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Original Research Paper

Respiratory Medicine

"COST EFFECTIVENESS COMPARISON OF LONG-ACTING MUSCARINIC ANTAGONISTS (LAMA) ADDED TO COMBINATION LONG-ACTING BETA-AGONISTS AND INHALED CORTICOSTEROIDS (LABA/ICS) [TRIPLETHERAPY] V/S LABA/ICS [DUAL THERAPY] IN MODERATE TO SEVERE ASTHMA"

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ABSTRACT

Background: Frequent exacerbations raise the risk of persistent asthma in adults and contribute to high treatment costs. Thus, the main goals of asthma management, are to reduce the rate of exacerbations, to achieve asthma control and from an economic perspective to reduce the burden of this disease through maximizing health gain with available resources. This study compares the costs and effectiveness of dual and triple therapy to achieve a better asthma control and good quality of life (QOL) at a lower cost. **Methods:** A prospective observational comparative study conducted at a hospital on 80 asthma patients, out of which 40 received dual and the other 40 received triple therapy. All subjects completed the Mini Asthma Quality of Life Questionnaire (MAQLQ) and Asthma Control Test (ACT) at baseline and after 2 and 4 weeks, respectively, of follow- up visits. **Results:** The mean of post FEV1 and PEFR between dual therapy (69.025±15.7 and 61.95±13.6 respectively) and triple therapy (73.925±11.5 and 69.725±9.2) showed significant improvement in lung function with triple therapy. At week 4, in dual therapy and triple therapy mean change from baseline in total ACT Score was 3.55±0.006 (P<0.05) to 4.675±0.49 (P <0.05) respectively and at week 2, in dual therapy and triple therapy mean change from baseline in MAQLQ score was 0.237±-0.03 (P<0.05) to 0.255±-0.005 (P<0.05) respectively. **Conclusion:** Triple therapy is more cost-effective than dual therapy to treat adults with moderate to severe asthma who are symptomatic despite current doses. In addition, it can improve QOL and better control of asthma.

KEYWORDS :

INTRODUCTION

The goal of economic evaluation in healthcare is to make sure that the limited resources are used as efficiently as possible. Different therapy options will have varying effects on both the cost and success of the patient's treatment. For instance, a specific therapeutic intervention could be financially more expensive even when it is clinically more beneficial than an alternative therapy. Economic tools, such as cost-effectiveness studies, are frequently used to enable net changes in costs and outcomes to be explicitly quantified in order to better advise decision-makers on how to value potential treatment alternatives. Economic analyses are particularly significant in diseases like asthma that place a high burden on the patient, healthcare system, and society due to high morbidity, costs of regular and acute management of the disease, and reduced productivity. These diseases aim to maximise health gains and clinical benefits with available resources.

An important amount of the expenditures associated with asthma are attributable to the negative effects of ineffective disease management, such as exacerbations necessitating hospitalisation or emergency room visits. (1)

Asthma is a prevalent chronic condition in which in addition to respiratory symptoms, activity restrictions, and exacerbations may necessitate emergency hospital care and may also be fatal. (2)

Airway inflammation caused by a variety of environmental stimuli is the basic pathophysiology of asthma exacerbation. Acute airway inflammation causes bronchospasm, mucus hypersecretion, and oedema, which results in reversible airway narrowing and higher airway resistance. A beta-2-agonist will typically provide momentary relief from the related symptoms. A faulty injury-repair mechanism and remodelling of the airway wall are the results of superimposed acute and subacute inflammatory episodes brought on by insufficient anti- inflammatory medication. In the end, this causes a thickening of the airway wall, various degrees of fixed airflow blockage, and diminished lung function (3). Accordingly, reducing the likelihood of exacerbations (inflammatory episodes) in the future by optimal use of inhaled corticosteroid (ICS)-containing controller medications is one of the main goals of asthma therapy, as underlined in worldwide guidelines. (4)

