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RATIONALE OF DERIPHYLLINE IN COPD PATIENTS AMONG URBAN POPULATION

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ABSTRACT

COPD is one of most common chronic disease affecting 0.5-1% of world's population that predominately in women. Emotional stress, air pollution, passive smoking and food habits play an important role in COPD. This present study is to ascertain rationality with of fixed dose combination-Deriphylline (theophylline and etophylline) SR in COPD patients after classifying according to GOLD guidelines in urban population. Patients were included in this study after receiving the patient consent form according to the ethical committee. Measurements such as Borg dyspnoea scale, St. George's respiratory questionnaire, Medical research council (MRC) breathlessness scale. Clinical evidence supports the effectiveness of multiple drug therapies, however in the absence of long term data. The purpose of this research is to provide an overview of different clinical approaches and highlight some of the important issues surrounding the choice of drugs to be used in COPD. The purpose of this research is to provide comprehensive disease management strategy, which included a patient education session, a self-treatment plan for exacerbations and a monthly follow-up, is associated with a lower hospitalization rate. This study is also designed to alleviate symptoms; to prevent exacerbations; to preserve optimal lung function; to improve activities of daily living, quality of life and survival; with minimal adverse effects from treatment.

KEYWORDS: COPD, Deriphylline, GOLD Guidelines.

INTRODUCTION

At present, COPD is the second most fundamental noninfectious malady on the planet, acquiring on some place the scope of 2.75 million passing yearly and overall mortality is foreseen to drastically increment by 2030. The expanding weight of COPD has enabled inquire about into novel treatment approaches (numbering new pharmacotherapies) and redesigned organization techniques.[5] An overall participation has been met, the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which searches for, among different goals, to give demonstrate based recommendations to an organized COPD organization procedure. In 2001, the GOLD chamber conveyed rules for the discovering, organization and balancing activity of COPD, including recommendations for drug store method of reasoning administration.[45]

The GOLD rules give an organizing structure to the request of the ailment earnestness in light of a blend of spirometric lung work and manifestations. In a departure from earlier principles, the GOLD tenets recognize a stage 0, which consolidates patients who won't not have reactions and still have standard lung work, yet are at threat of getting COPD by brilliance of tobacco smoking or certain normal exposures. Past stage 0, COPD is distinguished by the nearness of wind current obstacle as essentially characterized by a lessening in the constrained expiratory proportion (FEV1/FVC) underneath 70%. The seriousness of COPD is characterized in four phases gentle, direct, extreme and exceptionally extreme as indicated by the seriousness of weakness in the FEV1.[5]

The GOLD guidelines recommend a stepwise approach to manage disease organization, with bronchodilators being the foundation of treatment. Short-acting bronchodilators are recommended at to start with, as required, in smooth illness. As the disease progresses, standard upkeep treatment is appeared; for this, the principles observe that long-acting bronchodilators are more worthwhile. In more extraordinary infirmity, poly-medicate store gets the opportunity to be particularly typical and a trial of took in corticosteroids is recommended.[7]

DERIPHYLLIN IN COPD

In the significant rules for the treatment of COPD, Deriphylline is consigned to a third line bronchodilator after breathed in anticholinergics and β2 agonists. By the by, it is perceived that theophylline is a valuable treatment in patients with serious COPD as its withdrawal

prompts critical clinical intensifying of the ailment. Numerous more established clinicians have been persuaded by its clinical incentive in extreme sickness.[5]

Deriphylline was utilized as a bronchodilator in the treatment of aviation route illness in any case, to accomplish huge bronchodilatation equivalent with that of a β2 agonist, moderately high plasma fixations are required (10–20 mg/l). Deriphylline unwinds human aviation route smooth muscle in vitro through hindrance of phosphodiesterases (PDE), proteins that separate cyclic nucleotides in the cell bringing about expanded cyclic AMP focuses. Lamentably, at measurements of Deriphylline that repress PDE, symptoms that are additionally because of PDE restraint are basic such a large number of patients are not ready to endure Deriphylline at these "restorative" fixations.[5]

The bronchodilators starting at now available for use in COPD can be broadly requested into three classes: anticholinergics, β2 - sympathomimetic agonists and methylxanthines. Each one of the three have exhibited fruitful in upgrading lung work in patients with COPD, despite the way that the slim therapeutic extent of methyl-xanthines and their reasonably frail bronchodilator affect make them a less engaging starting helpful decision.[45]

