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Assessment of Role of Corticosteroids in Respiratory Diseases

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ABSTRACT

A prospective observational study was carried out for a period of 6 months in a 450 bedded tertiary care hospital. A total of 100 patients from general medicine and cardiology departments with age group greater than 18 years were included in the present study. The aim was to assess the role of corticosteroids in respiratory diseases in a tertiary care hospital. Objectives were to determine the benefits of corticosteroids for the treatment of patients with respiratory diseases, to assess the current prescribing pattern and drug interactions associated with the use of steroids.On analyzing the data, it was found that 60% patients were prescribed with nebulization and 30.6% were prescribed with parenteral. 45% patients who were prescribed with steroids had less number of hospital stay. Potential drug interaction were identified based on their severity and 14 were found to be major. Also, interactions between steroids were identified. The role of corticosteroids in respiratory diseases are for reducing inflammation and mucus production in the airway of the lungs. Mainly corticosteroids in the form of nebulization is prescribed to the patients. The most commonly prescribed glucocorticoid is budesonide. More number of corticosteroids with shorter duration reduce the side effects, decrease the length of stay, thereby it is cost effective and faster recovery. Our study deals with the need for creating more awareness among the general practioners on following standard prescribing guidelines. This study mainly emphasise on the role of corticosteroids in respiratory diseases providing necessory information about the benefits of corticosteroids and to improve the quality of life of the patients.

INTRODUCTION

Respiratory disease

Respiratory disease is a type of disease that affects the lungs and other parts of the respiratory system. It includes asthma, Chronic Obstructive Pulmonary Disease (COPD), pulmonary fibrosis, pneumonia, and lung cancer.

There are two types of respiratory diseases: infectious and chronic. Pulmonary infections are most commonly bacterial or viral. In the viral type, a pathogen replicates inside a cell and causes a disease, such as the flu. Chronic diseases, such as asthma, are persistent and long lasting. They can relapse and the patient can go into remission, only to suffer symptoms again at a later time.

The respiratory tract is divided into upper and lower parts: the upper respiratory tract consists of the sinuses, middle ear, pharynx, epiglottis and larynx, while the lower respiratory tract consists of the structures below the larynx, the bronchi, bronchioles and alveoli .[1]

Upper respiratory tract infection

An upper respiratory tract infection is an illness caused by an acute infection, which involves the upper respiratory tract, including the nose, sinuses, pharynx or larynx. This commonly includes nasal obstruction, sore throat, tonsillitis, pharyngitis, laryngitis, sinusitis, otitis media, and the common cold. [2]

Lower respiratory tract infection

LRTI are any infections in the lungs or below the voice box. These includes pneumonia, bronchitis, tuberculosis.

Symptoms of Lower respiratory tract infection include stuffed up or a runny nose, dry cough, lowers fever, mild sore throat, dull headache.

Corticosteroids in respiratory disease

Corticosteroids are steroid hormones that are produced in the adrenal gland. Mainly corticosteroids are classified into glucocorticoids and mineralocorticoids. They are involved in a wide range of physiological processes, including stress response, immune response and

regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels and behaviour.[3]

Mechanism of action

Corticosteroids have many cell- and tissue-specific anti inflammatory effects that have been extensively described. The corticosteroid enters the cell cytoplasm and binds with the inactive glucocorticoid receptor complex.

Consequently, the activated glucocorticoid receptor binds to DNA at the glucocorticoid response element sequence and promotes synthesis of anti-inflammatory proteins (transactivation) and inhibits transcription and synthesis of many proinflammatory cytokines (transrepression).

- Transactivation is also responsible for many adverse systemic effects of corticosteroids. Corticosteroids also reduce the number of T lymphocytes, dendritic cells, eosinophils, and mast cells in airways and reduce inducible nitric oxide production.[13]

Pharmacokinetics

The delivery device can alter efficacy and therapeutic index. Therapeutic index is improved by decreased oral bioavailability, increased systemic clearance, and prolonged residence time in the lung secondary to increased lipophilicity, which results in increased volume of distribution.[3]

Even ICSs with a greater therapeutic index produce systemic effects when administered in the high-dose range as defined by the guidelines. Younger and smaller children may be at a greater risk for adverse systemic effects because they can receive higher mg/kg doses of ICSs when administered by metered-dose inhaler (MDI) and valved holding chambers (VHCs), particularly with the newer static free VHCs, compared with older children.[6]

Pharmacodynamics

Drugs whose mechanisms are receptor mediated, corticosteroids exhibit a log–dose linear effect; thus, the clinical dose response is often described as flat because doubling the dose is relatively ineffective in producing significant changes in outcomes.