Asthma can be categorised as mild, moderate, or severe depending on the amount of treatment needed to keep symptoms and exacerbations under control (1). An estimated 50% to 75% of asthma patients have mild asthma(5), which is well-controlled with step 1 or step 2 medication. (1)

To maintain symptom management, prevent exacerbations, and minimize drug expenditures and adverse effects, the suggested course of treatment is stepwise. If patients are to receive treatment in line with their level of asthma control, which is typically measured by frequency and severity of symptoms, restriction of daily activities, use of rescue inhalers, and lung function, regular clinic visits, self-monitoring, and an asthma action plan are important. (6)

The aim of the this study was to compare the relative cost-effectiveness of Triple therapy and Dual therapy in adults and adolescents with moderate to severe asthma.

METHODOLOGY

Study Design

A hospital-based prospective observational comparative study in the department of Pulmonology, Owaisi Hospital and Research centre, Hyderabad was conducted on 80 Asthma patients for a period of six months. Patients with the following criteria were allowed to participate in this study: 1) Pts. with asthma. 2) Pts. in the Outpatient department. 3) Pts. of both genders (male and female) above 20 years. 4) Pts. who are

prescribed any one of the drug combinations 5) Pts, who are willing to give their informed consent to participate in the study. 6) Patients with comorbidities (HTN, DM, Hypothyroidism, OSA). Patients with the following criteria were excluded: 1) Patients who are not willing to participate in the study. 2) Pregnant women are excluded. 3) Patients below 21yrs and above 80yrs are excluded. 3) Patients receiving intensive care for asthma 4) Patients without Asthma. 5) Patients with COPD 6) Patients who are Tobacco smokers 7) Patients with a H/O Pulmonary Koch 8) Patients with a H/O Bronchiectasis. A complete history of the patients, laboratory investigations, treatment chart were extracted from their medical records and documented form. This study was approved by the Institutional Review Board (IRB) of Deccan College of Medical Sciences with IRB project No. 2022/35/004.

Study Outcomes

Our study outcomes are the post FEV1 and PEFR, MAQLQ and ACT score, the Cost difference of Triple and Dual therapy

Data Collection

Demographic details and the medical history of the patients was collected from patients. Data that was collected included patients age, gender, occupation, past medication history, personal history, allergies and exacerbation history. Post FEV1 and PEFR values were also obtained.

The Asthma Control Test (ACT) and Mini Asthma Quality of Life Questionnaire (MAQLQ) was administered to all the subjects in presence of experienced pulmonologists during two subsequent visits, at baseline and after 2 weeks for MAQLQ and 4 weeks for ACT to compare dual and triple therapy groups.

The evaluation of the relative pharmacoeconomic performance of the two different drug combinations (Triple therapy and Dual Therapy) was done by obtaining cost data during the subsequent visits of the subject for a period of two months.

Asthma Control Test (ACT):

ACT assesses the frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control. It consists of 5 items, with a 4-week recall (on symptoms and daily functioning). The scores range from 5 (poor control of asthma) to 25 (complete control of asthma), with higher scores reflecting greater asthma control. An ACT score >19 indicates well-controlled asthma. (7)

Mini Asthma Quality Of Life Questionnaire (MAQLQ):

It is used to measure the functional impairments that are most troublesome to adults (17-80 years) as a result of their asthma.

This instrument has 15 questions in the same domains as the original AQLQ (symptoms, activities, emotions and environment). The overall MAQLQ score is the mean of all 15 responses and the individual domain scores are the means of the items in those domains. (8)

Statistical Analysis

Data is presented as median with range, or as mean with standard deviation. Results of the ACT was presented as total questionnaire score and MAQLQ was presented as the mean for all answers.

Tests of statistical significance (t-test and Mann Whitney test) was used in the analysis of data using SPSS version 20. Results of Cost-effectiveness analysis was presented as cost, effectiveness and ICER where effectiveness will be presented as Asthma control obtained from ACT and quality of life obtained from MAQLQ.

