Original Article

Observation of the Improvement in Nocturnal Asthma Symptoms with Administration of Once Daily Sustained Released Theophylline

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Conflict of Interest: None
Received: 18-10-2017
Accepted: 22-11-2017
www.banglajol.info/index.php/JSSMC

Abstract:

Objective: *The aims and objective of this study to observe the improvement in Nocturnal Asthma symptoms and Quality of Life (QoL) with administration of once daily sustained release theophylline preparation.*

Background: *Nocturnal symptoms are a common part of the asthma. Nocturnal asthma is defined by a drop in forced expiratory volume in 1 second (FEV1) of at least 15% between bedtime and awakening in patients with clinical and physiologic evidence of asthma, which may include improvement in QoL.*

Methodology: *The patient with Chronic Persistent Asthma, both sex, age >18 to 50 years of age and preferably patients with nocturnal exacerbations were included in the study. All patients were diagnosed on the basis of clinical history, physical examination, chest X-ray and pulmonary function tests, in accordance with the clinical criteria for the diagnosis by the GINA. The recruitment period was between March 2017 and August 2017 Shaheed Suhrawardy Medical College Hospital, Dhaka.*

Results: *It was observed that 65(92.85%) was found exacerbation free night and 5(7.15%) patients were found exacerbation with sustained release Theophylline. There are significantly improved qualities of life between 1st follow up to 2nd follow up, 3rd follow up and 4th follow up p<0.001 which was statistically significant. Spirometry test was gradually improved between 1st visit of FEV1 to 2nd, 3rd and 4th visit of FEV1, (p<0.001) that was statistically significant.*

Conclusion: *Most of the patients were found exacerbation free night. There are significantly improved quality of life between 1st follow up to 2nd follow up, 3rd follow up and 4th follow up in Spirometry test. The value of FEV1 was gradually improve in the l st visit, 2nd, 3rd and 4th visit with sustained release Theophylline.*

Key Words:
FEV1, nocturnal exacerbation, Asthma

[J Shaheed Suhrawardy Med Coll 2017; 9(2): 74-77]
DOI: http://dx.doi.org/10.3329/jssmc.v9i2.37267

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Introduction

Asthma is defined as a chronic inflammatory disorder of the airways which manifests itself as recurrent episodes of wheezing, breathlessness, chest tightness and cough. It is characterized by bronchial hyper responsiveness and variable airflow obstruction, that is often reversible either spontaneously or with treatment.[1]

Nocturnal asthma is defined by a drop in forced expiratory volume in 1 second (FEV1) of at least 15% between bedtime and awakening in patients with clinical and physiologic evidence of asthma. Nocturnal asthma is associated with a circadian pattern in lung function, distal airway inflammation, glucocorticoid receptor affinity, pulmonary capillary blood volume, and beta-2 adrenergic receptor function may also contribute.[2]

Nocturnal asthma is common and approximately 30 to 70 percent of patients with asthma report nocturnal asthma symptoms at least once a month.[3,4] The occurrence of nocturnal asthma symptoms is also reflected in mortality statistics. As an example, over a one-year period, 53 percent of asthma deaths in one report occurred at night.[5]

As many as 75% of asthmatic subjects are awakened by asthma symptoms at least once per week, with approximately 40% experiencing nocturnal symptoms on a nightly basis. An extensive body of research has demonstrated that nocturnal symptoms of cough and dyspnea are accompanied by circadian variations- in airway inflammation and physiologic variables, including airflow limitation and airways hyper responsiveness. Nocturnal worsening of asthma is a well-described and important problem that must be considered in the management of patients with asthma[6]. In particular, nocturnal asthma symptoms are felt to be a characteristic feature of asthma that is not well-controlled[7,8].

Increasing awareness of the exaggerated circadian rhythm in bronchomotor tone that causes most asthmatic patients to have increase respiratory symptoms in the early morning has resulted in a search for such a sustained release molecule with superior dosing strategy that will provide maximal bronchodialatory activity at the time of reduced bronchial patency.

Objective of this Study

The objective of this study to observe the improvement in Nocturnal Asthma symptoms and Quality of Life (QoL) with administration of once daily sustained release theophylline preparation.

Materials and methods:

Sample size: A total of 70 patients with choronic persistent asthma, both sex, age > 18 to 50 years of age and preferably patients with nocturnal exacerbations were included in the study. March 2017 to August 2017 in Shaheed Suhrawardy Medical College Hospital, Dhaka.

Each patient underwent recording of medical, occupational, and smoking history; physical examination; chest radiography and spirometry as screening tests to ensure that they met the inclusion criteria. The spirometry was performed before and 20 minutes after inhalation of a bronchodilator at the first visit. Dyspnea was scored using the British MRC dyspnea scale (Moor-Jankowski 1976). Patients who met all the criteria were enrolled in study. The patients had been receiving sustained release of theophylline at evening. None of the patients was treated with anti-histamines, anti-leukotrienes, cromolyn, β-blockers, ACE inhibitors, oral prednisolone, and/or LABAs during the study. Some of the patients had discontinued these medications at least 4 weeks before enrollment. Patients were excluded if they had experienced an exacerbation within 4 weeks before enrollment. The use of a short-acting β_2-agonist or short-acting anticholinergic on demand was permitted. Physical examinations, spirometry, and MRC scoring, were performed at screening and baseline, and after 4 and 8 weeks of treatment.

