REVIEW ARTICLE

BRONCHIAL THERMOPLASTY IN SEVERE ASTHMA PATIENTS

Yosua Kevin Hermawan[1], Ida Ayu Ika Wari Utami[2]

[1] Department of Pulmonology and Respiratory Medicine, Wangaya General Hospital, Denpasar, Indonesia
[2] Department of Pulmonology and Respiratory Medicine, Wangaya General Hospital, Denpasar, Indonesia

ABSTRACT

Severe asthma is caused by chronic inflammation in the airway. Several treatments have been proposed to treat severe asthma. Bronchial thermoplasty is part of management that has been proposed to treat severe asthma. The treatment has been mentioned in asthma guidelines released by Global Initiative for Asthma (GINA) as an interventional management option in uncontrolled severe asthma. Bronchial thermoplasty is approved for patients with the age of at least 18 years old. The treatment is focus on airway smooth muscle by delivering radiofrequency ablation using bronchoscopy. Airway remodeling is an important feature in the disease course of asthma. There are three large randomized trial that has been done for bronchial thermoplasty. The trials recorded an increase in quality of life from asthma patients that have been treated and reduce in exacerbation frequency in long term follow up. The trials also show increased in emergency departments visit and asthma exacerbation for within a certain period after the procedure. Long term follows up of the patients that has undergone the procedure show no deterioration in terms of lung function, indicating a persistent effect of the bronchial thermoplasty. Better understanding in mechanisms of the procedure in the airway and more trials about safety and efficacy is still needed.

Keywords: Bronchial Thermoplasty, Airway smooth muscle, Interventional

INTRODUCTION

Severe asthma continues to become a challenge for physicians. Asthma is a disease caused by chronic inflammation in large and small airways. The clinical symptoms that are commonly seen are wheezing, cough, and dyspneu. Asthma treatment is centered on reducing the inflammation on airway smooth muscle (ASM) that can be achieved by inhaled bronchodilators and corticosteroids. Global Initiative for Asthma (GINA) define severe asthma as asthma that is uncontrolled despite the used of high dose Inhaled corticosteroids (ICS) and long-acting beta agonists (LABA) together with management of exacerbating factors.1 Asthma itself affect around 235 million people and it is estimated that around 5% asthma patients have severe asthma. They usually have limitations on their ability to perform daily activities thus leading to decreased quality of life. Severe asthma also contributes to significant increases of healthcare cost.2 There are couple of therapies for managing severe asthma. Monoclonal anti Interleukin-5 (anti IL-5) antibody such as mepolizumab and reslizumab has been found to be effective in improving asthma related outcomes. Mepolizumab is seen to reduce exacerbation rate by 50% and hospitalization rate by 64%. Reslizumab reduces the exacerbation rate by 54% compared to placebo. Reslizumab also reduces the risk of exacerbation by 60%. However, these drugs have high cost and can increase economic burden for the patients. Another treatment that also suggested for severe asthma is omalizumab, an anti-IgE antibody. Omalizumab is seen to reduce exacerbation rate compared to placebo. Group of patients can be seen with persistent symptoms even with this therapy.3

Correspondence :

Yosua Kevin Hermawan
Department of Pulmonology and Respiratory Medicine, Wangaya General Hospital, Denpasar, Indonesia
email: ina.j.chest@gmail.com

How to cite this article :

BRONCHIAL THERMOPLASTY IN SEVERE ASTHMA PATIENTS

Inflammation of airway and increase in mucous production the key factors in asthma pathogenesis. Airway smooth muscle inflammation can make narrowing of the airway resulting inducing asthma symptoms. Increase in ASM mass can be seen in asthma patients thus may have contribution to increase airway resistance, airway hyperreactivity, and promote the release of inflammatory cells.[4] Therefore the procedure with a purpose to reduce the ASM mass has been proposed. Bronchial thermoplasty (BT) is one of the interventional management indicated for patients with severe asthma to reduce the ASM mass. It has been approved by the US food and drug administration (FDA) in 2010 for the treatment of severe asthma. GINA recommends BT as a treatment option for asthma (Evidence B).[5]

Bronchial thermoplasty provides a new treatment option for patients with severe asthma that are difficult to treat with bronchodilators and corticosteroids. The procedure has not been used regularly as a mainstay treatment for severe asthma and there are still concerns about safety and effectiveness. This article provides description of the procedure and the comparison between past and recent studies about the safety and efficacy of the procedure to deliver better understanding of the procedure.