RESULTS

The number of patients enrolled in the study was 80, of which 40 patients to Group-A (Dual therapy) and 40 patients in Group B (Triple therapy). The data also reveals a slight increase in ACT and MAQLQ scores of the patients receiving triple therapy when compared to patients receiving dual therapy. No adverse events were reported. p value less than 0.05 or 0.05 is statistically significant.

Baseline Characteristics:

Table 1 represents the baseline data of the study population

CHARACTERISTICS	DUAL THERAPY (N=40) (GROUP A)	TRIPLE THERAPY (N=40) (GROUP B)
AGE (yrs.) [MEAN ± SD]		
21-35	28.2±4.8 (32.5%)	25.5±3.94 (1.5%)
36-50	44.4±4.6 (27.5%)	43.2±4.89 (30%)
51-65	57.3±3.5 (32.5%)	57.06±4.8 (42.5%)
66-80	69±2.1 (7.5%)	74.6± 7.6 (12.5%)
GENDER, n (%)	30 (75%)	27 (67.5%)
Female Male	10 (25%)	13 (32.5%)
WEIGHT (kg) [MEAN ± SD]	66.92±15.59	68.125±10.67
HEIGHT (cm) [MEAN ± SD]	163.3±6.57	159.5±6.98
EXACERBTION HISTORY (per year) n (%)		
1	7 (17.5%)	12 (30%)
2	18 (45%)	15 (37.5%)
3	12 (30%)	9 (22.5%)
4	3 (7.5%)	4 (10%)
SpO2 n (%)		
91-100	39 (97.5%)	38 (95%)
81-90	1 (2.5%)	2 (5%)
80 and below	0	0
ALLERGIES n (%)		
Dust allergy	14 (35%)	13 (32.5%)
Perfume and smell allergy	3 (7.5%)	4 (10%)
None	23 (57.5%)	23 (57.5%)
ACT Score [MEAN ± SD]	13.7±2.22	14.025±1.94
MAQLQ Score [MEAN ± SD]	3.405±0.301	3.46±0.27

- Plus-Minus values are Mean ± SD.
- Patients in dual therapy received Salmeterol/Fluticasone Propionate (50mcg/250mcg) in single inhaler
- Patients in triple therapy received Salmeterol/Fluticasone Propionate (50mcg/250mcg and Tiotropium (9mcg) in multiple inhalers.
- Wt. is measured in kg and Ht. is measured in cm.
- Scores of ACT range from 5 (poor control) to 25 (complete control), with higher scores reflecting greater asthma control. An ACT score >19 indicates well-controlled asthma.
- Scores of MAQLQ are measured on a 7 -points scale. The overall MAQLQ score is the mean of 15 responses. Reported minimal important difference determined to be 0.5.

Efficacy Analysis:

Lung Function:

The post FEV1 and post PEFR between Dual and Triple therapy were compared, Triple therapy seemed to be superior with greater improvement in FEV1 and PEFR.

Figure 1 and 2 represents the Box plots of FEV1 and PEFR

values of dual and triple therapy groups.

Table 2 represents the mean and standard deviation of post FEV1 and PEFR of dual and triple therapy group patients.

Table 2: Lung Function of patients

PFT Parameter	Dual Therapy (GROUP-A)	Triple Therapy (GROUP-B)
FEV1	69.025±15.7	73.925±11.5
PEFR	61.95±13.65	69.725±9.29

Box Plot Comparing FEV1 Between Dual And Triple Therapy Groups

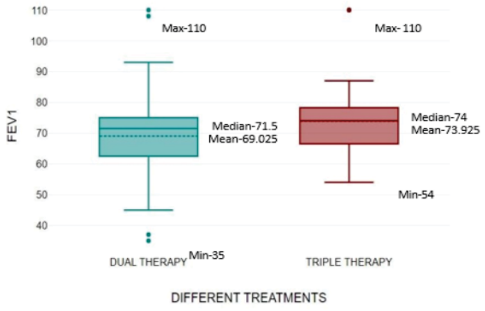

Figure 1: Box Plot Comparing FEV1 Between Dual and Triple Therapy Groups

- The solid line in the above box plot indicates median which is 71.5 in dual therapy and 74 in triple therapy while the dashed line indicates mean which is 69.025±1.57 in dual therapy and 73.925±1.15 in triple therapy.
- The above plot indicates there is significant improvement in mean FEV1 of triple therapy when compared with dual therapy.

