications in varying doses and combinations. Bronchial thermoplasty is an investigational and innovative procedure designed to reduce airway smooth muscle in severe persistent asthma with the intent to decrease bronchoconstriction and therefore, the frequency and severity of asthma symptoms [3,4]. It was approved by the Food and Drug administration in 2010 as a treatment for severe asthma [5].

Bronchial thermoplasty involves delivery of tightly controlled, therapeutic radiofrequency electrical energy to the airway wall by a special catheter electrode. This precisely controlled thermal energy heats the airway wall to a specific target temperature to reduce excessive airway smooth muscle. Reducing airway smooth muscle decreases the ability of the airways to constrict, thereby reducing the frequency of asthma attacks.

Procedure

Bronchial thermoplasty is performed during bronchoscopy under moderate anesthesia (conscious sedation). The only commercially available equipment is the Alair Bronchial Thermoplasty system, which consists of a radiofrequency controller and the catheter [5]. The catheter is a long, flexible device with an expandable array attached at one end. The catheter is passed through the working channel of a standard bronchoscope under direct visualization and expanded to contact the airway walls to deliver the radiofrequency energy when activated. This electric energy when passed from the electrode to the tissue is converted to thermal energy, thus reducing the airway smooth muscle. Smaller bronchi (3-10 mm diameter) distal to main stem bronchi are treated with thermoplasty under bronchoscopic visualization. The controller delivers the correct intensity and duration of energy. This usually consists of a series of temperature controlled bursts of radio frequency energy, each lasting 10-seconds.

Diffuse airway edema is a potential hazard if the entire tracheobronchial tree is treated at one session. Therefore it is advised that the procedure be performed in three separate sessions. Each session is spaced 3 weeks apart to minimize the risk of inducing an asthma exacerbation. The right lower lobe is usually treated during the first bronchoscopy followed by the left lower lobe during the second session. The right upper lobe and left upper lobe are treated during the third and final session. The right middle lobe is not treated because the bronchus leading to it is relatively long and narrow, raising concern about stenosis and a possible right middle lobe syndrome. Contiguous and non-overlapping areas are treated, moving the catheter from distal to proximal locations along the airway. During the second and third sessions, the previously treated areas are first visualized. New areas are treated only if the previous areas are well healed. If not, bronchoscopy should be postponed to a later date.

Patient selection is usually based on inclusion criteria that were used in prior trials of bronchial thermoplasty [6]. These include:

1) Documented diagnosis of asthma, i.e documented FEV1 reversibility or airway responsiveness by methacholine challenge testing

2) Nonsmoker or if ex-smoker (quit >1 year and less than 10 pack year history)

3) Symptomatic despite treatment with maintenance therapy (Inhaled corticosteroids >1,000 μg/day beclomethasone or equivalent) and a long-acting β2-agonist (LABA ≥ 100 μg/day salmeterol or equivalent), leukotriene modifiers, omalizumab (if used for at least 1 year prior), and/or oral corticosteroids <10 mg/day.

4) Stable asthma status (i.e. no severe exacerbation in last 4 weeks, FEV1 within 10% of personal best and no current respiratory tract infection).

5) No internal pacemaker or neurostimulator

6) No known unstable comorbid conditions that would preclude bronchoscopy

The early clinical studies have demonstrated that bronchial thermoplasty may be a promising intervention in the management of severe asthma. In 2004, Danek et al. found that thermoplasty at 65°C or 75°C (149°F or 167°F) attenuated the airway's response to methacholine in nonasthmatic dogs up to 3 years after treatment [7]. As early as 1 week after treatment, airway smooth muscle was seen to

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be degenerating or absent, and the effect was inversely proportional to airway responsiveness.

In 2006, Cox et al. performed the first study of bronchial thermoplasty in patients with mild to moderate asthma [8]. This was a prospective observational study in 16 patients with an average age of 30 years (range 24-58). The FEV1 in the intervention group was higher at 12 weeks and at 1 year after thermoplasty than at baseline but was not significantly different from baseline at 2 years. The symptom-free days increased from 50% to 73% at 12 weeks (p=0.015) after bronchial thermoplasty. In addition, airway hyper responsiveness decreased significantly, and the effect persisted over 2 years.

