Survey Analysis

A STUDY ON SIDE EFFECTS OF FIXED DOSE ANTI-HYPERTENSIVE COMBINATIONS

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ABSTRACT:

Background: Consistent drug treatment is very essential for a chronic disease such as hypertension More over a large number of population require more than one anti-hypertensives and most often fixed dose combinations are preferred. The importance on studying side effects of anti-hypertensive fixed dose combinations is an undebatable issue in a country, where a large number of irrational fixed dose combinations indulge beyond any restriction in the pharmaceutical market.

Methodology: On the basis of the study a total of 150 hypertensive patients prescribed with anti-hypertensive FDCs, who met the inclusion criteria of our study were randomly selected and their outpatient record were monitored and recorded for a period of 6 months. The data was then suitably analyzed.

Results: Pedal edema, cough, dizziness, fatigue, hyponatremia, hypotension, bradycardia, numbness of limb, chest pain, hyponatremic convulsion and claudication were the side effects observed in our study , but among them, pedal edema was the most frequently observed side effect followed by fatigue and dizziness. It is also to be noted that more number of side effects were observed in age ≤ 65 years and in patients with co-morbid conditions. The adverse effects were also classified according to system organ class and subjected to causality assessment.

Conclusion: During clinical trials, only a little of side effect profile is studied during the limited time period. Hence the real influence and outcome of FDCs with regard to side effects were not fully established. The present study could serve as a frame work upon which further studies can be done over a longer duration and including all available FDCs in the Indian market to screen the side effects of FDCs

KEYWORDS: Clinical pharmacist, Fixed dose combination, Hypertension, Side effects

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INTRODUCTION:

Hypertension is a single, chronic and preventable risk factor for morbidity and mortality worldwide. In India, the prevalence of hypertension is 27.1 and 26.4 per cent among men and women, respectively. The risk of hypertension was 6-8 times higher in elderly people and 2-3 times in 35-59 yr compared with 20-34 yr. Only <10 per cent of men and women were known hypertensives and more than half on treatment (55-68%)[11].

The ultimate public health goal of antihypertensive therapy is the reduction of cardiovascular and renal morbidity and mortality [1]. Drug selection in an individual is mainly based on his age and co-morbid conditions. Addition of a second drug (different class) can only be initiated when a single drug cannot reduce blood pressure adequately. According to JNC7, when BP is more than 20/10 mmHg above goal, drug therapy is initiated with two drugs, either as separate prescriptions or in fixed-dose combinations.

The usefulness of antihypertensive drugs depends not only on the degree to which blood pressure is lowered but also on the side effect profile. The side effects of anti-hypertensives affect tolerability and compliance by the patients. The present study evaluates the side effects of anti-hypertensive FDCs, even though FDCs are known to cause fewer side effects than their respective active pharmaceutical ingredients. The assessment of FDCs for their side effects is as important as monotherapy.

MATERIAL AND METHOD:

This prospective study was conducted in cardiology department of a tertiary care sector after obtaining approval from Institutional ethics committee. The study included all outpatients of both gender with an age ≥ 18 years. The main restriction to study was one with incomplete medical records & those who were not willing to participate in the study. The study also excluded pregnant and breast feeding women.

Based on inclusion and exclusion criteria 150 prescriptions issued during the period of 6 months were randomly collected and the relevant data was analyzed and tabulated in a specially designed data collection form and a side effect checklist. Patient's demographic details, pertinent laboratory and clinical information were collected during the outpatient hours and by reviewing the medical records. Those newly diagnosed patients were followed up as possible. All data collected were coded as per variables and entered in SPSS data sheet.

Statistical analysis was determined using the statistical software SPSS 13.0 for windows. The significant differences of side effect between drugs were analyzed using $\chi 2$ test. *P*-value of <0.5 was taken as statistically significant.

RESULTS:

The present study evaluates the side effects of anti-hypertensive FDCs, even though FDCs are known to cause fewer side effects than their respective active pharmaceutical ingredients. The assessment of FDCs for their side effects is as important as monotherapy.

Among 150 patients only 42 of them had side effects and the rest were free from side effects, which is depicted by Fig 1.