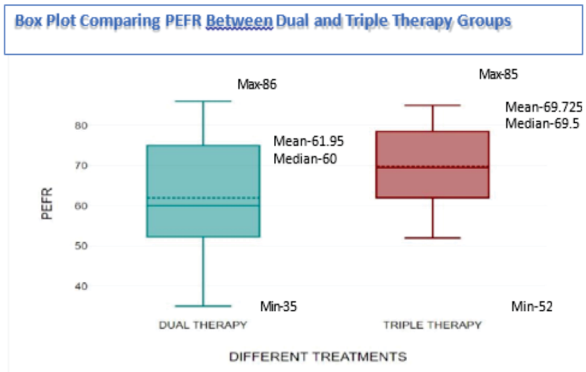

Figure 2: Box Plot Comparing PEFR Between Dual and Triple Therapy Groups

1. The solid line in the above box plot indicates median which is 60 in dual therapy and 69.5 in triple therapy while the dashed line indicates mean which is 61.95±13.65 in dual therapy and 69.725±9.29 in triple therapy.
2. The above plot indicates there is significant improvement in mean PEFR of triple therapy when compared with dual therapy.

ACT score and MAQLQ score:

The ACT score showed relevant improvements from the baseline for Group-B (triple therapy) after 4 weeks that is from 14.025±1.94 to 18.7±1.45 than Group-A (dual therapy) that is from 13.7±2.221to 17.25±2.227 as represented in Table 3 and Figure 3

The MAQLQ Score showed minimal improvements from the baseline for Group-B (triple therapy) after 2 weeks that is from 3.46±0.273to 3.715±0.268 than Group-A (dual therapy) that is from 3.405±0.301 to 3.642±0.271 as represented in Table 3 and Figure 4.

Table 3: ACT Score and MAQLQ Score

OUTCOME	DUAL THERAPY (GROUP A)	TRIPLE THERAPY (GROUP B)
TOTAL ACT SCORE Mean at baseline ± SD	13.7±2.221	14.025±1.94
Mean after 4 weeks ± SD	17.25±2.227	18.7±1.45
Mean change from baseline ± SD	3.55±0.006	4.675±-0.49
Difference Between Triple Therapy and Dual Therapy P value	1.125±-0.496 P<0.05	
TOTAL MAQLQ SCORE Mean at baseline ± SD	3.405±0.301	3.46±0.273
Mean at after 2 weeks ± SD	3.642±0.271	3.715±0.268
Mean change from baseline	0.237±-0.03	0.255±-0.005
Difference between Triple therapy and Dual therapy P value	0.018±-0.005 P<0.05	

- The data is presented as Mean ± SD
- P<0.05 is considered statistically significant
- Significant differences in the mean change from baseline in total ACT score were noted between dual and triple therapy with greater increase in total score from baseline in triple therapy group than dual therapy group.
- Minimal difference in the mean change from baseline in total MAQLQ score was noted between dual therapy and triple therapy with a little increase in total score from baseline in triple therapy group than dual therapy.