Results

Table-I

Number of exacerbation free night

	Number	Percentage
Exacerbation free night	65	92.86
Number exacerbation	05	7.14
Total	70	100.00

Regarding number of exacerbation free night, It was observed that 65(92.86%) was found exacerbation free night and 5(7.14%) patients were found exacerbation.

Table-II

Number of undisturbed sleep at night on admission

Number of undisturbed sleep at night	Number of patients	Percentage
1st follow up	36	51.43
2nd – 3rd follow up	29	41.43
3rd – 4th follow up	05	7.14
Total	70	100.0

It was observed that number of undisturbed sleep at night 36(51.43%) was found on 1st follow up, 29(41.43%) was on 2nd – 3rd visit and 05 (7.14%) on the 3rd – 4th visit.

Table-III

Improved in FEVI

	MeaniSD	Mean ±SD	P value
1st-FEV1-2nd FEV1	47.43(±5.97)	54.86(±4.62)	0.01
1st-FEV1-3rd FEV1	47.43(±5.97)	81.41(±6.16)	<0.001
1st-FEV1-4th FEV1	47.43(±5.97)	85.50(±5.79)	<0.001

There were significantly improved FEV1 between 1st follow up to 2nd follow up, 3rd follow up and 4th follow up. Here $p<0.001$, which was statistically significant.

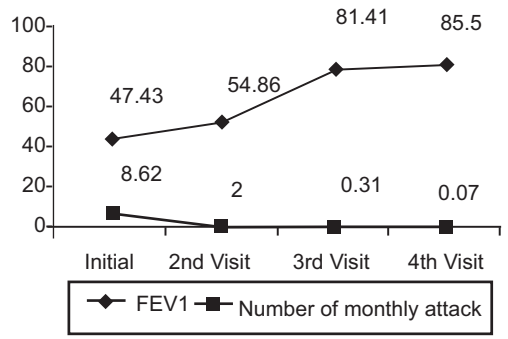

Fig.-1: *Improved in quality of life*

Table – IV

Mean changes in sipometry test

Changes in Spirometry Test			95% confidence interval of the difference		P value
	Mean	+SD	Lower	Upper	<0.00
1st-FEV1 – 2nd FEV1	7.43	±3.08	6.69	8.16	<0.00
1st-FEV1 – 3rd FEV1	33.98	±9.30	31.76	36.20	<0.00
3rd –FEV1 – 1st FEV1	38.07	±8.92	35.94	40.20	<0.00
4th FEV1 – 2nd FEV1	26.55	±8.15	34.61	28.50	<0.00
3rd -FEV1 – 2nd FEV1 4th FEV1	3064	±8.00	28.73	32.35	<0.00

Regarding mean change in spirometry test, It was observed that spirometry test the value of FEVI was gradually improved in 12st visit, 2nd visit, 3rd visit and 4th visit (p<0.001) that was statistically signficant.

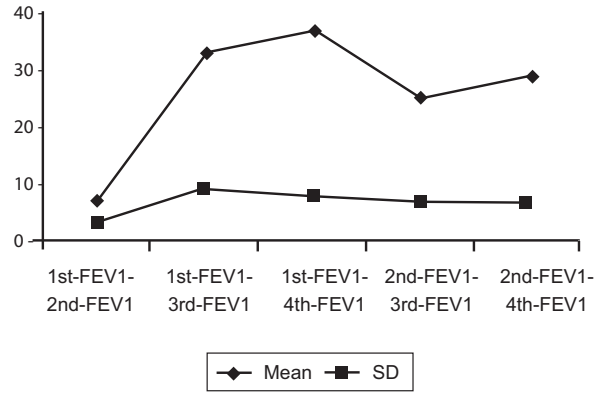

Fig.-2: *Mean changes in spirometry test*

Discussion

Regarding number of exacerbation free night, It was observed that 65 (92.86%) was found exacerbation free night and 5 (7.14%) patients were found exacerbation. Yiin KT, et al.[9]found that administration of Uniphyllin (10 mg/kg) once a day at 6 PM could maintain the blood level of theophylline within therapeutic range at least 12 to 24 hrs. The peak expiratory flow rate of the 6 cases we collected, were significantly improved.

It was observed that duration of undisturbed sleep at night 33 (47.1%) was found < 3 months, 26(37.1%) was between 4-5 months and 11(15.7%) was between 6 of months. Direct effects of sleep on breathing, such as changes in breathing pattern[10] and ventilator control[11, 12] are transient and on arousal return to the patterns found in wakefulness.