- The ICS dose response is further complicated because the various measures of response (lung function, bronchial hyper responsiveness, asthma symptom control, exacerbations,

sputum, and exhalation markers of inflammation) are downstream events from the direct anti-inflammatory effects that have been extensively reviewed.

- COPD, smoking, severe asthma, obesity, and vitamin D insufficiency. Patients with asthma who are homozygous for the variant allele rs37973, which maps to the glucocorticoid-induced transcript 1 gene (GLCCI1), show about one third the lung function response of that of those homozygous for the wild-type allele. [10]

- The variant occurs in about 16% of the population. Smoking, COPD, and severe asthma result in oxidative stress and influx of multiple inflammatory cytokines that produce glucocorticoid resistance through a number of heterogeneous molecular mechanisms that have been extensively reviewed.[3]

- Even in utero smoke exposure has been associated with diminished response to ICSs in school-aged children. There are ongoing prospective clinical trials to determine whether vitamin D supplementation restores ICS responsiveness in patients with insufficiency.[10]

Role of corticosteroids in respiratory disease

Steroids (corticosteroids) are anti-inflammatory drugs. Corticosteroids are used in many pulmonary conditions. Corticosteroids have a proven beneficial role in asthma, decreasing the risk and severity of respiratory distress syndrome (RDS), allergic bronchopulmonary aspergillosis, interstitial lung disease, Pulmonary eosinophillic disorders. Role of corticosteroids is controversial in many conditions e.g. bronchiolitis, hypersensitivity pneumonitis, bronchiolitis, acute respiratory distress syndrome, atypical pneumonias.[5] However these are used empirically in many of these conditions despite lack of clear evidence in favour. There is concern about their side effects, especially on growth. Systemic steroids are associated with significant adverse effects. Pulmonary conditions have a strategic advantage that inhaled corticosteroids are useful in many of these. Although inhaled preparations of corticosteroids have been developed to maximise effective treatment of lung diseases characterised by inflammation and reduce the frequency of harmful effects, these have not been eliminated. There are situations where only systemic steroids are useful. Clinicians must weigh the benefits against the potential detrimental effects.[5]

Role of steroids is well established in many pulmonary conditions and is instrumental in decreasing morbidity and mortality. In conditions like bronchial asthma, these have proved to be the only drug effective in prevention of mortality and improving the quality of life

significantly in majority of patients. However, there are conditions like bronchiolitis where inflammation is undoubtedly the underlying pathology but steroids have not been proved to be very effective. And in many conditions steroids have been used empirically without evidence. Steroids are used in prevention and treatment of many neonatal conditions. Most important condition in pulmonary diseases, which has derived maximum benefit from steroids i*9'-9/6s probably bronchial asthma.[14]

Drug interaction

An interaction is said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink, or by some other environmental chemical agents. The outcome can be harmful if the interaction causes an increase in the toxicity of the drug.

Some of the most important risk factors that lead to drug interactions include multiple drug therapy, multiple prescribers, multiple pharmacological effects of drug, multiple diseases, poor patient compliance, age of patient, drug-related factors.

METHODOLOGY

STUDY DESIGN

A prospective observational study was carried out.

STUDY LOCATION

The study is being conducted in general medicine and cardiology departments of a 450 bedded tertiary care hospital.

STUDY DURATION

The study was carried out for a period of 6 months.

STUDY POPULATION

100 patients were selected from the inpatient departments of tertiary care hospitals.

STUDY TOOLS

Data en/-try form, drug interaction checker.

STUDY METHOD

- Literature Survey**:**

A computerized literature and manual search was conducted to identify relevant studies, to determine the role of corticosteroids in respiratory diseases. Literatures which support the study were collected and reviewed for conducting the study.

- Data Collection :

A data entry form was specially designed for collecting patient details, relevant to the study purpose, during the ward rounds, patient data including the age, sex, current diagnosis, drug therapy, lab investigation, drug interactions, social history.

- Evaluation of Prescriptions:

All the prescriptions were evaluated for its appropriateness and potential drug-drug interactions were identified using Medscape. The results obtained from the study were statistically analyzed and submitted as a report.