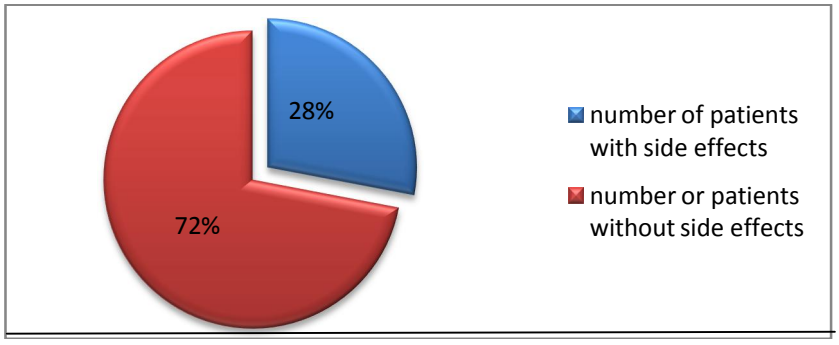
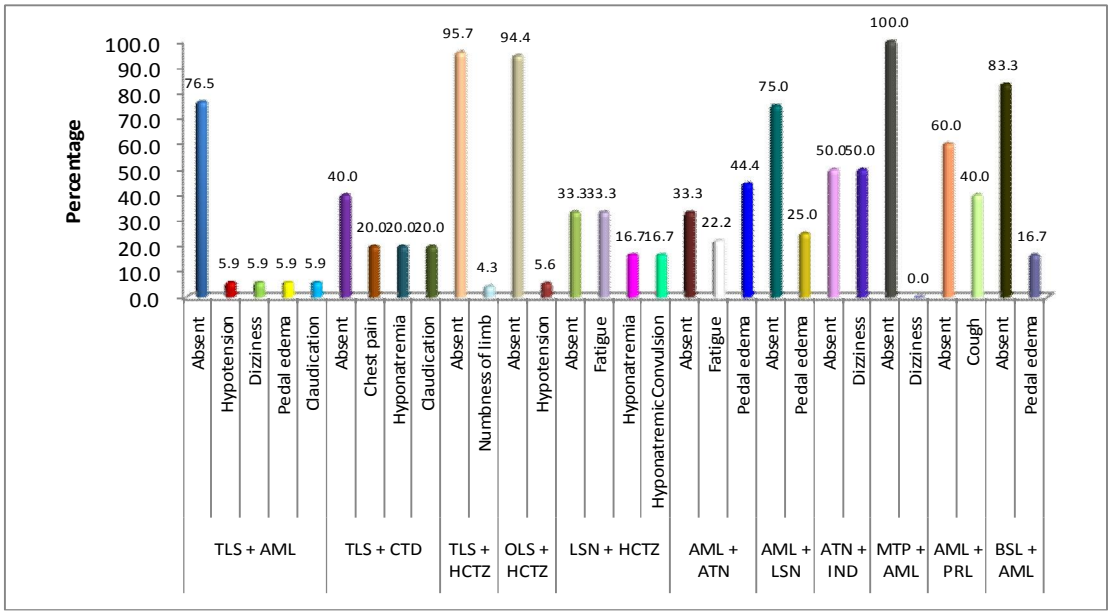


Fig1: Distribution of total sample with respect to presence or absence of side effects.

It is also to be noted that there was an equal distribution of side effects among both the genders.

The patients were screened for their side effects and were noted. The following graph (Fig 2 &3) shows the occurrence of side effects with each anti-hypertensive FDCs analyzed in this study.



OLS-Olmesartan; AML- Amlodipine; HCTZ- Hydrochlorothiazide; BSL- Bisoprolol; NBV- Nebivolol; SAML- S-amlodipine; ATN- Atenolol; TLS- Telmisartan; CLN- Cilnidipine; MTP- Metoprolol; LSN- Losartan; RML-Ramipril; CTD-Chlorthalidone; LCD-Lercanidipine;