RATIONAL USE OF DERIPHYLLIN IN COPD

Lung work in COPD is made by fundamental narrowing of the flight courses, united with the effects of cholinergic vagal bronchoconstrictive tone and decreased lung adaptable recoil. Bronchodilators upgrade the wind current imprisonment found in patients with COPD by conveying aeronautics course smooth-muscle loosening up, in spite of the way that β2 - agonists and anticholinergics finish this effect through different parts.[7]

Anticholinergic bronchodilators (particularly, tiotropium) convey unwinding of flight course smooth muscle through hostility of acetylcholine at M3-muscarinic receptors on avionics course smooth muscle, while β2-agonists start bronchodilation through induction of 2-receptors, prompting a development in cyclic adenosine monophosphate (as in like manner occurs with phosphodiesterase inhibitors, for instance, oral methylxanthines).[45]

The mechanical differentiations between these two classes of took in bronchodilator are reflected in the relative utility of each for the organization of COPD. Short-acting β2-agonists, for instance, albuterol, have an all the more brisk onset yet shorter traverse of movement than anticholinergics and thusly are generally suggested as a "secure" answer for

mitigate exceptional bronchospasm. Taken in anticholinergic drugs, for instance, ipratropium, have a slower onset and to some degree longer length of action. One after effect of the qualifications in their techniques for action is that the effects of joining anticholinergic and β2-agonist bronchodilators are included substance, giving more critical viability than either administrator alone.[45]

The two classes of master also differentiate in their nonbronchodilator impacts. For example, muscarinic receptors accept a section in overseeing natural liquid release, regardless of the way that the effect of antimuscarinics on sputum volume is variable.[6] Viral infections increase cho-linergic tone, an effect that may be direct killed by anticholinergics. Ex vivo, long-acting β2-agonists have shown cell impacts past those connected on bronchial smooth muscle, including consequences for mucociliary transport and neutrophils. These nonbronchodilator effects may give addi-tional benefits, regardless of the way that the significance (accepting any) of these effects to their clinical reasonability in COPD is starting at now dark.

GOLD TREATMENT GOALS

The GOLD rules indicate the accompanying handy targets that characterize successful sickness administration: to alleviate side effects, enhance practice resilience, anticipate and treat intensifications, avoid and treat entanglements, enhance wellbeing status, lessen mortality and forestall infection movement. The GOLD rules likewise take note of that these destinations ought to be accomplished with at least reactions.

While forestalling illness movement, averting and treating intricacies and decreasing mortality are essential objectives of treatment, there have up til now been no distributed reviews that have explored the adequacy of long-acting bronchodilators as for these results. We have, in this way, restricted our review to the impacts of these medicines on easing manifestations, expanding exercise resilience, counteracting intensifications and enhancing wellbeing status. We have likewise checked on the impacts on lung work information since, albeit enhanced lung capacity is not unequivocally expressed by the GOLD as a goal of treatment, it is a key measure of bronchodilator adequacy.[45]

MATERIALS AND METHODS

Study site was department of medicine, ESIC Hospital, Ayanavaram, study population was 50 COPD patients the study period was 9months Treatment duration was 6 months study design is Prospective open label trial.

The outcomes were measured by evaluating the adverse events, vital sign reporting and concomitant medications, Trough FEV1, FVC and FEV1/ FVC ratio, health status as determined using the St George's Respiratory Questionnaire (SGRQ).

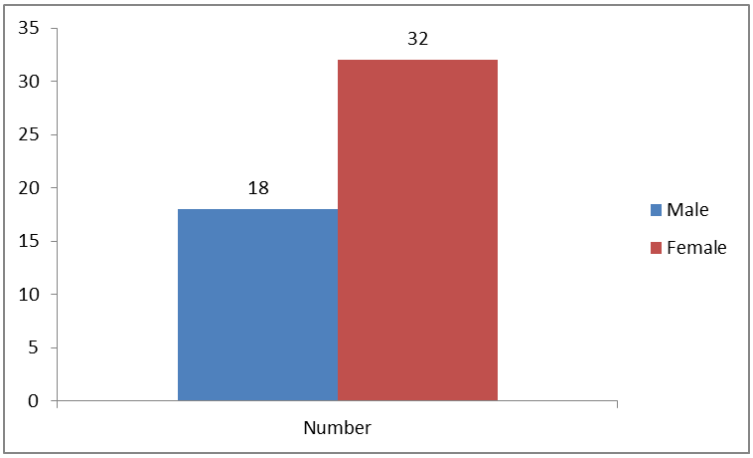
Any subject with COPD who has an indication to receive deriphylline retard 150mg once daily at the discretion of the investigator and has met all the inclusion criteria, may take part in the study. Patients enrolled satisfied the Inclusion criteria which was either gender, between the ages of 40 to 70 years, COPD Patients (inpatients), patients with moderate to severe COPD diagnosed as per GOLD guidelines, FEV1 < 50% of the one predicted at treatment start and/or, history of repetitive COPD exacerbations and/or, patient remains symptomatic despite regular bronchodilator therapy.