There are significantly improved qualities of life between 1st follow up to 2nd follow up, 3rd follow up and 4th follow up p<0.001 which was statistically significant. Helm SG and Meltzer[13] study found once-daily regimen of controlled release theophylline (Uniphyl tablets) with previous twice- or thrice-daily methylxanthine regimens. Three hundred asthmatic patients, 78 percent prone to nocturnal episodes during prior therapy, completed the investigation. Eighty-two percent of the patients were treated for moderate or severe disease. After a one-week evaluation of baseline theophylline therapy (with adjunctive medication), the patients substituted evening doses of the once-daily drug in approximate milligram-for milligram equivalent doses. Concomitant medications were allowed as before. Nighttime and morning asthma control improved significantly without deterioration in the evening, and without increased side effects. Once daily therapy resulted in markedly fewer night awakenings involving inhaler use (p <0.01) and near 60 percent reductions in the number of patients with night time or early morning exacerbations (p<0.01) Control of morning chest tightness, wheeze, and dyspnea Improved significantly (p<0.01) and patients' as well as investigators' global evaluations favored once-daily treatment (p<0.01) Morning peak expiratory flow rates improved both at home (p<0.01) and at the office (p = 0.05). The forced expiratory volume in one second at the office increased modestly in the entire group. It is concluded that Uniphyl is effective and well tolerated when administered in once-daily evening doses.

FEV1 measurements in patients treated with theophylline were significantly improved compared with those observed in patients treated with placebo at treatment week 8 and week 12 (p=0.004); these changes represented 8 and 16% improvements from baseline with placebo and theophylline, respectively, at week 12. Janson et al.[14] a decrease in estimated sleep time (P less than 0.05) and increase in nocturnal wakefulness (P less than 0.05) was seen with decreasing daytime FEV1 - measured as

percentage of the predicted value (%FEV1). There was also significant correlation between increasing age and decreasing % FEV I (P less than 0.01). Kawayama et al.[15] study observed that FEV I in the combinationgroup, but not in the theophylline alone, was significantly increased at 4 (1.56 ± 0.13 L, p <0.001) and 8 weeks (1.60 ± 0.13 L, p <0.001) from the baseline (1.40 ± 0.12 L). In the combination group, but not the theophylline alone group, the dyspnea score was significantly improved after 4 (p <0.01) and 8 weeks (p < 0.05) compared with baseline.

Conclusion

Most of the patients were found exacerbation free night with sustained release theophylline. There was significantly improved quality of life between 1st follow up to 2nd follow up, 3rd follow up and 4th follow up. The value of FEV1 3rd was gradually improved in 1st visit to 2nd visit, 3rd visit and 4th visit. p<0.001 that was statistically singnificant

References

1. Felemban HS, Motahar AJ, Alzamzami NM, Felemban WA, Adnan AM, Albishi SS. Causes and Management of Asthma. The EgyptianJournal of Hospital Medicine 2018; 70: 76-81. Xiongbin J. Nocturnal Asthma: A Special Type of Asthma. Glob J Allergy 2016; 2(1): 3-9.
3. Storms WW, Bodman SF, Nathan RA, Byer P. Nocturnal asthma symptoms may be more prevalent than we think. J Asthma 1994; 31: 313- 318
4. Fagnano M, Bayer AL, Isensee CA, Hernandez T,1-lalterman JS, et al. Nocturnal asthma symptoms and poor sleep quality among urban schoolchildren with asthma.AcadPediatr 2011; 11: 493-499.
5. Robertson CF,Rubinfeld AR, Bowes G. Deaths from asthma in Victoria: a 12-month survey. Med J Aust1990; 152: 511-517
6. Turner-Warwick M. Epidemiology of nocturnal asthma. Am J Med 1988; 85: 6-8.
7. NationalAsthma, Education and Prevention Program Expert panel report III. Guidelines for the diagnosis and management of asthma,Bethesda, MD: National Heart, Lung, and Blood Institute. 2007(NIH publication no. 08-4051)
8. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention.2015: 1-149.
9. Yiin KT, Chiang CD, Shill WL, Huang WL, JihKS, Lin TM, et al Sustained-release theophylline-uniphyllin in nocturnal asthmatics.Zhonghua Yi XueZaZhi(Taipei). 1989 Jan;43(I):43-8.
10. Douglas NJ, White DP, Pickett CK, et al. Respiration during sleep in normal man. Thorax 1982; 37: 840-4
11. Douglas NJ, White DP, Weil JV, et al. Hypoxic ventilator response decreases during sleep in normal men. Am Rev Respir Dis 1982; 125: 286-9
12. Douglas NJ, White DP, Weil IV, et al. Hyper-capnicventilatory response in sleeping adults. Am Rev Respir Dis 1982; 126: 758-62
13. Helm SG and Meltzer SM, Improved Control of Asthma in the Office Setting a Large-Scale Study of Once-Daily Evening Doses of Theophylline. The American Journal of Medicine] 988; 85(suppl I B):30-33
14. Janson C, Gislason T, Boman G, Hetta J, RoosBE. Sleep disturbances in patients with asthma. Respir Med. 1990; 84(1): 37-42.
15. Kawayama T, Tomoaki Hoshino T, Ichiki M, Tsuda T, Kinoshita M, Takata S, and Koga T. Effect of add-on therapy of tiotropium in COPD treated with theophylline. International Journal of COPD 2008:3(1) 137-147