Original Article

A Multicenter Study on the Safety and Efficacy of Bronchial Thermoplasty in Adults with Severe Asthma

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ABSTRACT

Background and Aim: Bronchial thermoplasty (BT) is a treatment option for patients with severe asthma. BT involves controlled delivery of radiofrequency energy using a bronchoscopic catheter, thereby reducing bronchial hyperreactivity. Herein, we describe our experience on the safety and efficacy of BT in severe asthma. **Methods:** This was a retrospective multicenter study of subjects who underwent BT at four centers across India. **Results:** We included 36 subjects (mean ± standard deviation [SD] age, 50.9 ± 11.5 years, women [69.44%]) undergoing 105 BT treatment sessions. All the subjects met the American Thoracic Society/European Respiratory Society criteria for severe asthma, 22.2% were requiring oral maintenance glucocorticoids. The mean ± SD baseline %predicted forced expiratory volume in one second (FEV1) was 62.07 ± 18.54. The median interquartile range (IQR) annual asthma exacerbation rate in the year preceding BT was 3.5 (1–10). We encountered intraprocedural complications in 7 (6.7%) sessions. An exacerbation of asthma following BT occurred in 6 (5.7%) procedures. We observed a significant improvement in the asthma control test and the asthma control questionnaire scores following BT. The quality of life (asthma quality of life questionnaire) also significantly improved. We noted a significant reduction in the number of exacerbations following BT (median [IQR], 3 [1–10] per year pre-BT versus 0.5 [0–3] per year post-BT, $P < 0.001$). No significant change occurred in the %predicted FEV1 following BT. **Conclusion:** BT is a feasible treatment option in patients with severe asthma. More extensive studies are required to establish the efficacy of BT in real-life settings.

KEY WORDS: Bronchial asthma, bronchial thermoplasty, spirometry

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INTRODUCTION

A subset of patients with asthma has poor symptom control despite adequate adherence to optimal medical treatment with inhaled drugs. This subset, constituting approximately 5%–10% of all asthmatics, represents the

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group of severe asthma.[1] The management of severe asthma necessitates exploration of additional modalities to achieve symptom control and improve the health-related quality of life. The modalities for the treatment of severe asthma include biological agents and bronchial thermoplasty (BT). Although the exact prevalence data in India are lacking, an estimated 1–2 million adults in India have severe asthma.[2]

BT is an option that can be considered in patients with severe asthma who fail to achieve asthma control with the recommended drug treatment.[3] The procedure involves sequential application of radiofrequency (RF) energy to the medium and larger size (3–10 mm) airways. A dedicated bronchoscopic catheter is used for this purpose. The therapy involves sequential RF treatment of the right lower lobe, left lower lobe, and both upper lobes (right middle lobe is not treated) in this sequence during separate bronchoscopy sessions. The BT treatment aims to ablate the hypertrophied airway smooth muscle to reduce bronchial hyperreactivity. The treatment is reasonably safe, although early complications following individual bronchoscopy sessions have been described.[4] Although the use of BT has been proposed primarily in non-TH2 asthma, clinical trials on BT, recruited patients regardless of the asthma phenotype.

The evidence for the efficacy and safety of BT has been demonstrated by randomized controlled trials (RCTs).[4-6] Subsequently, case series from various demographic regions have highlighted the utility and safety of this modality in real-life settings.[7,8] BT was recently made available in India. Guidelines on the technical performance and patient selection for BT in India were recently published.[2] However, there is no published experience on the utility and safety of BT in severe asthma from India. We collated the experience with the initial cases undergoing BT at four centers across India.

METHODS

Study design

This study involved a retrospective review of the subjects who underwent BT at four centers across India (All India Institute of Medical Sciences, New Delhi [KM, TMS, SM, PT, VH, AM, RG], Yashoda Hospitals, Somajiguda, Hyderabad [VNM], Royal Care Hospitals, Coimbatore [VRP, AS, MS], and Postgraduate Institute of Medical Education and Research, Chandigarh [KTP and RA]). The procedures were performed after written informed consent from all subjects at individual centers. All the four facilities are tertiary care centers with established interventional bronchoscopy programs.

Subjects

Clinical data from consecutive subjects older than 18 years of age undergoing BT at the four facilities were retrospectively collected and analyzed. The following information was extracted: (1) the number of subjects, (2) age and gender; (3) spirometry values; (4) exacerbation history; (5) treatment details; (6) technical aspects of the procedure; (7) anesthesia; (8) procedural complications; (9) measures of asthma control at baseline and follow-up, wherever available.