The Exclusion criteria for this study were pregnant and breast feeding woman, patients with glaucoma, ulcers, overactive thyroid gland, hypertension, patients with liver, kidney, heart disease, hypersensitivity to deriphylline or any of its excipients and serious illness/disease, not adequately controlled, or with a potential to interfere with the patients' participation in the present study, according to the investigator/physician's judgment. Meta-analysis is the process of combining study results that can be used to draw conclusions about therapeutic effectiveness or to plan new studies. Hence the important design and statistical issues of this process are reviewed. The design issues include protocol development, objectives, literature search, publication bias, measures of study outcomes and quality of the data. The statistical issues include consistency (homogeneity) of study outcomes and techniques for pooling results from several studies. Guidelines are provided to assess the quality of meta-analyses based. As an explicit strategy for summarizing results, meta-analysis may help clinicians and researchers better understand the findings of clinical studies.

RESULTS AND DISCUSSION

TABLE 1 FIGURE 1- GENDER WISE DISTRIBUTION.

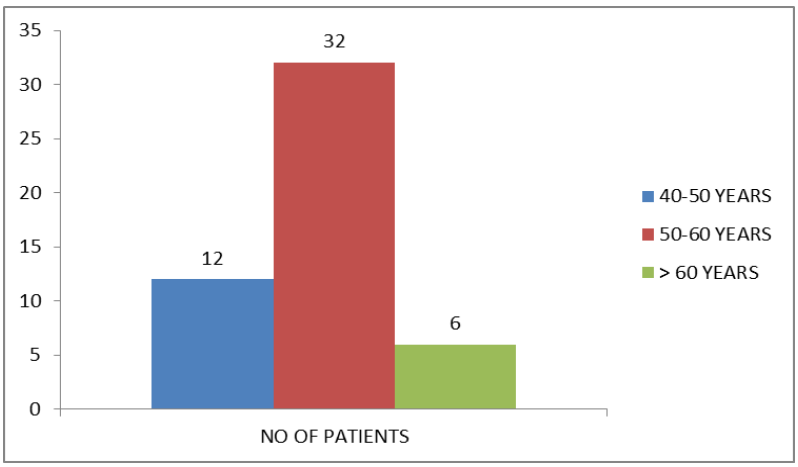
GENDER	NUMBER	%
Male	18	36
Female	32	64
Total	50	100



As per the study protocol we enrolled 68 patients. After classifying the patients according to GOLD guidelines, the dropouts were 18 patients. Among which female population was 12 and male patients were 6. 50 patients were studied throughout the research work. Among the 50 patients as shown in the table 1 and figure 1, male population was 36% and female population was 64%.

TABLE 2: FIGURE 2- AGE WISE DISTRIBUTION.

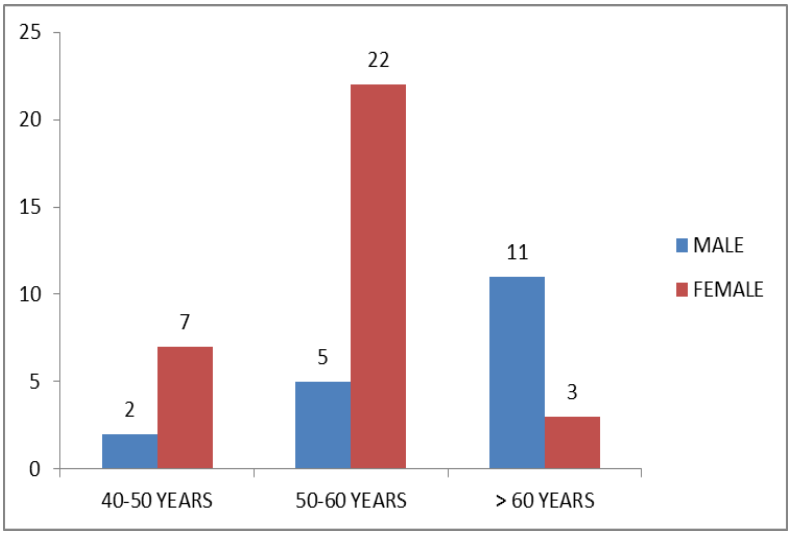
AGE	NO OF PATIENTS	%
40-50 YEARS	12	24
50-60 YEARS	32	64
>60 YEARS	6	12
Total	50	100



After gender classification, age wise distribution was done. In this, 50-60 years had more predominant clinical symptoms when compared with other groups.