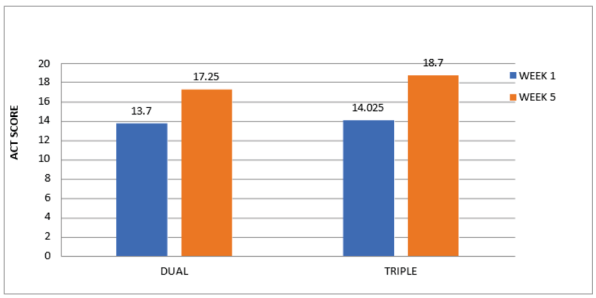

Figure 3: Graph Showing Mean Change in ACT Score

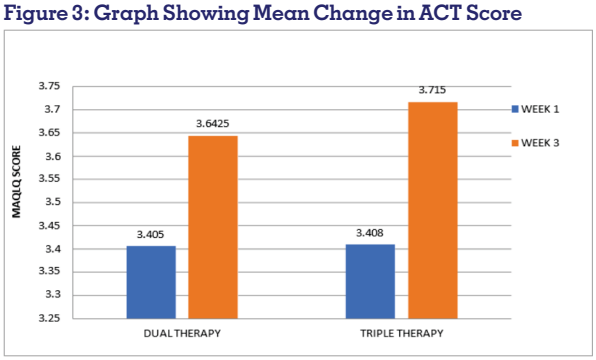

Figure 4: Graph Showing Mean Change in MAQLQ Score

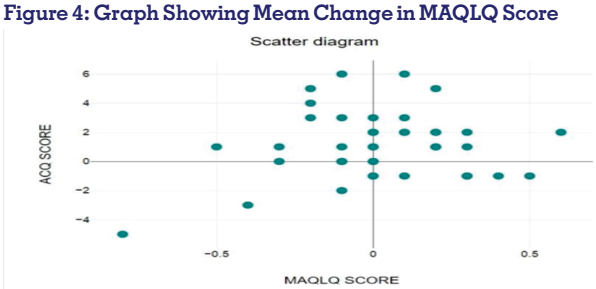

Figure 5: Graph Showing Correlation Between ACT Score and

MAQLQ Score

Correlation analysis:

The ACT score showed a significant correlation with MAQLQ Score (r = 0.0208, P<0.05). MAQLQ increased with the increasing levels of asthma control.

Figure 5 represents the correlation between ACT and MAQLQ score.

Cost Effectiveness Analysis

Direct and indirect cost:

The above data represents the Mean ± SD of cost in dual and triple therapy groups

The data includes both direct costs (consultation cost, medication cost, laboratory cost) and indirect cost (travel cost).

It indicates that the mean of consultation, laboratory and travel cost was found to be higher in dual therapy group when compared with triple therapy group while the medication cost of dual therapy group was lower than that of triple therapy group.

However, the mean of total cost of triple therapy group was found to be significantly lower than dual therapy group.

Table 4: Mean of Direct and Indirect Costs

COSTS	GROUP A (DUAL)	GROUP B (TRIPLE)
Consultation cost	295±101.4	267.5±91.6
Medication cost	1772.75±576.2	1858.50±5.13.3
Laboratory cost	1385.5±839.6	1085.62±222.8
Travel cost	477.12±276.4	453±251.3
TOTAL COST	3,930.38± 1110.8	3773.6±726.1

Incremental Cost Effectiveness Ratio of Dual And Triple therapy:

ICER = COST (A) - COST (B) (INR) ÷ Effectiveness A (%) - Effectiveness B (%)

A is Dual therapy

B is Triple therapy

ICER of dual and triple therapy with asthma control as a benefit

ICER (ACT) = (3930.38-3773.6035) ÷ (3.55-4.675)

=(156.7765)÷(-1.125)

= -139.36 INR

ICER of dual and triple therapy with QOL as a benefit

ICER (MAQLQ) = (3930.38-3773.6035) ÷ (0.2375-0.255)

= (156.7765) ÷ (-0.0175)

= -8958.656 INR

The additional cost required to achieve a better asthma control was found to be139.36 INR

The cost required to achieve clinically significant improvement in MAQLQ score or to achieve a good QOL was found to be 8958.656 INR

Negative value denotes that improvements in effectiveness were achieved at a lower overall cost with triple therapy.

