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A study on the safety profile and clinical outcomes in patients using tulobuterol transdermal patch as an add on therapy in stable chronic obstructive pulmonary disease

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ABSTRACT

Background: Tulobuterol Transdermal Drug Delivery (TTD) may be beneficial in COPD management. We aimed to study the effect of adding TTD to Triple Inhalation therapy (TI).
Materials and Methods: Participants on TTD and TI (TTD-TI cohort) and, TI only (TI cohort) were identified at the out-patient pharmacy counter. There was no loss to follow-up from 35 participants each enrolled in the cohorts. They were assessed with Modified British Medical Research Council questionnaire (modified Medical Research Council), COPD Control Questionnaire (CCQ) and COPD Assessment Test (CAT). The latter two were repeated at the end of six months. The change in score were compared with Mann-Whitney-U test.
Results: Mean age of participants in years was 63.4 and 65.7; 31% and 20% were females and rest were males in TTD-TI and TI cohorts respectively. All of them had modified Medical Research Council grade 2 or above. CCQ and CAT scores were comparable at baseline. Change in both CCQ and CAT scores were statistically significant between the cohorts ($p<0.001$). Median (minimum, maximum) change in CCQ score were -0.6(-2.8, 0) in TTD-TI cohort and 0.3(-2 to 1.2) in TI cohort. Median (minimum, maximum) change in CAT score were -4(-16, -2) in TTD-TI cohort and 2(-7 to 7) in TI cohort. All of the participants in TTD-TI cohort and, 5(14.3%) and 7(20%) participants improved in TI cohort by CCQ and CAT score respectively.
Conclusions: There would be a subjective improvement with addition of tulobuterol transdermal patch on to triple inhalation therapy for older persons with COPD.

1. Introduction

India is affected more than other countries by Chronic Obstructive Pulmonary Disease (COPD). In India, Disability Adjusted Life Years (DALYs) per case of COPD was 1.7 times the global average in 2016.[1] There is no cure for COPD and it needs to managed by pharmacological treatment, smoking cessation support, regular exercise and, vaccines to prevent pneumonia.[2] Pharmacological treatment can improve health status, exercise tolerance and thus quality of life of COPD patients.[3] Triple therapy with inhaled corticosteroid (ICS), long acting beta 2 agonist (LABA) and long acting muscarinic antagonist (LAMA) is effective in preventing exacerbation in COPD.[4]

Most of the patients make technical errors in using inhalers even after training.[5] An ideal inhaler shall be independent of hand-mouth coordination, shall have easy technique and, deposit reliable dose in lower airways at low

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inspiratory flow. None of the devices for inhalation therapy satisfy all the criteria.[6] In this context, tulobuterol was the first beta-2 agonist which became available as a transdermal drug delivery system.[7]

In transdermal drug delivery of Tulobuterol, 80% to 90% of the drug gets absorbed with a lag time of four hours and peak concentration in blood reaching at nine to twelve hours.[8] Tulobuterol transdermal patch could be timed to coincide peak concentration in blood and morning dip in respiratory function.[7] Morning is the time at which COPD patients are affected most because,[9] respiratory function is at its lowest.[10] Transdermal drug delivery would be an option to treat patients with doubtful adherence to inhaled therapy.[11] Transdermal drug delivery is devoid of technical sophistication which patient must learn to use inhalers appropriately.[12]

We came across prescriptions of triple inhalation therapy and transdermal tulobuterol patch. There may an intuitive relevance to this practice though not in any standard guidelines. In this context, we planned to study the effect of adding on transdermal tulobuterol treatment to triple inhalation therapy.

2. Materials and Methods

2.1. Study design, setting and period

This was a prospective cohort study with six months follow-up period conducted in Pushpagiri Institute of Medical Sciences and Research Centre,Tiruvalla during the year 2020.

2.2. Study participants

The participants on Tulobuterol Transdermal Drug Delivery with Triple Inhalation Therapy (TTD-TI) were newly started on Tulobuterol 2mg patch and on triple inhalation therapy (ICS/LABA/LAMA). The other cohort of participants were on Triple Inhalation Therapy (TI) but not prescribed Tulobuterol patch. Follow up of participants were planned to be terminated if they crossed over during the next six months however, none of them did cross over. The participants had to be adults with stable COPD to participate in the study.

2.3. Sample size

A pilot study was conduct with eight patients each and mean change in CAT score was calculated after two months period. The difference between means in the two groups was 2.3 and standard deviation was 3.4. Sample size calculated was thirty five each in the cohorts with $\propto$ error of five percent and power of eighty percent.