2. What is Bronchial thermoplasty

Bronchial thermoplasty is a procedure that need a specific device called Alair bronchial thermoplasty system. The system consists of an RF controller and flexible Alair catheter that can expand electrode array. The electrode will then deliver thermal energy to ASM. Bronchoscopy that is used for performing the procedure is recommended to have an outer diameter of 4.9 – 5.2 mm and a minimum of 2.0 mm working channel. The Bronchial thermoplasty procedure consists of 3 bronchoscopy sessions at 3 week intervals, each lasting for around 30-60 minutes. The first two sessions involve the lower lobe of the lungs, with the last session explore the upper lobe. Right middle lobe does not included in the procedure to prevent right middle lobe syndrome. The treatment is divided into multiple sessions to avoid diffuse airway inflammation that might induce exacerbation of asthma. Organized treatment plan and systematic approach such as distal to proximal part or right to left to ensure all regions treated properly are crucial for a proper and safe treatment. Once the bronchoscopy has reached the targeted part, the Alair catheter will be inserted into the working channel. The catheter will expand into 4 electrodes until they touch the airway wall. Direct contact with airway wall must be ensured to maximize the therapy. Each activation of the electrode can target around 5 mm sections of bronchus. Full treatment can consist of 30-70 activation per lobe. The efficacy may depend on how thorough the procedure was performed. The procedure can be carried in sedation or general anesthesia. Bronchial thermoplasty through laryngeal mask airway (LMA) is preferred compare to endotracheal tube (ETT) to prevent bronchospasm. Doses of lidocaine that can be use is up to 600 mg. Patients that will undergo the procedure will be given prednisone 50 mg/day for 3 days. Spirometry should be done before BT to provide comparison of lung function before and after the procedure.[3,6]

Fig 1. Alair Catheter[6]

3. Post Procedure Management

Patients that have undergone BT should expect worsening respiratory symptoms. The symptoms usually present 1 week after the procedure and will improve within 2 weeks. Some study also found an increase in emergency department visit in group of patients that has undergone BT. The risk of exacerbation is found to be highest during the first 7 days after the procedure. Patients should be closely observed after the procedure, and discharged only when vital

signs are stable. Chest x-ray can be considered in patients with deteriorating condition. The routine use of nebulized bronchodilators is for few days is recommended to prevent mucous plug. Patients should be informed about the potential adverse effects such as exacerbation of asthma symptoms.[7]

4. Patient Selection

Bronchial thermoplasty has been used in a couple of countries as a treatment option for patients with severe persistent asthma aged 18 years or older. It is indicated for patients that already have high dose inhaled corticosteroids but still experience persistent symptoms. Bronchial thermoplasty is not recommended for patients that have implanted devices such as pacemaker. Bronchial thermoplasty should be avoided in patients with allergies to medication used in the procedure such as sedation drugs. Patients that have been treated with BT before are also contraindicated to avoid airway scarring or stricture. The ideal patient for BT is non-allergic, non-eosinophilic (non-type 2) severe asthma that has persistent symptoms despite high dose ICS and LABA. However, patients with allergic or eosinophilic (type 2) asthma that has received biologic therapy and not responding to the therapy may also be considered.[7]

5. Airway Smooth Muscle in Severe Asthma

Airway remodeling is an important feature in asthma that can contribute to severity of asthma. It is distinguished by several structural changes. Neoangiogenesis and hypertrophy of airway smooth muscle cells are commonly found. Increased deposition of extracellular matrix (ECM) protein in reticular basement membrane (RBM), and submucosa are contributed into the thickening of airway wall. Hypertrophy of the muscle also can be seen from asthmatic patients. Airway smooth muscle cells derive from mesenchymal precursors and present all along the respiratory tract from trachea to the bronchioles. The increase in ASM mass contributes to bronchial obstruction, reduces lung function, and increase chance of exacerbation. Severe asthma patients that has unreversible obstruction are shown to have significantly thicker airway walls.[4] Airway hyperplasia can be promoted by growth factors such as transforming growth factor β (TGFβ), and chemical or mechanical stress. Inflammation of the bronchial epithelium causes the bronchial epithelial cells to secrete Thymic Stromal Lymphopoietin (TSLP) that can promote allergic responses and airway remodeling. It induce inflammation by promoting the differentiation of naïve $CD4^+$ T cells into Th2 cells. TSLP can activate human lung fibroblast to release type 1 collagen and promote the proliferation of ASM cells. It also shown to cause goblet cell metaplasia and increase mucus production. The direct assessment of airway smooth muscle can be assessed from bronchial biopsies. It can identify bronchial alteration such as, inflammatory cells infiltration, Extracellular matrix accumulation, and ASM hyperplasia.[9,10]