STUDY APPROVAL

The protocol of the study was submitted to institutional human ethics committee of hospital (IHEC). Protocol was approved by the institutional human ethics committee with approval no. SJPCEC/P25/PP/2016/026 and Hospital no. SJCP/DIR/A.15/2018-2019.

STUDY CRITERIA

Inclusion criteria

- Patients prescribed with corticosteroids having respiratory disease.
- Patients with respiratory tract disease.
- Inpatients of general medicine and cardiology department.
- Patients above 18 years**.**

Exclusion Criteria

- Patients who are not prescribed with corticosteroids.

- Patients without respiratory tract disease.

RESULTS

During the study period a total of 100 cases were screened randomly. The patients who satisfy the inclusion criteria were enrolled in this study. The data collected were organized, tabulated and described with the help of tables and graphs.

1. DISTRIBUTION BASED ON AGE

Our study included inpatients above 18 years of age. As the prescriptions were screened, more number of subjects was between the age group of 68-78 years.

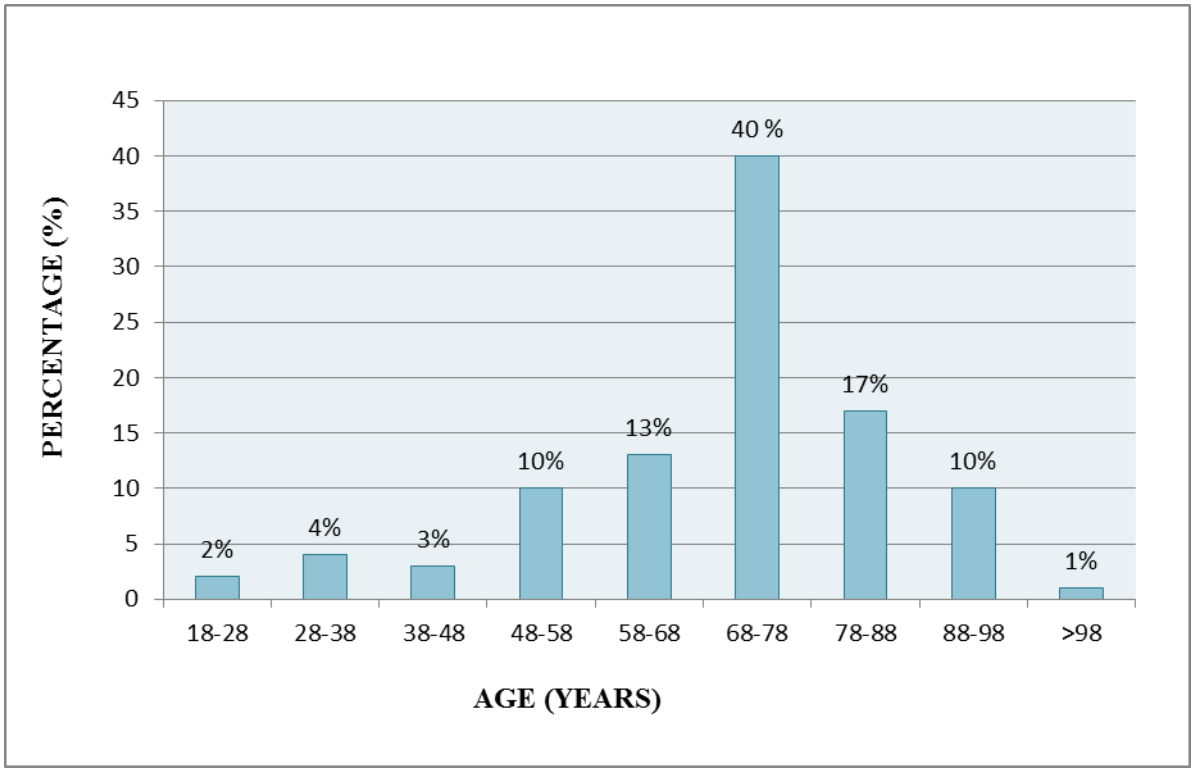

FIGURE NO. 1: DISTRIBUTION BASED ON AGE GROUP (N = 100)

2. DISTRIBUTION BASED ON GENDER (N=100)

Among the 100 prescriptions analyzed, 54% of the prescription was male patients and only 46% were female patients.