The AIR (Asthma Intervention Research) trial, A randomized trial in moderate to severe persistent asthma, was the first large unblinded, prospective, randomized multicenter trial to evaluate the efficacy of bronchial thermoplasty [9]. This study included 112 patients who had been treated with inhaled corticosteroids and LABA and in whom asthma control was impaired when the LABA were withdrawn. These 112 subjects were randomly assigned to either bronchial thermoplasty or a control group. The number of mild (but not severe) exacerbations per week was significantly lower at 3 and 12 months in the thermoplasty group compared to control group (p=0.005). Rescue medication use was also significantly less at 3 and 12 months. At 12 months, there were significantly greater improvements in the morning peak expiratory flow, percentage of symptom-free day's symptom scores, Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Questionnaire (ACQ) scores compared to control. This trial found that thermoplasty improved asthma symptoms in moderate to severe persistent asthma within 3 months and the effect lasted 1 year.

Adverse events (dyspnea, wheezing, cough, and chest discomfort) immediately after treatment were more common in the bronchial-thermoplasty group than in the control group but were similar during the period from 6 weeks to 12 months after treatment.

The RISA (Research in Severe Asthma) trial was conducted to examine the safety and efficacy of bronchial thermoplasty in symptomatic severe asthma [10]. The RISA trial included patients who were on high doses of an inhaled corticosteroid (>750 μg of fluticasone or its equivalent per day), a long-acting beta(2)-agonist, and/or prednisone (≤ 30 mg/day). Thirty-four patients were randomized to undergo bronchial thermoplasty, or to receive medical treatment. This trial showed that patients with severe persistent asthma had significant improvement in clinical measures of asthma (use of rescue inhaler, AQLQ and ACQ scores) even at 1 year compared to the control group. Serious adverse events (transient worsening of asthma symptoms, hospitalizations during the treatment period and segmental collapse of the most recently treated lobe) occurred more often in patients in the treatment group than in the control group, but 1 year after the procedure the adverse-event rates were similar.

AIR 2 trial was a double-blind study in which the control group underwent sham thermoplasty [6]. This intention to treat study was conducted to evaluate the effectiveness and safety of bronchial thermoplasty versus a sham procedure in subjects with severe asthma who remain symptomatic despite treatment with high-dose inhaled corticosteroids and long-acting beta (2)-agonists. A total of 288 adult subjects (196 patients in the thermoplasty group and 101 in the sham treatment group) were well matched, and more than 80% in each group met the American Thoracic Society criteria for severe refractory asthma. The thermoplasty group had significantly higher AQLQ scores at 6, 9, and 12 months than at baseline and the sham treatment group. The thermoplasty group also had significantly fewer severe exacerbations in the post-treatment period (>6 weeks after treatment) compared with the sham treatment group (0.48 vs. 0.70 exacerbations per patient per year). Six percent more bronchial thermoplasty subjects were hospitalized in the treatment period (up to 6 week after thermoplasty), but in the posttreatment period (6-52 week after thermoplasty), the intervention group experienced fewer severe exacerbations, emergency department visits, and days missed from work/school compared with the sham group. A 2011 follow up phase of the Asthma Intervention Research 2 trial showed persistence of effectiveness of bronchial thermoplasty in patients with severe asthma even at 2 years [11].

In summary, clinical trials showed that bronchial thermoplasty was relatively safe, and produced better clinical outcomes in patients with severe asthma when medical therapies did not control their symptoms. Patient selection is very important. In addition, patients need to be observed and monitored closely during and after the treatment period, as airway complications and asthma exacerbations can occur up to 6 weeks after the procedure. About 80% of all study patients had multiple symptoms of asthma and other symptoms in the treatment period.

The most frequent side effects of bronchial thermoplasty were symptoms of airway irritation such as cough, dyspnea, wheezing, and bronchospasm. The mean time to onset was less than 1.7 days, and the mean time to resolution was 4.6 days [8].

In conclusion, as experience with the procedure increases, we will be better able to characterize which patients may benefit from it. In addition, the knowledge gained by the longer-term study of airway smooth muscle function alterations will potentially drive the discovery of other innovative therapies for severe asthma.

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