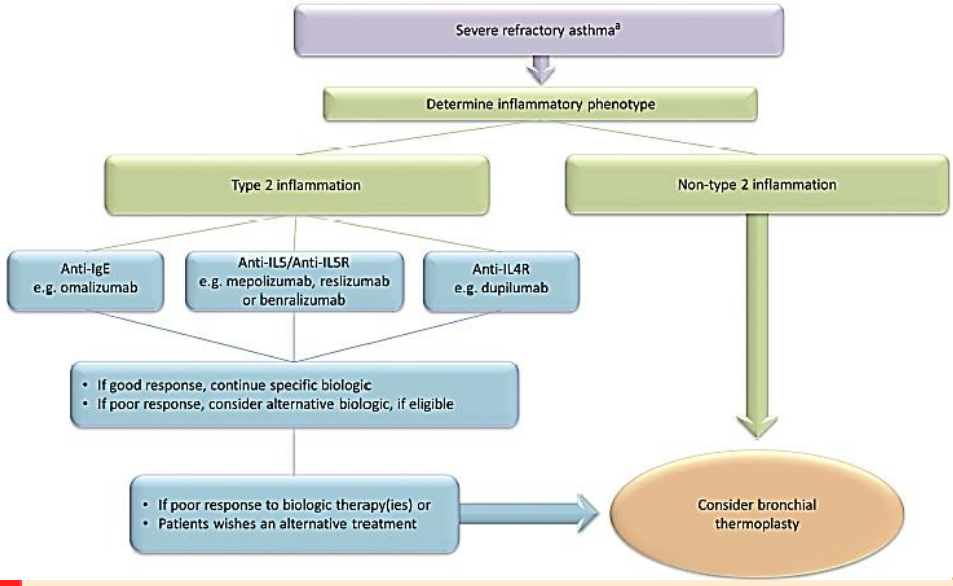

Fig. 2 Algorithm for BT patient selection[7]

6. Effect on Airway

Bronchial thermoplasty action on the airway includes alteration epithelial cells, and glands. However, the precise mechanism of bronchial thermoplasty is uncertain. The role of BT in airway is often associated with ASM. Bronchial thermoplasty was proposed as an interventional therapy to reduce airway smooth muscle, decrease the contractility of ASM by interfering the interaction of actin-myosin, and reduce the secretion of pro inflammatory mediators. The procedure has been trialed on experimental animals and has shown reduction in ASM mass. A small study on group of patients that has undergo BT 2 years prior reported decrease in airway wall thickness through computed tomography (CT) scan. Another study that includes 10 patients that have undergone BT, reported an increase in airway volume 4 weeks after the procedure. In another study, bronchial biopsy was performed on 14 individuals that had undergone BT 6 weeks prior. The biopsy showed a reduction in the amount of α-smooth muscle actin. However, whether the reduction of airway smooth muscle mass contributes directly to the severity and frequency of asthma is uncertain and needs further research.[11,12]