TABLE NO 1: DISTRIBUTION BASED ON GENDER (N=100)

GENDER	NO. OF PATIENTS (N=100)	PERCENTAGE (%)
MALE	54	54
FEMALE	46	46

3. DISTRIBUTION BASED ON LENGTH OF HOSPITAL STAY (N=100)

The distribution of hospitalization among the patients was as follows: 1-5 days (45%), 6-10 days (44%), 11-15 days (10%), 16-20 days (1%).

TABLE NO. 2: LENGTH OF HOSPITAL STAY (N=100)

LENGTH OF HOSPITAL STAY (DAYS)	NO. OF PATIENTS (N=100)	PERCENTAGE (%)
1-5	45	45
6-10	44	44
11-15	10	10
16-20	1	1

4. NUMBER OF DRUGS PER PRESCRIPTION (N=100)

Out of the 100 prescriptions analyzed, majority of the prescription included 6-10 drugs(52%) and the least was 1-5 drugs (2%), rarely >20 drugs(2%).

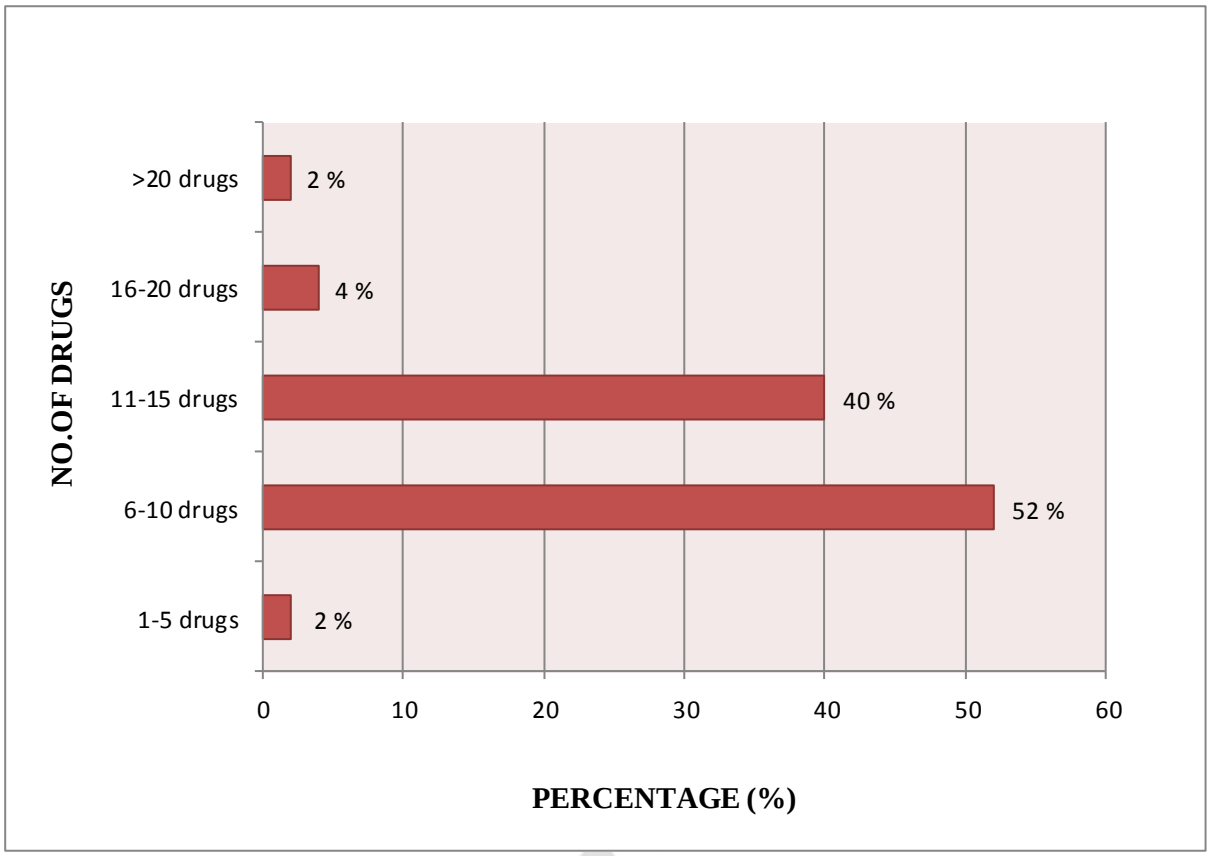

FIGURE NO. 2: NO. OF DRUGS PER PRESCRIPTION (N=100)

5. NUMBER OF STEROIDS PER PRESCRIPTION (N=100)

In this study, 59% of patients were prescribed with one corticosteroid, followed by 32% of patients with two.

