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A PHARMACOVIGILANCE STUDY TO ANALYZE THE ADVERSE DRUG REACTIONS IN PATIENTS TREATED WITH ANTIHYPERTENSIVE DRUG IN TERTIARY CARE TEACHING HOSPITALS

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Abstract:

Introductions:- Hypertension is the most common cardiovascular disease and most important public health problem. Increased arterial pressure causes hypertrophy of the left ventricle leads to pathological changes in the vasculature. Pharmacovigilance analysis study provided an insight into the drug use pattern and rational use of drugs. The outcomes of the present study contribute to us as well as public knowledge about drugs effectiveness and theirs safety concern.

Material & Methods: This Pharmacovigilance analysis study was a Prospective and observational study conducted in Department of Pharmacology, Santosh Medical College and Hospital, Santosh Deemed To be University (SDTU), Ghaziabad in Collaboration with Department of Medicine, Muzaffarnagar Medical College, Muzaffarnagar during the period of June 2019 to December 2022. The study was approved by IEC, of Santosh Deemed to be University, Ghaziabad in 2019. The study was a part of PhD thesis of corresponding author. The Individual Data for Pharmacovigilance analysis was collected for 6 months of period with the help of –Suspected Adverse Drug Reaction Reporting Form V. 1.3 and –Medicines Side Effect Reporting Form (For Consumers) v.1.0. Statistical analysis was done by SPSS v- 20 and Excel-Sheet.

Results: A total of 242 Hypertensive patients following inclusion and exclusion criteria of both genders were observed in the study. Out of 242 patients a total 47 patients showed 25 types of ADRs were recorded and assessed for 6 months. Among 47 patients, the prevalence of ADRs was

predominantly higher in the patients having higher age group, i.e., > 40 years of age (70 %.). Compared to monotherapy (15-25%), combinational therapy (using more than one medicine) was linked to a higher proportion of adverse drug reactions (27.3-36.4%). The anti-hypertensive drugs combinations most frequently linked to ADRs were ARB+CCB+DU (36.36%), followed by CCB + BB (28.57%), ARB + CCB (27.27(19.35%), ACEI(25%), ARB + DU (16.67%), BB (15.15%) and ARB (15%).

Conclusion: The results of the above study would be useful for the physicians in rational selection of drug therapy for treatment of hypertensive patients. The present data suggest that the ADR monitoring needs to be done in hospital settings continuously so that untoward effect caused by different medicines can be identified and documented.

Key points: ADR, Pharmacovigilance, Hypertension, Antihypertensive Drugs, Efficacy and drug safety.

1. Introduction

Hypertension is the most common cardiovascular disease and most important public health problem. [1] The prevalence of hypertension increases with age; about 50% of people between the ages of 60 – 70 years old have hypertension. In 90% patients, the cause is idiopathic. Around 81.5% of peoples with hypertension are aware they have it and 74.9% are being treated with anyone of the antihypertensive drug. According to previous physicians 'experts, report hypertension is likely to end up being an epidemic in the near future and 1/3 of the population suffer from hypertension by the year 2023. [2]

Although symptoms are usually absent, persistently elevated blood pressure causes long-term damage to numerous organs and can result in overt cardiovascular disease, chronic kidney damage and stroke, and is a frequent cause of premature death. Intensive control of blood pressure and the importance of pharmacological intervention in all high-risk individuals with hypertension is very important study. [3]

Antihypertensive medications are frequently linked to Adverse Drug Reactions (ADRs) due to long-term therapy and use of two or more medications. [4] Pharmacovigilance studies for monitoring ADRs related to antihypertensive agents have been previously conducted by many workers in different parts of the world [5-7]. Monitoring of ADRs in India is in its infancy [8]. A study conducted in the Indian capital reports that 22.3% of the patients experienced ADRs [9]. Another report on ADR monitoring in northern India mentions that 5.9% of all visits to the medical department are drug related, and ADRs accounted for 45% of events [10].