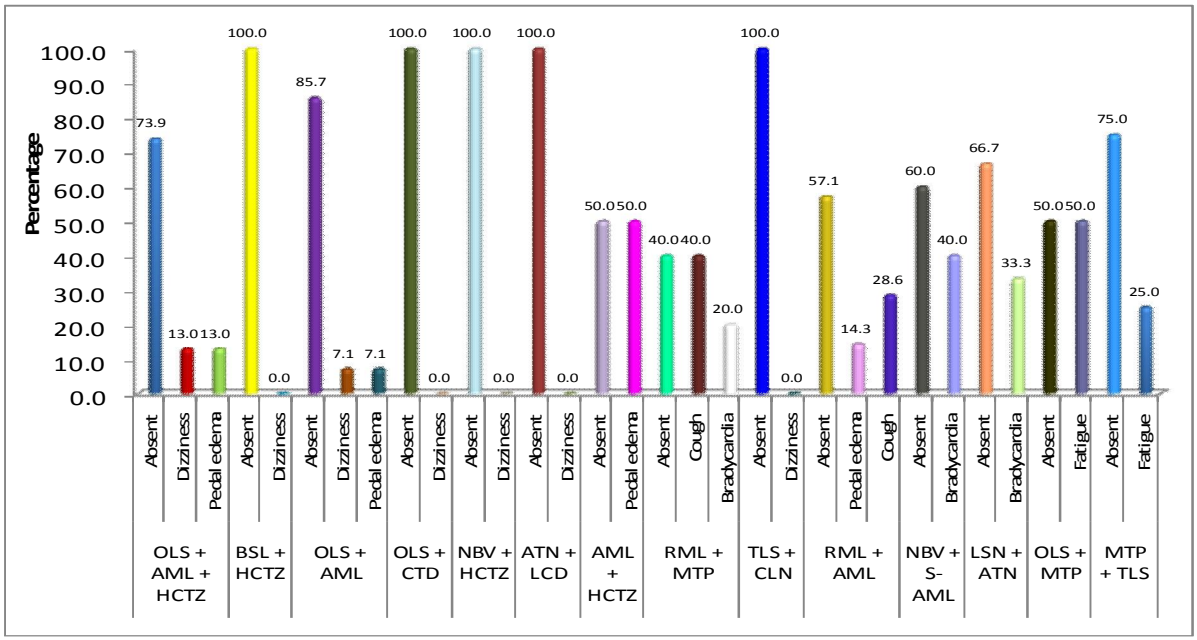


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Fig 2 and 3: Distribution of side effects in patients

The graph shown below represents the relationship of side effects caused by FDCs according to age.

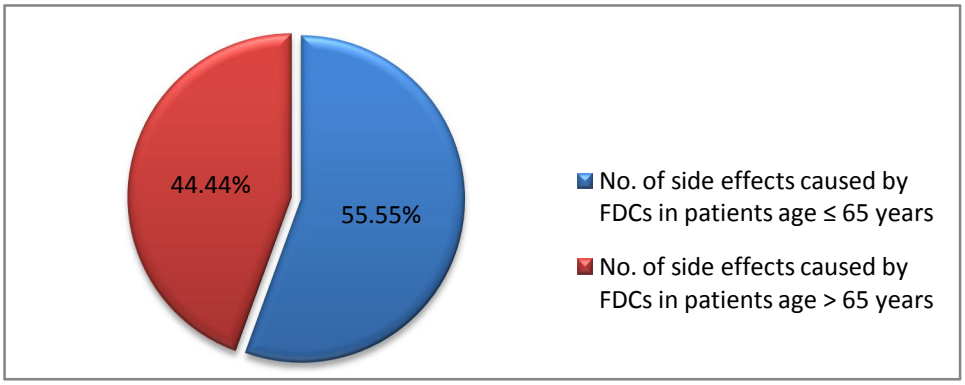

Fig 4: Number of side effects caused by FDCs classified according to age.

On analysing the collected data, the following graph shows the association between occurrence of side effect and comorbidities in the study population

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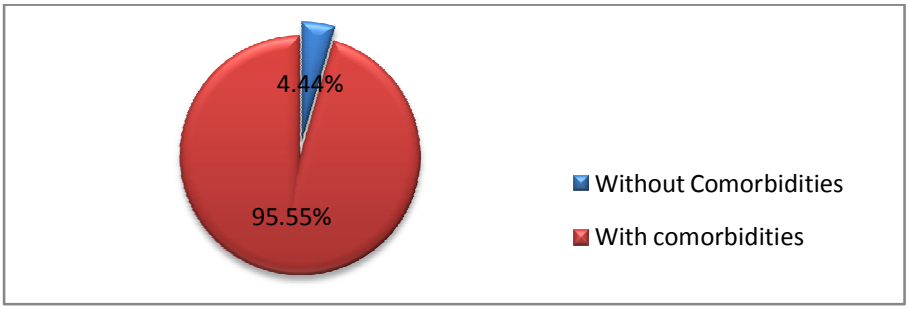

Fig 5: Graph showing distribution of Co-morbidities and side effects.

More number of side effects were observed in age ≤ 65 years and in patients with co-morbid conditions.

The graph shown below represents the percent of FDCs causing side effects.