TABLE 3: FIGURE 3- AGE WISE DISTRIBUTION IN GENDER.

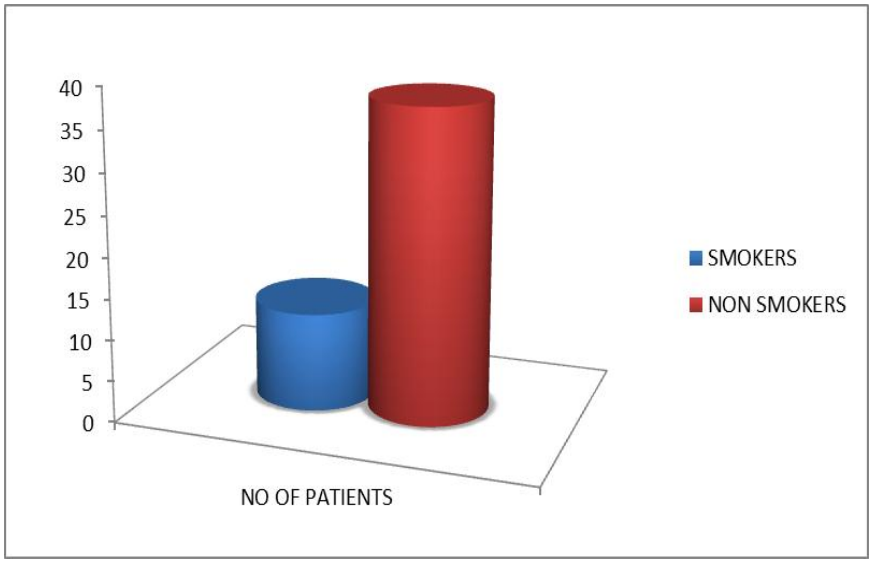
AGE	MALE	FEMALE
40-50 YEARS	2	7
50-60 YEARS	5	22
> 60 YEARS	11	3
Total	18	32



The intergroup analysis shows that predominantly female population has more number of cases in 40-50years and 50-60 years. While >60 years male population had more cases when compared with female population. These changes can be attributed to the physiological changes to age advancement.

TABLE 4: FIGURE 4- DISTRIBUTION OF SMOKERS IN THE STUDY POPULATION.

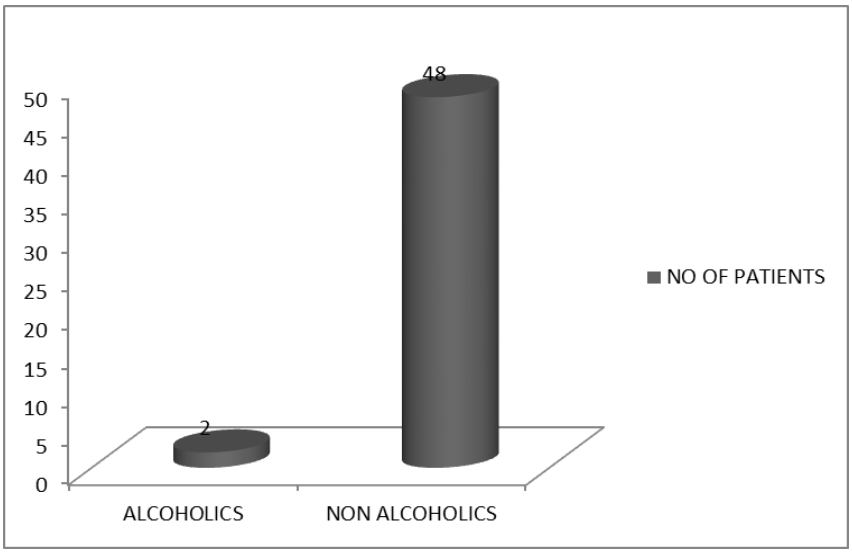
PARAMETERS	NO OF PATIENTS	%
SMOKERS	12	24
NON SMOKERS	38	76



24% of the populations were smokers and 76% of the populations were nonsmokers. Among 18 male population only 12 were smokers. Other were nonsmokers as shown in table no:3 and figure no:3.

TABLE 5: FIGURE 5- DISTRIBUTION OF ALCOHOLICS IN THE STUDY POPULATION.