Adverse drug reactions (ADRs) are considered among the leading causes of morbidity and mortality if not addressed in time. Around 6% of hospital admissions are estimated to be due to ADRs and about 6-15% of hospitalized patients experience a serious ADR. [11]

Pharmacovigilance analysis study provided an insight into the drug use pattern and rational use of drugs (prescribe well documented drug at an optimal dose, together with the correct information). The outcomes of this study contribute to our knowledge about drugs ADRs prevalence, effectiveness and safety. [12] The information on pattern of Pharmacovigilance analysis of drug utilization can be useful for designing a drug policy and reviewing the health care budget. A Pharmacovigilance analysis study can be used to evaluate the pattern of use a particular class of drugs according to age group patients, gender group patients, and morbidity at various levels of health care systems which may contribute to make improvements in the drug policy of health care systems. The triplet issue of rationality and minimization of ADRs demands a careful contemplation during any drug analysis study in a developing country, like India. [13]

As we know Spontaneous reporting of ADRs is considered as the foundation of post-marketing drug safety surveillance [14]. The main function of spontaneous reporting is to detect early signals of new, rare, and serious ADRs. Under reporting of ADR's is a common problem in Indian PV system. There is an inadequate nationwide awareness and poor knowledge about PV among health

care professionals [15].
Previous study showed that Lack of knowledge of where and how ADRs should be reported also affects reporting. The reason for poor reporting includes no financial incentives, legal aspects, apprehension that the serious ADRs are already documented when a drug is introduced into the market and that a single report would make no difference, ignorance (that only serious ADRs are to be reported) and lack of time or overload of patients [16].
We also know that the under reporting issues are resolved due to accessible reporting facilities like toll-free dial numbers, messages, mail, ADR forms with vernacular languages and outsourcing of PV activity by different multinational companies with awareness among the healthcare sector and public [17, 18] . In light of supporting PVPI, the present study was undertaken to analyze the Adverse Drug Reactions in Patients Treated with Antihypertensive Drug in Tertiary Care Teaching Hospitals.

2. MATERIALS AND METHODS:

This Pharmacovigilance analysis study was a Prospective and observational study conducted in Department of Pharmacology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad in Collaboration with Department of Medicine, Muzaffarnagar Medical College, Muzaffarnagar during the period of June 2019 to December 2022. The study was approved by IEC, of Santosh Deemed to be University, Ghaziabad in 2019. The study was a part of PhD thesis of corresponding author. All those hypertensive patients above 18 years old of both genders treated with antihypertensive Medications and willing to give their written consent were included in the study. Pediatric patients, Pregnant and lactating mother‘s patients were not included in the study.

Sampling Methods: The Individual Data for Pharmacovigilance analysis was collected for 6 months of period with the help of **–Suspected Adverse Drug Reaction Reporting Form V. 1.3" And "Medicines Side Effect Reporting Form (For Consumers) V.1.0"**. Statistical analysis was done by SPSS v-20 and Excel-Sheet.
Causality Assessment: Causality assessment (CA) is a method of evaluating the relationship between drugs exposed and reported adverse drug reactions. Causality assessment of ADRs was carried out by using the WHO-UMC scale.
Severity Assessment Scale - Hartwig's and Siegel Scale: Seriousness of an ADR is related to its life threatening nature. It defined as any untoward reaction to the medicinal product that may require inpatient hospitalization or may result in prolongation of existing hospitalization, or death. Hartwig‘s Severity Assessment Scale was used to evaluate the seriousness of reported ADR.
Preventability Scale - Schumock and Thornton: Modified Schumock and Thornton scale were used to identify the preventability of ADR, thereby improving drug use.