7. Safety and Efficacy

Bronchial thermoplasty is reported to be able to minimize the exacerbation frequency and increase quality of life (QOL) in the long run. There are currently three large randomized trials that are being conducted for bronchial thermoplasty. The first randomized trial is Asthma Intervention Research (AIR) trial. The trial involves 112 subjects where 56 the subjects undergo BT procedure. The study asses the frequency of mild asthma exacerbations during 3 periods of time and uses asthma quality of life questionnaire (AQLQ) as predictor of QOL. The trial show there was increase in the QOL of patients in the BT group at 12 months evaluation. The trial also records an increase in adverse events including hospitalization after treatment for 6 weeks to 12 months. The second randomized trial is Research in Severe Asthma (RISA) trial. The study involves 32 subjects, 15 subjects were treated with BT and medical management and 17 subjects were treated with medical management alone. The study results show improvement in the asthma control questionnaire (ACQ) scores indicating better asthma control. The third randomized trial is AIR 2 study. This study compares the effectiveness of BT to sham procedure which involves 288 subjects, where 190 of the subjects was treated with BT. Both groups underwent three bronchoscopy procedures. The goal was to evaluate using AQLQ between the sham group and BT group at baseline and the average of AQLQ score in 3 periods of time. The result shows an increase adverse events such as exacerbation and emergency visit during the treatment period which is from first procedure until 6 weeks after the procedure in the BT group. These events is especially high in the first week after treatment. After the treatment period, the subjects are followed up until 12 months after the procedure and shown improvement in the AQLQ score in the BT group compared to the sham group (79% and 64% respectively).[7] Long term follow-up study for BT has been conducted to evaluate the safety and benefit of BT. The study is done five years after the first one and show that the patients in BT group has no increase in hospitalizations or emergency room (ER) visits due to exacerbation of asthma and show no deterioration of forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1). Another long-term study that has been done is BT 10+ which BT effect on patients 10 years after the procedure has been done. This study aims to the safety and benefit of BT in a longer period of time. The study shows no increase in hospitalization, severe asthma exacerbation, and emergency room visit rate.[13]

Study/Trial	Method/Design	Population	Key Findings
AIR Trial (Cox et al)	Multicenter randomized control trial	112 subjects; 56 in each group	Increase in QOL of patients in BT group at 12

			months evaluation
RISA Trial (Pavord et al)	Double blind, multicenter randomized control trial	32 subjects; 15 in BT group and 17 in control group	Improvement in ACQ scores for patients in BT group
AIR 2 Trial (Castro et al)	Multicenter randomized control trial	288 subjects; 190 in BT group and 98 in sham group	Improvement in AQLQ score in BT group
AIR 2 Trial 5 years follow up (Thomson et al)	Multicenter observational study	162 subjects from the BT group in AIR 2 trial	Improvement in hospitalization and ER visit rate are persistent. Pulmonary function test show no deterioration
BT10+ (Chaudhuri et al)	Multicenter observational study	192 subjects from AIR trial, AIR 2 trial, and RISA trial	The decrease in hospitalization, exacerbation, and ER rate are maintained

Table 1. Study/Trial Comparison[7,13]

8. Conclusion

Bronchial thermoplasty has been used in some countries as a treatment option for severe asthma based on small numbers of clinical trials. Bronchial thermoplasty able to improve QOL of asthma patients. However, the adverse events such as emergency visit increases within certain periods of time after the procedure. The patients have to be informed that BT is not the definitive treatment and asthma and patients has to be examined thoroughly before the procedure. Long term study indicate that the procedure is safe and has persistent effect on the airway. Bronchial thermoplasty also provides a more cost-effective treatment of choice in this group of patients. Better understanding of the mechanism of BT is still needed. Bronchial thermoplasty is an invasive treatment therefore the medical professionals involved should be able to decide when it is best to give the treatment. In the future, more clinical trials about safety and efficacy of BT is still needed.

References

1. Global Initiative for Asthma. Difficult-To-Treat & Severe Asthma in Adolescent and Adult Patients, 2023. Available from: www.ginasthma.org
2. Goorsenberg AWM, d'Hooghe JNS, Srikanthan K, ten Hacken NHT, Weersink EJM, Roelofs JJTH, et al. Bronchial thermoplasty induced airway smooth muscle reduction and clinical response in severe asthma the TASMA randomized trial. Am J Respir Crit Care Med. 2021;203(2):175–84.
3. Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, et al. Management of severe asthma: A European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2020;55(1).
4. Hassoun D, Rose L, Blanc FX, Magnan A, Loirand G, Sauzeau V. Bronchial smooth muscle cell in asthma: where does it fit? BMJ Open Respir Res. 2022;9(1):1–13.
5. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023. Updated July 2023. Available from: www.ginasthma.org
6. Tan LD, Yoneda KY, Louie S, Hogarth DK, Castro M. Bronchial Thermoplasty: A Decade of Experience: State of the Art. J Allergy Clin Immunol Pract. 2019;7(1):71–80.
7. Thomson NC. Recent developments in bronchial thermoplasty for severe