Procedure

The procedures were performed according to protocols at respective institutions considering the local resources. Subjects were planned for BT if they met the American Thoracic Society/European Respiratory Society (ATS/ERS) criteria for severe asthma. BT was performed in three separate bronchoscopy sessions for treating the right lower lobe, left lower lobe, and both upper lobe in this sequence. The individual bronchoscopy sessions were spaced 2–3 weeks apart. Subjects received premedication with oral prednisolone 30–50 mg once a day, beginning 3 days before each bronchoscopy treatment session. Procedures were performed under general anesthesia, and a supraglottic airway device or an endotracheal tube was used as an airway conduit for the bronchoscope. A 4.2 mm bronchoscope with a 2.0 mm working channel was used to perform BT. A systematic bronchoscopic approach for treating the segmental airway was followed. A dedicated assistant marked the treated segments on a chart provided by the manufacturer for each treatment session. The number of activations delivered and any procedural complications were noted. The subjects were observed for any immediate complications and were followed up following discharge.

Outcomes

The primary outcome was to study the clinical and procedural characteristics including safety of BT. Secondary outcomes included the change in asthma control, exacerbation rate, and quality of life following BT.

Statistical analysis

Data are presented as mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables and as number with percentage for categorical variables. Descriptive and summary statistics were performed. Statistical analyses were performed using the STATA statistical analysis software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

RESULTS

We included 36 subjects. The mean (SD) age of the subjects was 50.9 (11.5) years (range, 27–70 years), with the majority being women (69.4%). Ten of the 36 (27.8 %) subjects were aged 60 years or more, four (11.1%) were 65 years or older. All were never smokers and fulfilled the ATS/ERS criteria for severe asthma. Nasal symptoms were present in 15 (41.7%). The median disease duration of asthma was 10 (IQR, 5–30) years. Uncontrolled asthma (GINA

criteria) was present in 35 (97.2%). The baseline mean (SD) percent predicted forced expiratory volume in one second (FEV_1) was 62.1% (18.5 %). The predicted FEV1 was less than 60% in 17 (47.2%) subjects while in eight (22.2%), the percentage predicted FEV1 was < 50%. The median exacerbation rate in the preceding year was 3.5 (IQR, 1–10). Five subjects (13.9%) had a history of severe exacerbation requiring mechanical ventilation in the past. All subjects were receiving high-dose inhaled corticosteroids, long-acting beta-2 agonists and leukotriene receptor antagonists at the time of the evaluation for BT. Eight subjects (22.2%) were requiring regular oral maintenance glucocorticoids. A history of the current or previous use of omalizumab (anti-immunoglobulin E treatment) was seen in four subjects each (22.2%). The baseline data including the asthma control test (ACT), asthma control questionnaire (ACQ), and asthma quality of life questionnaire (AQLQ) scores are summarized in Table 1.

Overall, 105 BT sessions were performed in 36 subjects. All procedures were performed under general anesthesia. Laryngeal mask airway was used in all but one patient (97.2%). Similarly, a 4.2 bronchoscope was used in all but one patient (97.2%). The mean total number of activations per patient (mean ± SD) was 225.5 ± 60.5 (session 1: 79.9 ± 17.9, session 2: 68.6 ± 16.9, and session 3: 89.4 ± 27.0). Intraprocedural complications (hypoxemia, bronchospasm, and minor bleeding) occurred in 7 (6.7%) sessions. An exacerbation of asthma following a BT session occurred in 6 (5.7%) procedures. Subjects were discharged on the same day following 59 of the 105 (56.2%) BT sessions. The other procedural details are summarized in Table 2.

Table 1: Baseline demographic and clinical characteristics of asthma subjects undergoing bronchial thermoplasty (*n*=36)

Characteristic	Value
Age (years), mean±SD (range)	50.89±11.53 (27-70)
Gender, *n* (%)	
Male	11 (30.56)
Female	25 (69.44)
BMI (kg/m^2), mean±SD (range)	27.50±4.93 (21.2-33.1)
Smoking status, *n* (%)	
Never smoker	36 (100)
Smoker	0
Nasal comorbidity, *n* (%)	15 (41.67)
Disease duration (years), median (IQR)	10 (5-30)
Absolute eosinophil count (cells/mm^3), median (IQR)	152 (68-444)
Total IgE (kUA/L), median (IQR)	292 (62-1288)
Severe asthma by ATS/ERS criteria, *n* (%)	36 (100)
Asthma uncontrolled by GINA criteria, *n* (%)	35 (97.22)
Exacerbations in last year, median (IQR)	3.5 (1-10)
Emergency visits in last year, median (IQR)	2 (0-3)
Hospitalizations in last year, median (IQR)	2 (0-3)
Exacerbations requiring mechanical ventilation, *n* (%)	5 (13.89)
Baseline ACQ score, mean±SD	3.2±1.39
Baseline ACT score, mean±SD	13.3±5.6
Baseline AQLQ score, mean±SD	3.84±1.37
Baseline FEV_1 (percent predicted), mean±SD	62.07±18.54
Baseline therapies, *n* (%)	
High dose ICS	36 (100)
LABA	36 (100)
LAMA	24 (66.67)
LTRA	36 (100)
Theophylline	15 (41.67)
Omalizumab, current use	4 (11.11)
Omalizumab, former use	4 (11.11)
Maintenance oral corticosteroid	8 (22.22)