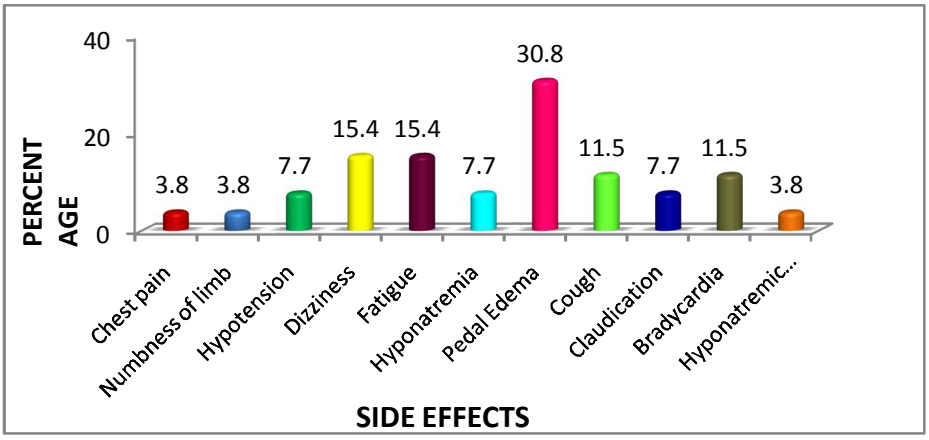

Fig6 : Graph showing distribution of side effects with FDC

MANAGEMENT OF SIDE EFFECTS:

On analyzing the prescriptions for side effects, the following graph shows how side effects were managed in the hospital.

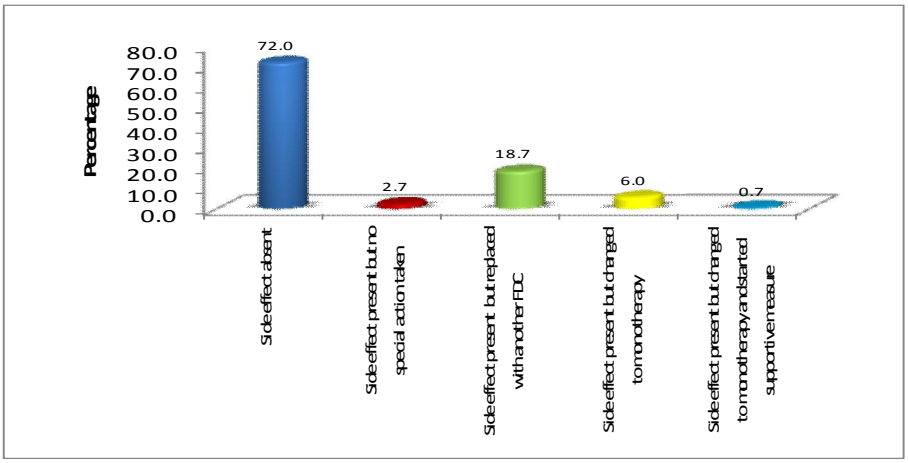

Fig 7: Graph showing management of side effects.

COMPARISON OF SIDE EFFECTS OF FDCS: The side effects of three anti-hypertensive FDCs were compared among each other for the risk of developing side effects and were tabulated as follows

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Table 1: Details of comparison between two FDCs

FDCs	**SIDE EFFECTS**	**NO SIDE EFFECTS**	**P- VALUE**
Olmesartan +HCTZ + Amlodipine	26.1 (6)	73.9 (17)	0.040
Telmisartan + HCTZ	4.3 (1)	95.7 (22)	
FDCs	**SIDE EFFECTS**	**NO SIDE EFFECTS**	**P- VALUE**
Olmesartan +HCTZ + Amlodipine	26.1 (6)	73.9 (17)	0.857
Telmisartan + Amlodpine	23.5 (4)	76.5 (13)	
FDCs	**SIDE EFFECTS**	**NO SIDE EFFECTS**	**P- VALUE**
Telmisartan + HCTZ	4.3 (1)	95.7 (22)	0.070
Telmisartan + Amlodpine	23.5 (4)	76.5 (13)	

There was statistically significant difference in the occurrence of side effects between Olmesartan / amlodipine/HCTZ and telmisartan/HCTZ (p=0.070) at 0.5 level of significance. The graph shown below is the graphical representation of the above table.