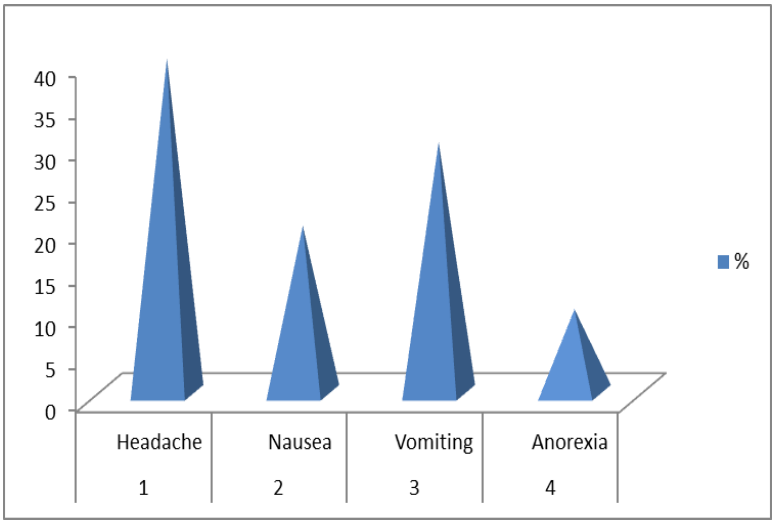
PARAMETERS	NO OF PATIENTS	%
ALCOHOLICS	2	4
NON ALCOHOLICS	48	96



The table no: 5 and figure no:5 represents alcoholics were 4% of the population and were male. Rest of the populations were non alcoholics.

TABLE 6: FIGURE 6 -ADVERSE EFFECTS OBSERVED IN THE GROUP.

S NO	ADVERSE EFFECTS	%
1	Headache	40
2	Nausea	20
3	Vomiting	30
4	Anorexia	10



The table 6 and figure 6 represents the side effects that were observed during the study period predominantly nausea and vomiting were observed which was 20% and 30% respectively. Headache and Anorexia were observed in 40% and 10% respectively.

TABLE 7 FIGURE 7- CHART FOR DRUG THERAPY.

GOLD STAGE	DRUG THERAPY	NO OF CASES	%
I	DERIPHYLLINE	19	38
II	DERIPHYLLINE +CEFOTAXIM/ DERIPHYLINE+ AMBROXOL/OR ALL 3 DRUGS	20	40
III	DERIPHYLLINE+ AMBROXOL+ STEROIDS	11	22

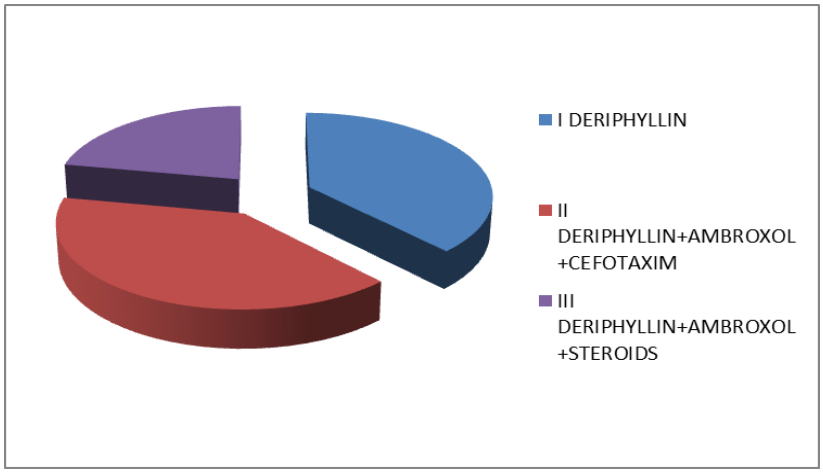


Table no: 7 and figure no: 7 exhibits the treatment given the GOLD classification of patients. 19 patients where in stage I who was prescribed only Deriphylline. 20 patients where in stage II and treated with deriphylline, cefotaxim and or ambroxol.11 patients along with stage II treatment, steroids where added in the stage III patients.

TABLE 8 - ST.GEORGE RESPIRATORY QUESTIONNAIRE BEFORE MEDICATION-AVERAGE ANSWERING OF QSTNS.

HEALTH STATUS	PART1 (Out of 8 Qstns)	PART2 (Out of 8 Qstns)
GOOD	5.5	6.5
FAIR	7	7.4
POOR	7.7	7.8

TABLE-9-AFTER MEDICATION-AVERAGE ANSWERING OF QSTNS.