ACQ: Asthma control questionnaire, ACT: Asthma control test, AQLQ: Asthma quality of life questionnaire, BMI: Body mass index, FEV_1: Forced expiratory volume in 1 s, ICS: Inhaled corticosteroid, LABA: Long-acting beta-2 adrenergic agonist, LAMA: Long-acting muscarinic antagonist, LTRA: Leukotriene receptor antagonist, SD: Standard deviation, IQR: Interquartile range, ATS: American Thoracic Society, ERS: European Respiratory Society, GINA: Global Initiative for Asthma

There was significant improvement in measures of asthma control following BT, including ACT (mean [SD] Pre-BT, 10.3 [4.4]; Post-BT, 20.5 [4.8], $P < 0.001$) and ACQ (Median [IQR] Pre-BT, 3.91 [3.1–4.6]; Post-BT 1.08 [0.83–1.3], $P < 0.01$). The quality of life significantly improved after BT as assessed using the AQLQ (Mean [SD] Pre-BT, 2.89 [1.18]; Mean [SD] Post-BT 5.59 [0.96], $P < 0.001$). There was also a significant reduction in the number of exacerbations following BT (Median [IQR], 3 [1–10] per year pre-BT *vs.* 0.5 [0–3] per year post-BT, $P < 0.001$). No significant change was observed in the predicted FEV_1 following BT [Table 3]. Sixty-four percent of subjects with previously "not well controlled" asthma by GINA criteria achieved asthma control, and 50% of subjects were able to reduce their controller medicine usage.

DISCUSSION

We found BT to be a relatively safe modality in subjects with severe uncontrolled asthma. BT was associated with an improvement in asthma control and a reduction in exacerbations in patients undergoing the procedure. There were no significant effects on lung function. Procedural complications occurred in 6.7% BT sessions (all were transient and reversible) while worsening of asthma symptoms occurred in a small proportion (5.7%) following the procedure. This study is the first published multicenter experience of BT from India.

The US-Food and Drug Administration approved BT based on the findings of the AIR-2 study.[6] There has been considerable debate regarding the inclusion characteristics of patients in the BT trials and the endpoints reported.[9] The long-term safety and efficacy data of patients included in the RCTs have been published that lend support to the persistence of clinical benefits with BT.[10-12] Multiple case series comprising of real-life patients, have also reported the data on the safety and efficacy of BT.[8,13,14] The most crucial step is choosing the right candidate for BT. Poor control of asthma may be due to numerous modifiable factors. These must be addressed appropriately before considering a patient for BT.[2] All the patients reported in this multicenter study fulfilled the criteria of severe asthma despite correction of modifiable factors.