TABLE NO. 3: NO. OF STEROIDS PER PRESCRIPTION (N=100)

NO. OF STEROIDS	FREQUENCY (N=100)	PERCENTAGE (%)
ONE	59	59
TWO	32	32
THREE	8	8
FOUR	1	1
FIVE	0	0

6. TYPES OF DOSAGE FORM (n=150)

A proper estimation on the drug prescription was carried out and steroids were grouped based on the dosage forms. Comparatively higher rates were identified on inhalational corticosteroids (60%), followed by parenteral (30.6%) and oral (9.33%).

TABLE NO. 4: TYPES OF DOSAGE FORM (n=150)

DOSAGE FORMS	FREQUENCY (n=150)	PERCENTAGE (%)
NEBULIZED	90	60
PARENTERAL	46	30.6
ORAL	14	9.33

7. TYPES OF STEROIDS PRESCRIBED (n=150)

7 different corticosteroids were commonly prescribed, out of which Budesonide (42.66%) was observed with the highest rate, Hydrocortisone (21.33%), Fluticasone Propionate (17.33%), Methyl Prednisolone (8.0%), Betamethasone (7.33%), Prednisolone (2.66%) and Dexamethasone (0.66%) with the least.

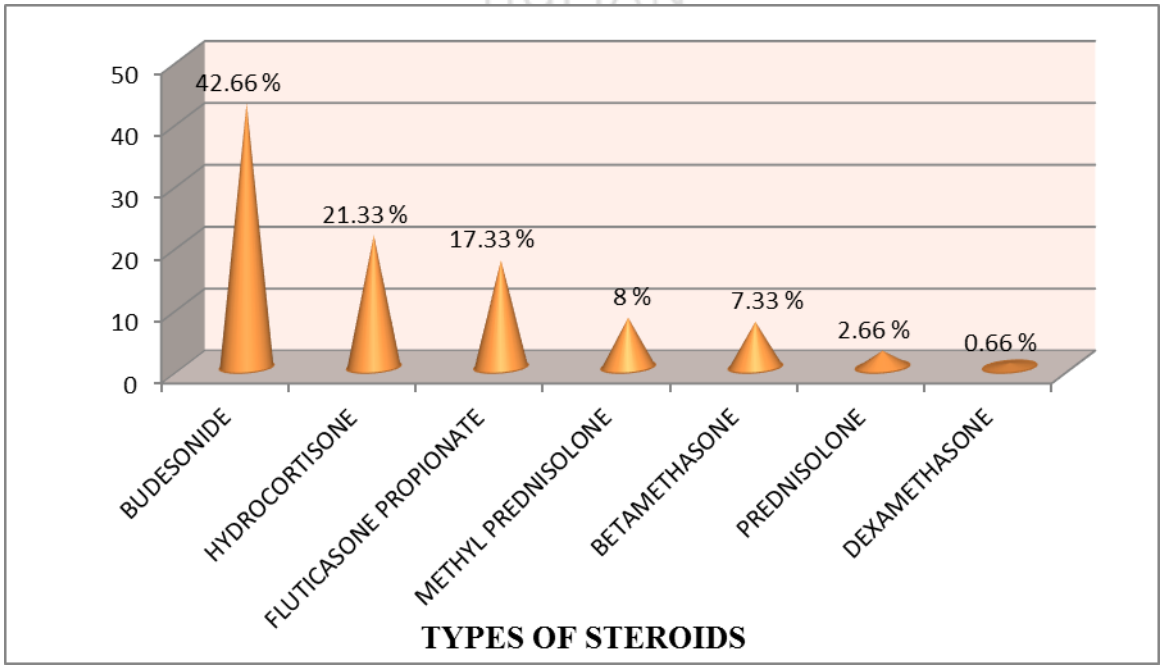

FIGURE NO. 3: TYPES OF STEROIDS PRESCRIBED (n=150)

8. TREATMENT REGIMEN (N=100)

In this study, 76% of patients were on monotherapy and 24% were on combination therapy (Bronchodilator+Corticosteroid).