DISCUSSION:

Adults with frequent exacerbations are more likely to develop persistent asthma, which increases treatment costs. As a result, reducing the rate of exacerbations, achieving asthma control, and, from an economic perspective, reducing the burden of this disease by maximizing health benefits with available resources are the main goals of asthma management. (2) One method is to track changes in trough forced expiratory volume in one second (FEV1), asthma-related QOL, and asthma control (as measured by the ACT) and (AQLQ) or MAQLQ) and (FEV1 [measured in liters]). ICERs must also be evaluated in terms of the relative importance of each improvement when compared to alternative treatments. (1) Current recommendations state that add-on tiotropium can be considered as an "alternative controller choice" at step 4 and as a "recommended add-on treatment" at step 5 for adolescents and adults (over the age of 12) with a history of exacerbations. (2) The findings of our study add to the body of research supporting the use of LAMA (Tiotropium) as a treatment option for adults with moderate to severe asthma who are adding other treatments step by step. In their study, Eckard et al. confirm that the addition of tiotropium results in appreciable improvements in lung function. (9) We compared the post FEV1 and PEFR of patients receiving dual therapy (LABA/ICS) with those receiving triple therapy (LAMA+LABA/ICS), and the results showed that triple therapy improved lung function more effectively than dual therapy. Our findings are consistent with earlier research Jefferson et al. using Markov model found that triple therapy in patients with moderate to severe asthma was cost effective. (10) Our findings showed that adding LAMA (Tiotropium) to the LABA/ICS combination (Salmeterol/fluticasone propionate) significantly improved lung function and health-related quality of life and asthma control when compared to using only LABA/ICS (Salmeterol/fluticasone propionate). According to Rosenberg et al., triple therapy was significantly associated with fewer severe asthma exacerbations and mild changes in asthma management when compared to dual therapy. There were no discernible differences in death or quality of life between triple and dual therapy. (11) The symptom control in asthma was assessed by the ACT score, which indicated that triple therapy had clinically meaningfuland statistically significant improvements in asthma control compared to the dual therapy group. After 4 weeks, the triple therapy group showed a greater increase in ACT score than dual therapy. The health-related quality of life was measured using MAQLQ. Our results indicated that there was a minimal mean change in MAQLQ score from the baseline for patients receiving triple therapy (0.255-0.005) in comparison to dual therapy (0.237-0.03) MAQLQ score after 2 weeks. Furthermore, a correlation analysis was performed and a correlation was determined between ACT scores and MAQLQ scores, which means that the ACT score showed a significant correlation with the MAQLQ score (r = 0.0208, P 0.05). The MAQLQ increased with the increasing level of asthma control. The results of Tesfalidet Gebremeskel Zeru et al. showed that the quality of life is thought to be directly and strongly related to asthma control. (12) For cost effectiveness analysis, ICER was determined. The results indicated that the additional cost required to achieve better asthma control was 139.36 INR. The cost of achieving a clinically significant improvement in MAQLQ score or a high quality of life was found to be 8958.656 INR, whereas the negative value shows that improvements in effectiveness were obtained with triple therapy at a lower overall cost.

CONCLUSION

The triple therapy, consisting of LAMA (tiotropium bromide) and LABA/ICS (salmeterol/fluticasone propionate), significantly improves lung function in patients with asthma symptoms who also take LABA/ICS, according to the findings of this study. The ACT shows a significant improvement in asthma control between patients receiving triple therapy and those receiving dual therapy. The study supported the advantages of triple therapy for symptomatic patients with airflow obstruction over dual therapy. In conclusion, there are very few advantages to having a high quality of life. These results suggest that triple therapy is more cost-effective than dual therapy for treating patients with moderate to severe asthma who still have symptoms despite taking their current medications.

Limitations In This Study:

- Our study has certain limitations

- Firstly, we did not consider exacerbation rate as an outcome because of short duration of our study.
- Lack of spirometry data to calculate the change in FEV1.
- There are very smaller number of assessments in the literature to contrast the research's findings.

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