HEALTH STATUS	PART 1 (Out of 8 Qstns)	PART 2 (Out of 8 Qstns)
GOOD	2.7	3.2
FAIR	5	4.8
POOR	5.9	6.3

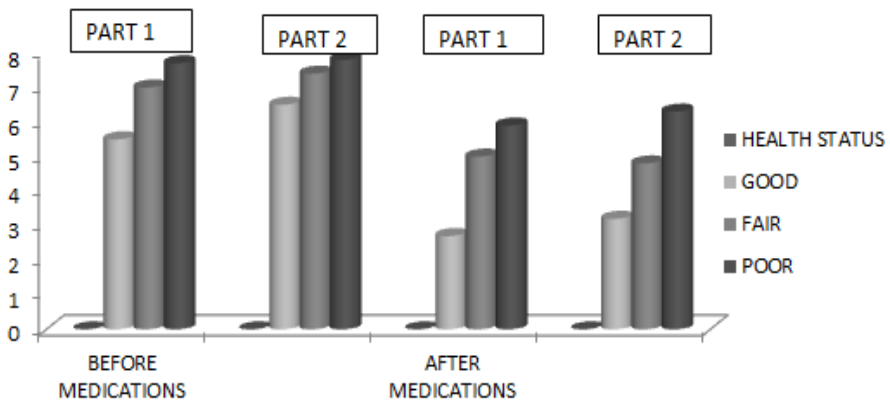


FIGURE-8- ST.GEORGE QUESTIONARE BEFOREAND AFTER MEDICATION.

Before and after the treatments patients answered St. George's questionnaire which comprises two parts of 8 questions in each part Before the treatment, according to health status the patient were asked to answer the questions in which patents with poor health before the treatment were 7.7/8,7.8/8 and after the treatment improvement was seen as 5.9/8,6.3/8 fair health status patients scored 7/8and 7.4 after the treatment 5/8 and 8/8 respectively and after the treatment 2.7/8. These slopes helped us to evaluate the patient treatment plans was effective.

TABLE 10 BREATHLESSNESS SCALE -BEFORE MEDICATION.

	MRC SCALE	BORG DYSPONEA SCALE	MODIFIED MEDICAL DYSPONEA SCALE
CATEGORY 1	2	3	1
CATEGORY 2	3	4	2
CATEGORY 3	4	5	3

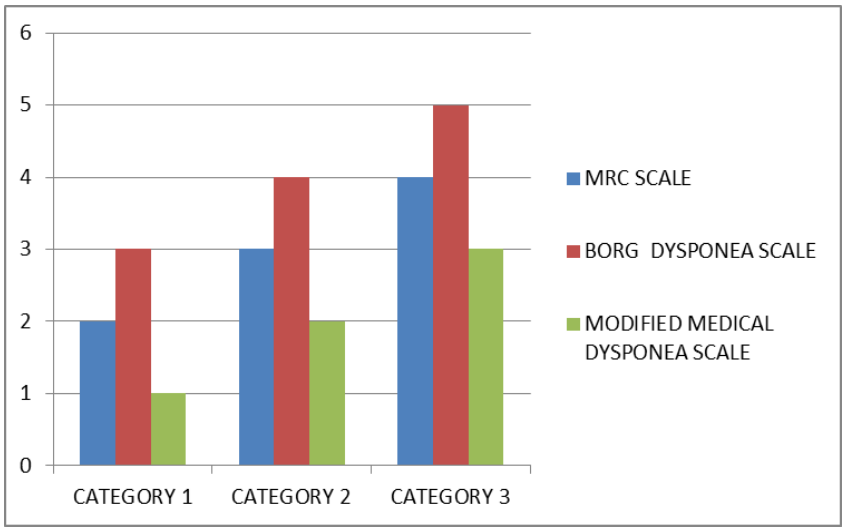


FIGURE 9- BREATHLESSNESS SCALE-BEFORE MEDICATION.

TABLE 11 BREATHLESSNESS SCALE -AFTER MEDICATION.