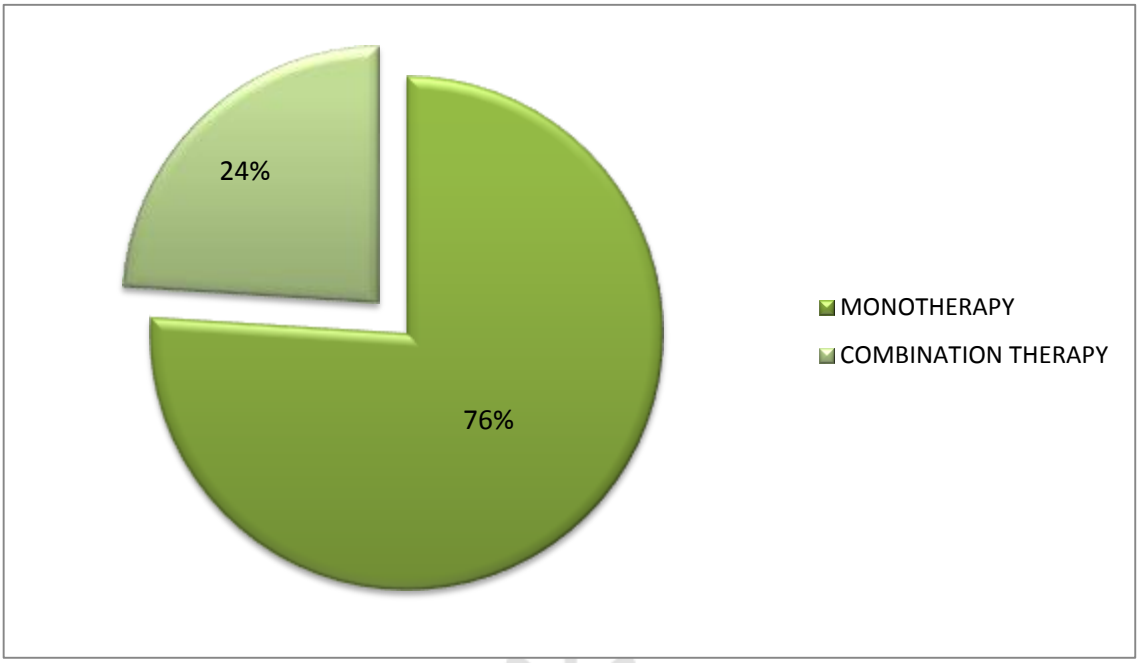

FIGURE NO. 4: TREATMENT REGIMEN (N=100)

9. DIAGNOSIS (N=100)

The accounts of hospital admissions were mainly due to respiratory diseases, LRTI (52%), COPD (36%) and Bronchial Asthma (12%).