3. OBSERVATIONS:

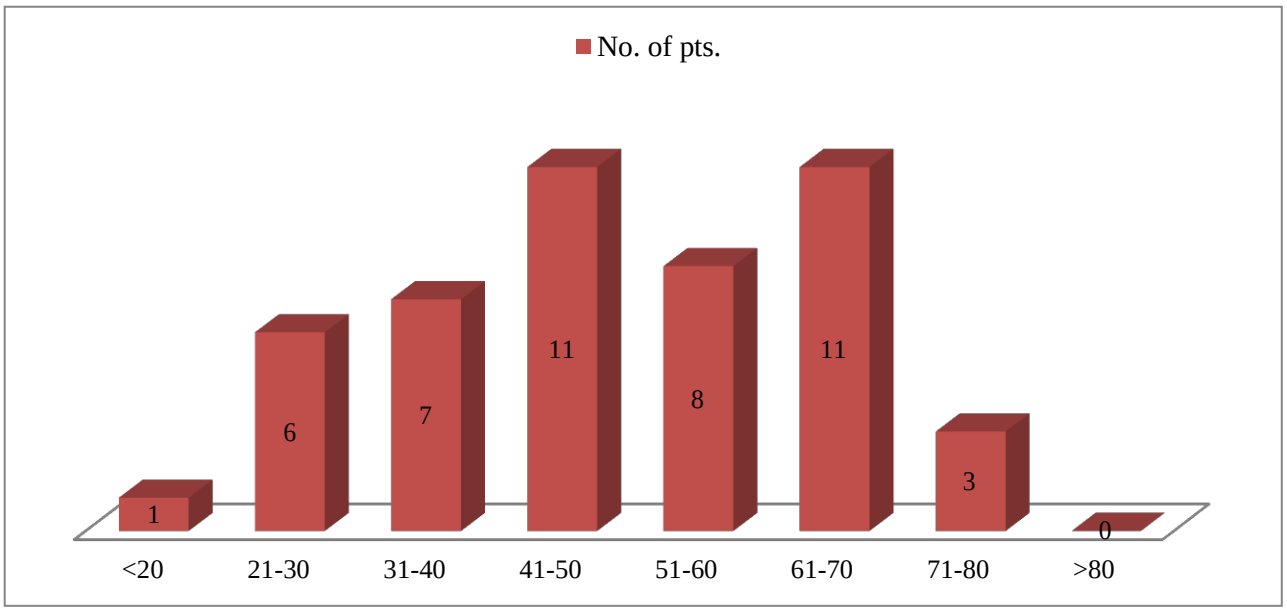


Fig-1 Age wise Distribution of ADRs

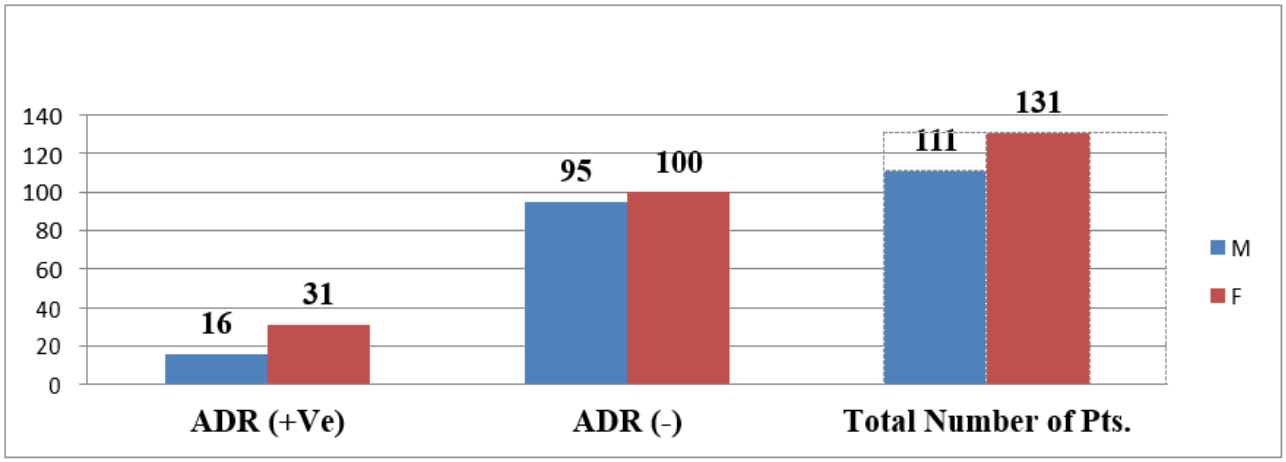


Fig. 2- Gender wised Distribution of ADRs.

Table: 1- Prevalence of ADRs.

Class of Drugs	Total numbers of Pts.	Number of Pts showing	ADR Prevalence (%)
ACEI	4	1	25
ARB	100	15	15
ARB + CCB	44	12	27.27
ARB + DU	12	2	16.67
ARB+CCB+DU	11	4	36.36
BB	33	5	15.15
CCB	31	6	19.35
CCB + BB	7	2	28.57
ADRs Prevalence	242	47	19.42