2.4. Sampling technique

Participants were approached to ascertain eligibility when transdermal tulobuterol patch prescriptions were produced at the out-patient pharmacy counter. Participant for the comparison cohort was approached when consecutive prescription with triple inhalation therapy without transdermal tulobuterol patch was produced.

2.5. Study tool

The data form was administered by investigators which included basic demographic details, Modified British Medical Research Council questionnaire, COPD Control Questionnaire (CCQ) and COPD Assessment Test (CAT). (3) CCQ and CAT were repeated after 6 months from enrolment.

2.6. Ethical considerations

Institutional Ethics Committee approved the study protocol vide letter number PCP/E3/01B/2019. Participation was voluntary and written informed consent was obtained. Privacy and confidentiality are maintained.

2.7. Analysis

Data was analysed with EZR ('Easy R') software developed by Jichi Medical University Saitama Medical Centre, Saitama, Japan.[13] Age was summarised as mean and standard deviation. Gender and modified Medical Council Research grades were summarised as frequency and proportion. CAT and CCQ scores were summarised as median and range. Change in CAT and CCQ scores in both groups were compared with Mann Whitney U test. Negative difference in scores represent improvement and positive difference represent deterioration.

3. Results

We enrolled 35 participants each into the cohort of Tulobuterol Transdermal Drug Delivery with Triple Inhalation Therapy (TTD-TI) and, cohort of Triple Inhalation Therapy (TI). These cohorts were assessed at enrolment and after 6 months. There was no loss to follow up.

The mean age of study participants was 63.4 years and 65.7 years in TTD-TI and TI cohorts respectively. Nearly one-third and one-fifth were females in the TTD-TI and TIP cohorts respectively and the rest were males. (Table 1)

None of the participants had grade 1 modified Medical Research Council at the time of enrolment. Table 2 shows that 18(51%) and 20(57%) had grade 2 in TTD-TI and TI cohorts respectively, 4(11%) had grade 4 modified Medical Research Council in TTD-TI cohort. Rest of them had grade 3 modified Medical Research Council. Median CCQ score was 3.7 and 3.4 in TTD-TI and TI cohorts respectively.

Median of CAT score was 27 in both cohorts.

After six months, CCQ and CAT assessment were repeated and the difference from baseline was calculated. In the TTD-TI cohort, there was an improvement with median of -0.6 (range from -2.8 to 0). CAT scores showed improvement by median of -4 (range from -16 to -2). None of them deteriorated in TTD-TI cohort. In TI cohort, there was predominantly deterioration in CCQ scoring with median 0.3 (range from -2.0 to 1.2) and CAT scoring with median 2 (range from -7 to 7). Only five and seven participants improved by CCQ and CAT scores respectively in TI cohort. The change in CCQ scores and CAT score in the cohorts were represented by box plot and compared by Mann-Whitney-U test. The improvement in CCQ and CAT in the cohort of TTD-TI was statistically significant (p<0.001) compared to TI cohort (Figures 1 and 2). Two participants (5.7%) reported local irritation with tulobuterol patch.

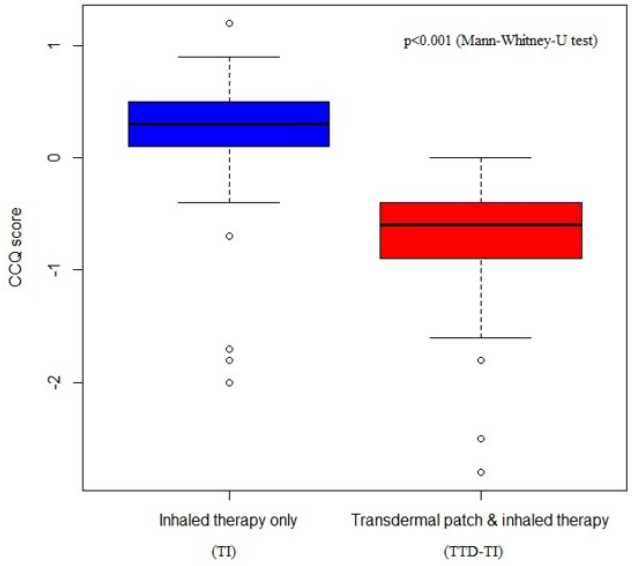

Fig. 1: Change in COPD control questionnaire (CCQ) score after 6 month of observation