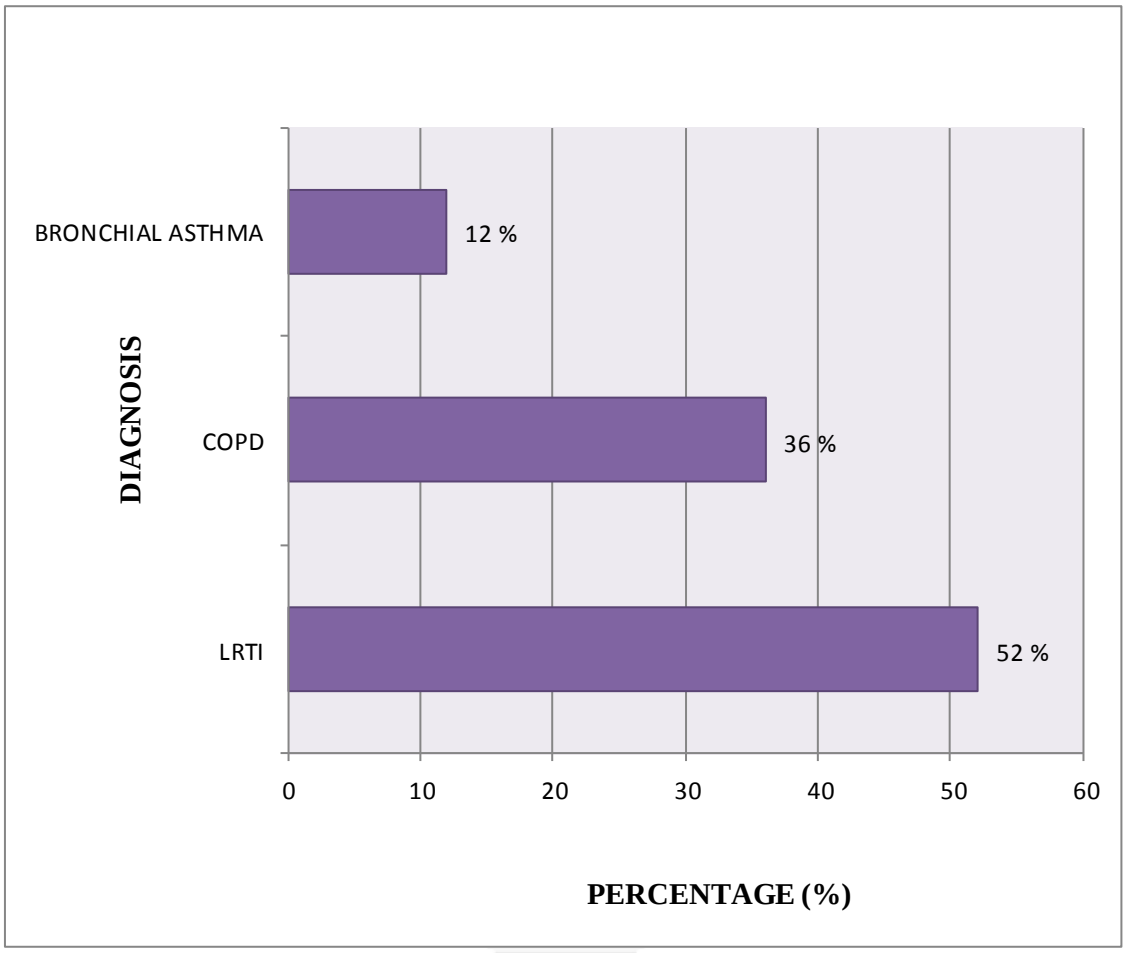

FIGURE NO. 5: DIAGNOSIS (N=100)

The drug interactions were categorized into major, moderate, minor based on severity and was observed as 8.22%, 69.69%, 22.07% respectively. More frequently identified major potential drug-drug interactions were between Hydrocortisone and Theophylline. More number of corticosteroids with shorter duration reduce the side effects, decrease the length of stay, thereby it is cost effective and faster recovery.

TABLE NO. 5 INTERACTIONS WITH STEROIDS

DRUGS	EFFECT	INFERENCE	FREQUENCY
Hydrocortisone + Theophylline	Hydrocortisone will decrease the level of theophylline by affecting hepatic enzyme CYP3A4 metabolism.	Use with caution.	14
Nifedipine + Prednisolone	• Nifedipine will increase the level of prednisolone by affecting hepatic enzyme CYP3A4 metabolism. • Nifedipine will decrease the effect of prednisolone by P-glycoprotein efflux transporter.	• Use with caution. • Use with caution.	2
Hydrocortisone + Furosemide	Either increases the effect of the other by pharmacodynamic synergism.	Risk of hypokalemia especially with strong glucocorticoid activity.	4
Methylprednisolone + Theophylline	Methylprednisolone will decrease the level of theophylline by affecting hepatic enzyme CYP3A4 metabolism.	Use with caution.	1
Clarithromycin+ Methylprednisolone	Clarithromycin will increase the level of methylprednisolone by affecting hepatic enzyme CYP3A4 metabolism. Clarithromycin will increase the effect of methylprednisolone by P-glycoprotein efflux transporter.	Use alternative.	1

Betamethasone+ Ciprofloxacin	Either increases toxicity of the other by other.	Use with caution. Co-administration of quinolone antibiotics and corticosteroids may increase the risk of tendon rupture.	1
Betamethasone + Levofloxacin	Both increases the effect of the other.	Use with caution. Co-administration of quinolone antibiotics and corticosteroids may increase the risk of tendon rupture.	1
Methylprednisolone + Moxifloxacin	Both increases the effect of the other.	Use with caution. Co-administration of quinolone antibiotics and corticosteroids may increase the risk of tendon rupture.	1
Methylprednisolone + Torsemide	Either increases the effect of the other by pharmacodynamic synergism.	Risk of hypokalemia especially with strong glucocorticoid	1

		activity.	
Methylprednisolone + Calcium carbonate	Methylprednisolone decreases the level of calcium carbonate by increasing elimination	Significance unknown	1
Methylprednisolone + Montelukast	Methylprednisolone will decrease the level of Montelukast by affecting hepatic enzyme CYP3A4 metabolism.	Significance unknown	1
Dexamethasone + Theophylline	Dexamethasone will decrease the level of theophylline by affecting hepatic enzyme CYP3A4 metabolism.	Use with caution.	3
Clarithromycin + Hydrocortisone	Clarithromycin will increase the level of hydrocortisone by affecting hepatic enzyme CYP3A4 metabolism	Avoid or use alternative	2
Prednisolone + Glimepiride	Prednisolone decreases effect of glimepiride by pharmacodynamic antagonism.	Significance unknown.	1