Table 2: Performance characteristics and complications

Characteristic	Value
Premedication with oral prednisolone (mg), *n* (%)	36 (100)
30	6 (16.6)
40	13 (36.1)
50	17 (47.2)
Bronchoscope diameter (mm), *n* (%)	
4.2	35 (97.2)
4.9	1 (2.8)
Anaesthesia, *n* (%)	
General anesthesia	36 (100)
Airway conduit, *n* (%)	
Laryngeal mask airway	35 (97.2)
Endotracheal tube	1 (2.8)
Number of BT sessions performed (sessions), *n* (%)	
3	33 (91.7)
2	3 (8.3)
Session 1 (right lower lobe)	
Activations, mean±SD	79.9±17.9
Complications, *n* (%)	2 (5.6)
Catheter malfunction, *n* (%)	1 (2.8)
Successful completion, *n* (%)	36 (100)
Same-day discharge, *n* (%)	12 (33.3)
Postdischarge exacerbation, *n* (%)	3 (8.3)
Session 2 (left lower lobe)	
Activations, mean±SD	68.6±16.9
Complications, *n* (%)	3 (8.3)
Catheter malfunction, *n* (%)	1 (2.8)
Successful completion, *n* (%)	35 (97.2)
Same-day discharge, *n* (%)	25 (69.4)
Postdischarge exacerbation, *n* (%)	3 (8.3)
Session 3 (both upper lobes) (*n*=33)	
Activations, mean±SD	89.4±27.0
Complications, *n* (%)	2 (6.1)
Catheter malfunction, *n* (%)	2 (6.1)
Successful completion, *n* (%)	33 (100)
Same-day discharge	22 (66.7)
Postdischarge exacerbation, *n* (%)	0
Total activations per patient, mean±SD	225.5±60.5
Procedural complications (all sessions, *n*=105), *n* (%)	7 (6.7)
Hypoxemia	2 (1.9)
Bronchospasm	2 (1.9)
Minor bleeding	3 (2.9)
Postdischarge exacerbation (all sessions, *n*=105), *n* (%)	6 (5.7)
Same day discharge (all sessions, *n*=105), *n* (%)	59 (56.2)

BT: Bronchial thermoplasty, SD: Standard deviation

Table 3: Evaluation of change in clinical parameters before and after bronchial thermoplasty

Parameter	Pre-BT	Post-BT	*P*
FEV_1 (percentage predicted), mean±SD	57.2±17.4	57.3±15.3	0.97
ACT score, mean±SD	10.3±4.4	20.5±4.8	<0.001
ACQ score, median (IQR)	3.91 (3.1-4.6)	1.08 (0.83-1.3)	<0.01
AQLQ score, mean±SD	2.89±1.18	5.59±0.96	<0.001
Exacerbations per year, median (IQR)	3 (1-10)	0.5 (0-3)	<0.001

FEV_1: Forced expiratory volume in 1 s, SD: Standard deviation, ACT: Asthma control test, ACQ: Asthma control questionnaire, IQR: Interquartile range, AQLQ: Asthma quality of life questionnaire, BT: Bronchial thermoplasty

The clinical characteristics of patients who are considered for BT in real-life settings are frequently different from those included in the clinical trials. This difference was also evident in this study. Nearly half of the patients (47.2%) had a predicted FEV1 that was below 60%, and 11.1% were older than 65 years. Age higher than 65 years and a percent predicted FEV1 < 60 are considered as conditional inclusion criteria for BT.[2] A lower FEV1 may be associated with a greater risk of complications during and following the procedure, while safety data on older patients are sparse.[2,4,15,16] A history of asthma exacerbation requiring mechanical ventilation was present in 14% of patients. Indeed, a history of asthma exacerbation requiring mechanical ventilation is also considered a relative contraindication for BT.[2] This highlights that patients with relative contraindications may be considered for BT after a careful risk-benefit assessment.

The technical performance of the procedure was according to the available recommendations in most of the cases. A thin bronchoscope and general anesthesia were routinely used. The mean activations delivered (overall activations, mean [SD], 225.5 [60.5]) were high. In a previous study, a similar higher total number of activations was associated with a good response to BT.[17] The asthma control and the quality of life improvements were observed in patients wherein a follow-up data were available. Data on exacerbation rate on follow-up were available for most subjects. A significant reduction of exacerbations on follow-up supports the clinical benefit of BT.

What are the clinical implications of our study? The findings of this study suggest that BT is a feasible treatment option that may be offered to subjects with severe asthma who fail to improve and achieve asthma control with initial controller treatment. These subjects must be counseled in detail regarding the available options for severe asthma management, and an asthma phenotyping should be attempted. The available choices of various biological agents should also be discussed, and the decision for BT may be taken after a careful risk-benefit assessment. Importantly, those with relative contraindications to BT including those with FEV1 <60% and age >65 years may also benefit from BT, and these patients may also be offered an option for BT.

Our study has a few limitations. The data on follow-up for asthma control parameters and the quality of life were not available for all the subjects. The analysis was therefore performed only for subjects wherein a complete pre-post data were available. The sample size is small, and there is a lack of a control group.

CONCLUSION

Bronchial asthma is a major health concern across both the developing and the developed countries.[18] BT is a relatively safe treatment option for patients with severe asthma who remain uncontrolled despite initial controller treatment. Procedure-related complications are uncommon, and there is a small risk of worsening of asthma following the procedure. The preliminary experience suggests that the therapy appears efficacious.

More extensive studies on real-life patients are required to establish the performance characteristics of this modality compared with other treatment options like biological agents.

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Conflicts of interest
There are no conflicts of interest.

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