	MRC SCALE	BORG DYSPONEA SCALE	MODIFIED MEDICAL DYSPONEA SCALE
CATEGORY 1	1	2	0
CATEGORY 2	2	3	1
CATEGORY 3	3	4	2

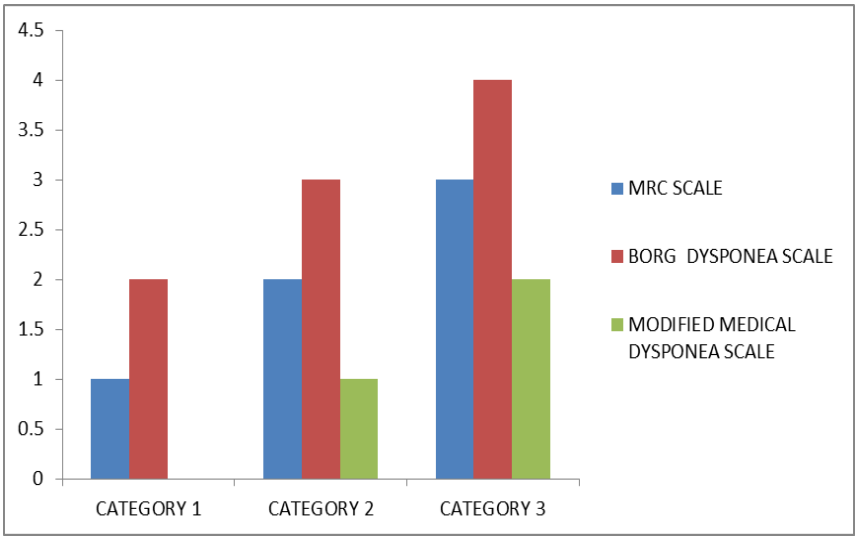


FIGURE 10- BREATHLESSNESS SCALE-AFTER MEDICATION.

Table no 10, Figure no 9, Table no 11, Figure no 10 shows the breathlessness scale before and after the treatment. This is one of the most significant scale that treatment after classifying the patients according to GOLD guidelines has minimum medications and maximum therapeutic efficacy.

TABLE -10- GOLD GUIDELINES-CLASSIFICATION AND STAGES OF COPD.

CLASSIFICATIONS	GOLD STAGE	NO OF CASES	TYPICAL AGE. YR	TYPICAL SYMPTOMS	APPROPRIATE INVESTIGATIONS	FEV1/FVC% PREDICTED	FEV1 ,%PREDICTED	DURATION	THERAPY	OTHRER TREATMENTS
AT RISK	0	0	NONE	NONE	NIONE	NONE	NONE	NONE	NONE	NONE
MILD	I	19	>35	PRODUCTIVE COUGH	SCREENING SPIROMETRY	<70	≥80	3DAYS	DERIPHYLLINE	SMOKING CESSATION
MODERATE	II	20	>50	PRODUCTIVE COUGH, REDUCED PHYSICAL ACTIVITY WITH OR WIOTHOUT EXTERNAL DYSPNEA,EPISODES OF ACUTE BRONCHITIS	SPIROMETRY BEFORE AND AFTER BRONCHO-DIALATOR	<70	<80&≥50	5 DAYS	DERIPHYLLINE, AMBROXOL, CEFOTAXIM	SMOKING CESSATION, REHABILITIVE EXERCISE
MODERATELY SEVERE	III	11	>60	PRODUCTIVE COUGH,DYSPNEA WITH MODERATE EXERTION, OCCASIONAL EXACERBATIONS	SPIROMETRY BEFORE AND AFTER BRONCHO-DIALATOR, SPUTUM AFB, CHEST X-RAY	<70	<50&≥30	5 DAYS	DERIPHYLLINE,AMBROXOL, STEROIDS	SMOKING CESSATION, RAHABILATIVEEXERCISE, SUPPLEMENTAL OXYGEN
SEVERE	IV	NONE	>70	NONE	NONE	NONE	NONE	NONE	NONE	NONE

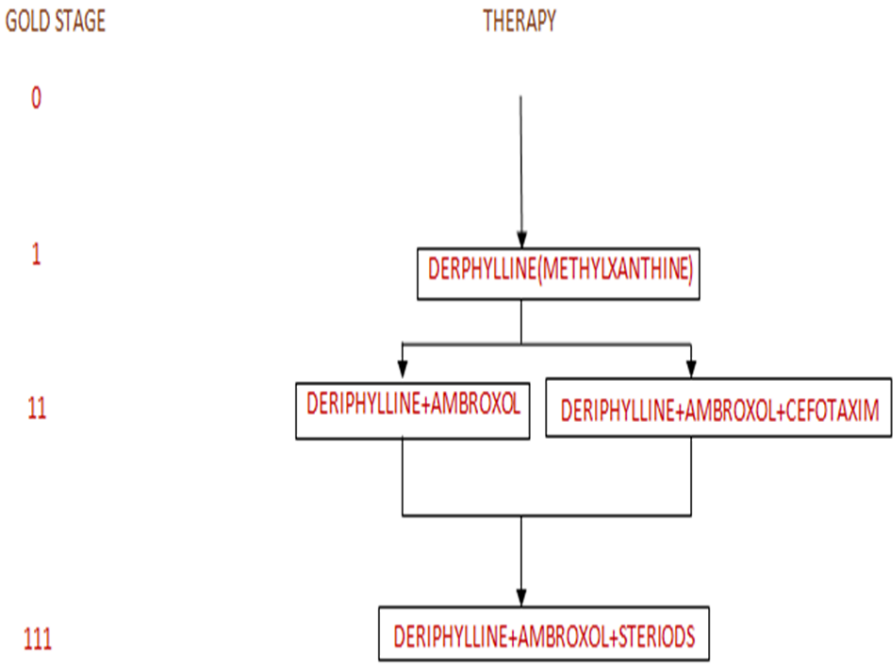


FIGURE-11: GOLD GUIDELINES CLASSIFICATION AND TREATMENT PLAN.