4. Discussion

Transdermal tulobuterol patch had been in use worldwide for treatment for more than two decades.[7] Ichikawa and Sagiura had reported review of literature pertaining to use of transdermal drug delivery of tulobuterol.[14] They quoted Abe et al., and suggested that tulobuterol patch is beneficial when added on to tiotropium, it was comparable to inhalation of bet 2 agonist as reported by Fukuchi et al, better than oral theophylline according to Minami et al and, higher adherence compared to inhalers as reported by Mochizuki et al.[14]

Inhaled corticosteroid is added on to the mainstay of dual therapy with bronchodilators (LAMA/LABA)

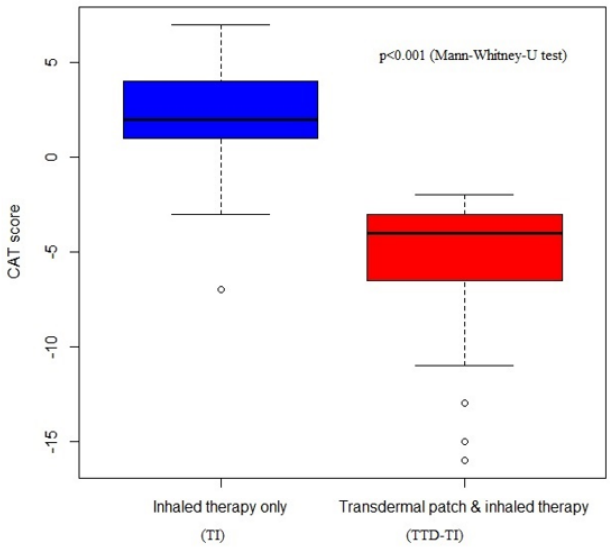

Fig. 2: Change in COPD assessment test (CAT score) after 6 months of observation

after exacerbation.[15] In our study, a large proportion of participants had modified Medical research Council grade 2 which may be a cause of concern. Many COPD patients would be continued on triple therapy though they no longer need triple therapy.[16]

In our study, we found that tulobuterol transdermal drug delivery was beneficial as add on therapy to triple inhalation therapy in terms of improvement CCQ and CAT scores. Mean age of the study participants was above 60 years in our study. Older patients may not master the technique of using inhalers resulting inadequate drug delivery.[7] This would explain the improvement in the cohort with additional therapy of tulobuterol patch. Importance of our study is in the documentation of the practice of prescription addition of transdermal tulobuterol to triple inhalation therapy. It has a pragmatic relevance considering the technical difficulties of inhaler use. However, cost effectiveness and probable overdosing of beta 2 agonist is not considered in the approach. Average annual out of pocket expenditure for COPD treatment is about fifty thousand Indian Rupees in private sector.[17]

The study has limitations which restricts interpretation and generalization of the findings. Investigators were not blinded and the assessment tools are prone to reporting bias. Confounding factors were not adjusted in assessing the outcome. The findings of these study need to be substantiated with a rigorous study design which also address cost effectiveness and adverse drug reactions of beta 2 agonists.

Table 1: Demographic profile of study participants

Variables and categories			Cohorts	
			TTD-TI	TI
1	Age†		63.4, 10.2	65.7, 10.5
2	Gender‡	Female	11 (31.4%)	7 (20%)
		Male	24 (68.6%)	28 (80%)

TTD-TI – Tulobuterol Transdermal Drug Delivery with Triple Inhalation Therapy TI – Triple Inhalation Therapy †Mean and standard deviation; ‡Frequency and proportion

Table 2: Assessment of study participants at enrolment

Variables and categories			Cohorts	
			TTD-TI	TI
1	Modified Medical Research Council	Grade 2	18 (51.4%)	20 (57.1%)
		Grade 3	13 (37.1%)	15 (42.9%)
		Grade 4	4 (11.4%)	0 (0%)
2	CCQ		3.7 (2.2 to 5.5)	3.4 (2.7 to 4.5)
3	CAT		27 (18 to 39)	27 (20 to 35)

TTD-TI – Tulobuterol Transdermal Drug Delivery with Triple Inhalation Therapy TI – Triple Inhalation Therapy CCQ – COPD Control Questionnaire CAT – COPD Assessment Test †Frequency and proportion; ‡Median (Minimum, Maximum)

5. Conclusions

Add on therapy with tulobuterol transdermal patch on to triple inhalation therapy is in practice. There would be a subjective improvement in older persons with stable COPD with this intervention. The objective evidence for this intuitive practice is yet to be explored.

6. Acknowledgements

None.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

8. Source of Funding

None.

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