DISCUSSION

"Assessment of Role of Corticosteroids In Respiratory Diseases" was conducted in 450 bedded tertiary care hospital. During the study period a total of 100 cases were screened randomly. The patients who satisfy the inclusion criteria were enrolled in this study. The data collected were organized, tabulated and described with the help of tables and graphs.

- Age: Our study included inpatients above 18 years of age. As the prescriptions were screened, more number of subjects was between the age group of 68-78 years.

- Gender: Among the 100 prescriptions analyzed, 54% of the prescription was male patients and only 46% were female patients.

- Length of hospital stay: The distribution of hospitalization among the patients was as follows: 1-5 days (45%), 6-10 days (44%), 11-15 days (10%), 16-20 days (1%).

- No. of drugs per prescription: Out of 100 prescriptions analyzed, the no. of drugs per prescription was as follows: 1-5 drugs (2%), 6-10 drugs(52%), 11-15 drugs (40%), 15-20 drugs (4%) and >20(2%).

- No. of steroids per prescription: In this study, 59% of patients were prescribed with one corticosteroid, followed by 32% of patients with two, 8% were prescribed with three and 1% with four.

- Type of dosage forms: A proper estimation on the drug prescription was carried out and steroids were grouped based on the dosage forms. Comparatively higher rates were identified on inhalational corticosteroids (60%), followed by parenteral (30.6%) and oral (9.33%).

- Types of Steroids: Of the 100 prescriptions screened, 7 different corticosteroids were commonly prescribed, out of which Budesonide (42.66%) was observed with the highest rate, Hydrocortisone (21.33%), Fluticasone Propionate (17.33%), Methyl Prednisolone (8.0%), Betamethasone (7.33%), Prednisolone (2.66%) and Dexamethasone (0.66%) with the least.

- Treatment Regimen: In this study, 76% of patients were on monotherapy and 24% were on combination therapy (Bronchodilator+Corticosteroid).

- Diagnosis: The accounts of hospital admissions were mainly due to respiratory diseases, LRTI (52%), COPD (36%) and Bronchial Asthma (12%).

- Drug Interactions: Computerized drug-drug interactions were used to find out potential drug-drug interactions. Out of 100 subjects, the potential drug-drug interaction were not found only in 24% of the populations. The drug interactions were categorized into major, moderate, minor based on severity and was observed as 8.22%, 69.69%, 22.07% respectively. More frequently identified major potential drug-drug interactions were between Hydrocortisone and Theophylline. More number of corticosteroids with shorter duration reduce the side effects, decrease the length of stay, thereby it is cost effective and faster recovery.

CONCLUSION

The role of corticosteroids in respiratory diseases are for reducing inflammation and mucus production in the airway of the lungs. Their efficacy comes from their broad anti inflammatory and immunosuppressive effects. Due to continously increasing social and economic burden, a significant attention is being paid to the optimal management of the disease and its associated exacerbation.

Mainly corticosteroids in the form of nebulization is prescribed to the patients. The most commonly prescribed glucocorticoid is budesonide (42.6%). The drugs are prescribed in monotherapy and in combination form (bronchodilator + corticosteroid). More number of corticosteroids with shorter duration reduce the side effects, decrease the length of stay, thereby it is cost effective and faster recovery.

The guidelines show that combinational therapy is mainly followed but after completion of this study we see that corticosteroids are prescribed in the form of nebulization. As Standard treatment guidelines is not followed by the hospital, we discussed with the clinical pharmacist and he suggested about the awareness program to be conducted for the physicians.

From the study, we can observe that corticosteroids are prescribed in the form of nebulization but the systemic treatment is found to be more effective and comfortable, hence the study findings was communicated to the physician.

Thus, this study mainly emphasised on the role of corticosteroids in respiratory diseases providing necessory informations about the benefits of corticosteroids and to improve the quality of life of the patients.

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