Fig.3 Types of Reactions presented in ADRs Report

Fig: 4- WHO-UMC Causality Assessment Scale for ADRs

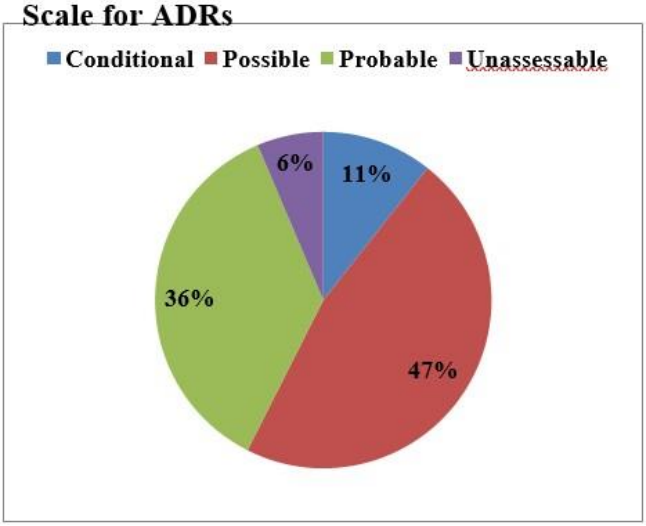


Fig: 5- Preventability Scale of ADRs

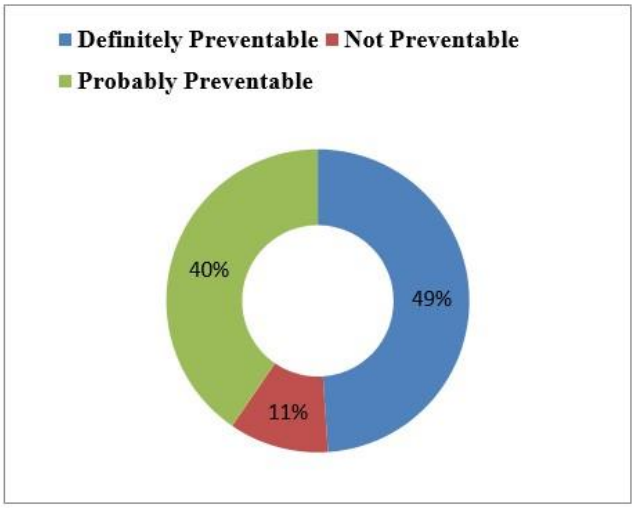
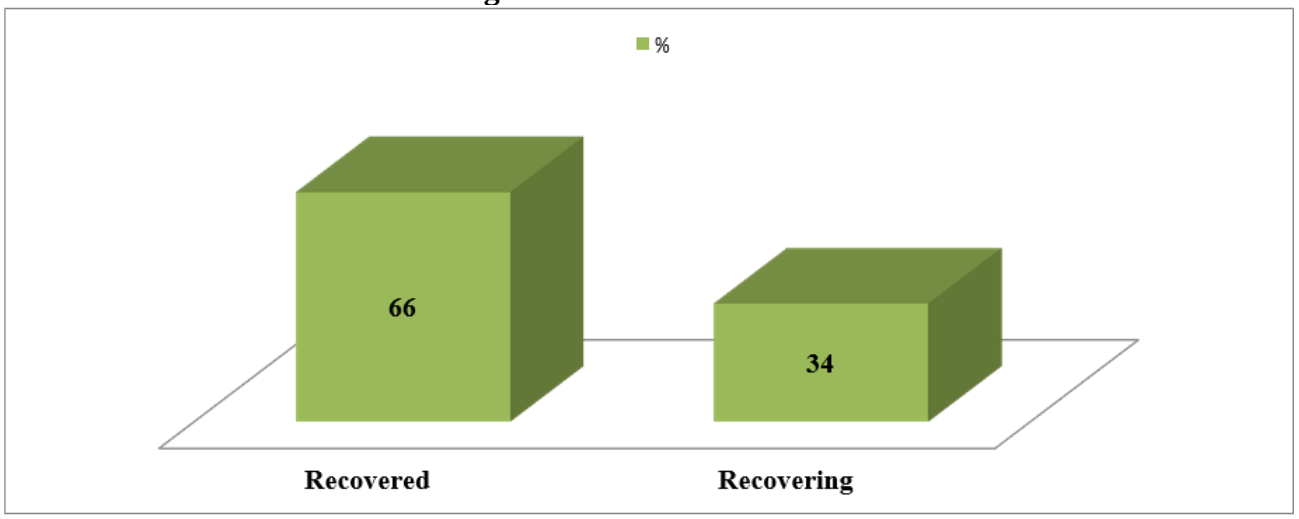


Fig.: 7-Out-comes of ADRs.