DISCUSSION

Throughout the entire study the bronchodilators have shown liberal improvements in lung work differentiated and fake treatment, regardless of the way that relationships are made troublesome by the immense number of end centers used. Each of the three long-acting bronchodilators make extraordinary upgrades in lung work that resemble those saw with ipratropium. These are overseen for 24 h by virtue of tiotropium and 12 h in the occurrences of salmeterol and formoterol disregarding the way that the change in FEV1 domain under the twist from 0 to 12 h with salmeterol differentiated and ipratropium was seen at just a fraction of the time focuses in one of two reviews. With long haul organization, both tiotropium and salmeterol fundamentally enhanced morning trough (pre measurements) FEV1 when contrasted and both fake treatment and ipratropium at record-breaking focuses more than 1 year.

Blend treatments seem to enhance the bronchodilator impacts of long-acting β2-agonists. The concurrent organization of salmeterol and ipratropium delivered an added substance impact on post measurements FEV1 and a mix with either theophylline or fluticasone expanded the impact of salmeterol on trough FEV1.[36]

The blend of formoterol twice day by day and ipratropium four times every day additionally enhanced morning trough FEV1 contrasted and a mix of salbutamol and ipratropium. Throughout the entire the acting bronchodilators, hence, have shown practicality over circumstances of either 12 h (salmeterol, formoterol) or 24 h (tiotropium). The primary direct relationship of different classes of long-acting bronchodilators found that salmeterol and tiotropium effectsly influenced day 1, yet zenith and ordinary FEV1 were through and through higher with tiotropium from day 15 onwards and trough FEV1 was on a very basic level higher at 24 weeks. It makes the feeling that the qualification toward the finish of the audit (24 weeks) may be normal, to some degree, to the way that the response to tiotropium was kept up, while the response to salmeterol lessened over the time course of the survey, proposing the change of tachyphylaxis.

Distinctive surveys have not displayed tachyphylaxis to the bronchodilator effect of salmeterol. The last observation may reflect the by and large shorter (12 to four months) traverse of most trials, since an extra 24-week trial exhibited that the bronchodilator sufficiency of salmeterol in regard to fake treatment reduced after some time, suggesting tachyphylaxis. Such tachyphylaxis would be solid with the decreasin bronchodilator ampleness seen in whole deal (90-day) examinations of albuterol (since both albuterol and salmeterol are fragmented agonists). Strikingly, a 12-month examination of formoterol (a full agonist) did not reveal verification of tachyphylaxis, regardless of the way that the most punctual time point assessed in this survey was 3 months after begin of study prescription, so that the probability of early onset tachyphylaxis can't be maintained a strategic distance from.

SUMMARY AND CONCLUSION

In developing countries like India, combination of slow releasing formulation of theophylline and etophylline (Deriphylline - Retard) is commonly used in the treatment of COPD. Low cost and efficacy of these methyl xanthines could be the reasons. Less awareness on safety profile and non-availability of other oral alternatives could also contribute to the usage of these drugs. In this scenario, we tried to explore the efficacy and safety profile of theophylline and etophylline combination in stable cases of COPD.

Deriphylline produces an improvement in the airway obstruction. The data drawn from this study showed that deriphylline retard was an effective drug after classifying the patient according to GOLD guidelines. On the basis of the results, we conclude that the side effects are not significant at the prescribed doses.

It has been recognized that deriphylline has an anti-inflammatory and immunomodulatory effects in COPD and asthma even at low doses (Plasma concentration 5-10 MG/L). According to the previous studies done by Villani et al., in 1997, a significant improvement in FEV1, FVC and other spirometric parameters in the β2 responders among the COPD patients treated with doxofylline 400 mg thrice a day 6 was reported. Also Marino O et al., in 1988, compared doxofylline with theophylline SR in COPD patients and concluded that the spirometric variables had improved in both treatments. Thus, it may even clear that it is preventing the progression of the disease. Furthermore, clinical trials for employing the interactions of deriphylline and corticosteroids, in asthma and COPD are the thrust area for research in future clinical practice.

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