4. Results and Discussion

The present study was conducted among 242 hypertensive patients to analyze the adverse effect profile of antihypertensive drugs in Department of Pharmacology Santosh Medical College and Hospital in collaboration with tertiary care teaching hospital in the outpatient department of Medicine at the Muzaffarnagar Medical College, Muzaffarnagar. A total of 242 Hypertensive patients following inclusion and exclusion criteria of both genders were observed in the study. Out of 242 patients a total 47 patients showed 25 types of ADRs were recorded and assessed for 6 months. Among 47 patients, the prevalence of ADRs was predominantly higher in the patients having higher age group, i.e., > 40 years of age (70 %.). Adverse drug reaction observed with respect to age is depicted in **Fig. 1.**

Age is a very important factor that affects the occurrence of ADRs. It is widely acknowledged that elderly patients are mainly at risk for ADRs primarily due to increased chronic disease, polypharmacy (concomitant prescription of five or more drugs), and age-related physiological changes affecting the pharmacokinetics and pharmacodynamics of drugs. [18-20]

Within the study population, Gender wise distribution showed that female patients (65.96%) developed more ADR than Male (34.04%). as presented in **Fig. 2**

Interpretations of Global post-marketing surveillance data on spontaneous reports from individual case reports indicate that women, from puberty and onwards and especially in their reproductive years, report more ADRs than men. [21] The difference in susceptibility pattern of ADRs between

male and female is due to the physiological characteristics, such as weight, intestinal transit velocity and fat percentage, and genetic/metabolic and hormonal differences. [22]

Compared to monotherapy (15-25%), combinational therapy (using more than one medicine) was linked to a higher proportion of adverse drug reactions (27.3-36.4%) as shown in **Table-1.** Numerous epidemiological research on the risk factors for ADRs have revealed that patients receiving combinational medications have a higher probability of developing an ADR than those receiving monotherapy.[23-24] Combinational therapy must be discouraged since they increase the risk of ADRs brought on by drug-drug interactions. So for the treatment of hypertension, it is advised to only prescribe medications that are absolutely necessary especially with monotherapy. [25-26]

The anti-hypertensive drugs combinations most frequently linked to ADRs were **ARB+CCB+DU** (36.36%), followed by **CCB + BB** (28.57%), **ARB + CCB** (27.27(19.35%), ACEI (25%), **ARB + DU (16.67), BB (15.15) and ARB (15%).** Similar findings were revealed by the studies conducted by ***Paudel et al.*** **[27],** ***Khursid F et al*****. [28] and** ***Basak SC et al*****. [29]** as shown in **Table 1.**

The ADRs associated with CNS (Headache, anxiety, Gen. Body Ache, Back Pain) were found to be most frequent in our study followed by CVS ADRs (Palpitations) and gastrointestinal ADRs (abdominal pain, acidity). This is supported by previous studies which report gastrointestinal ADRs among the top three ADRs [30-32] as shown in **Fig. 3.**

Our study also showed that according to WHO causality assessment scale 47% of the ADRs were Possible which means that these reactions are caused by the use of antihypertensive drugs and not due to any disease or by the use of other drugs and clinical improvement is seen when the drug id de challenged. Probable ADRs were seen in 36 % of the patients which could be due to presence of a disease or simultaneous use of other drugs. 11% of ADRs showed conditional type and 6% of ADRs were un-assessable type as shown in **Fig. 4**. Whether the preventability scale showed that 49% of ADRs were definitely preventable type, 40% ADRs were Probably Preventable type and 11% of ADRs were not preventable types as shown in **Fig.5.**

So our study was inconsistent with a prospective observational study done by ***Meena Shrivastava et al.,*** which revealed that among 1475 ADRs, most of the ADRs belonged to probable (55.89%) followed by possible categories [33] .

The outcome of the study showed that 66% of the patients were recovered from ADRs and 34 % of Patients were recovering from ADRs.

5. Conclusion:-

As we know adverse drug reaction is _a response to a drug that is noxious and unintended and occurs at doses normally used in human for the prophylaxis, diagnosis, and treatment of disease, or for modification of physiological function. As expected, combination therapy was associated with higher number of ADRs as compared to mono-therapy and Female patients were more prone to developed ADRs as compared to Male Patients due to variation in physiological system of body makeup. The present study is a part of PhD thesis work on Pharmacovigilance study in our university Santosh Deemed to be University in collaborations with Department of Medicine Muzaffarnagar Medical College, Muzaffarnagar, Uttarpradesh. The results of the above study would be useful for the physicians in rational selection of drug therapy for treatment of hypertensive patients. The present data suggest that the ADR monitoring needs to be done in hospital settings continuously so that untoward effect caused by different medicines can be identified and documented.

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work data collection and making the causality assessment of the study.

7. Conflict of Interest: No

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