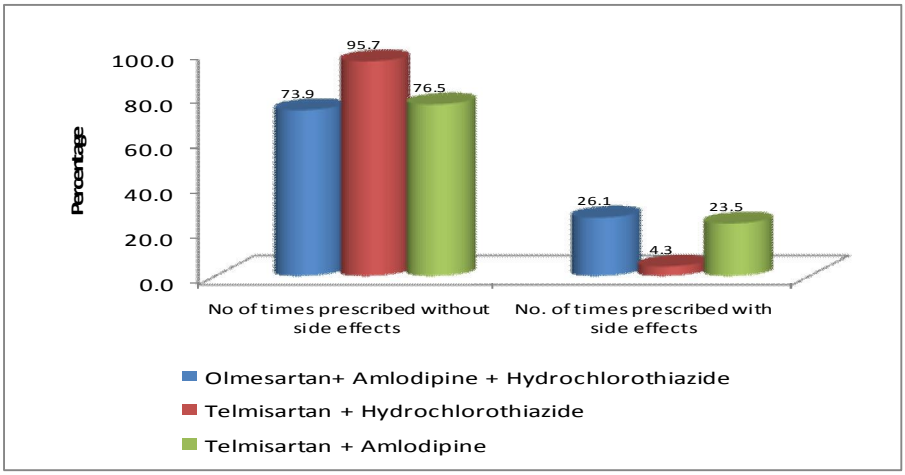

Fig 8: Comparison of frequency of side effects between FDC.

WHO-SYSTEM ORGAN CLASSIFICATION (SOC) OF ADVERSE EVENTS:

The side effects observed in the study were classified according to WHO-SOC and tabulated as follows.

Table 2: ADR according to WHO-SOC.

ADR	SOC ID	No: of patients affected
Chest pain	11	1
Numbness of limb	8	1
Hypotension	11	2
Dizzinesss	8	4
Fatigue	22	4
Hyponatremia	6	2
Pedal edema	22	8
Cough	13	3
Claudication	12	2
Bradycardia	11	3
Hyponatremic convulsion	8	1

Table 3: SOC ID with their respective criteria

SOC ID	SOC Criteria
6	Metabolism and nutrition
8	Nervous system disorders
11	Cardiac disorders
12	Vascular disorders
13	Respiratory, thoracic and mediastinal disorders
22	General disorders and administration site conditions

The adverse effects were classified according to system organ class, the most commonly observed adverse reactions being general disorders and administration site conditions (12 patients), followed by nervous system and cardiac disorders (6 patients each).

NARANJO ADR PROBABILITY SCALE:

The causality assessment of ADR occurred in patients based on Naranjo ADR probability scale.

Table 4: Distribution of ADR probability

ADR probability	No of ADR in study population
Definite	0
Probable	4
Possible	7
Doubtful	0

DISCUSSION:

The usefulness of antihypertensive drugs depends not only on the degree to which blood pressure is lowered but also on the side effect profile. The side effects of anti-hypertensives affect tolerability and compliance by the patients. The present study evaluates the side effects of anti-hypertensive FDCs, even though FDCs are known to cause fewer side effects than their respective active pharmaceutical ingredients. The assessment of FDCs for their side effects is as important as monotherapy.

From a total of 150 patients only 42 of them had side effects and the rest were side effect free. There was an equal distribution of both genders among them.

The side effects observed were pedal edema, cough, dizziness, fatigue, hyponatremia, hypotension, bradycardia, numbness of limb, chest pain,

hyponatremic convulsion and claudication respectively.

No side effects were observed with combinations such as metoprolol/amlodipine, bisoprolol / HCTZ, olmesartan / chlorthalidone, nebivolol / HCTZ, atenolol / lercanidipine, telmisartan / cilnidipine, and s-amlodipine / HCTZ.

More number of side effects were observed in age ≤ 65 years and in patients with co-morbid conditions.

In this study, pedal edema was the most frequently observed side effect followed by fatigue and dizziness. Pedal edema was seen in combinations with amlodipine.

In the present study, more side effects were observed with the triple drug combination (olmesartan/amlodipine/HCTZ) and the dual drug combination (atenolol/amlodipine).Due to limited study period, the side effects of all FDCs were neither assessed fully nor the patients were adequately reviewed, which is the major limitation encounted in screening the side effects.

Most of the side effects were managed by replacing the FDCs causing side effect with another FDC or a monotherapy.

Among the FDCs, three of the most commonly prescribed FDCs were selected and compared for their side effects.The FDCs selected were olmesartan / amlodipine / HCTZ, telmisartan / HCTZ, and telmisartan / amlodipine. There was statistically significant difference in the occurrence of side effects between olmesartan / amlodipine/HCTZ and telmisartan / HCTZ (p=0.070) at 0.5 level of significance. The risk of occurring side effect with olmesartan / amlodipine/HCTZ was found eight times higher than telmisartan / HCTZ. But there was no significant difference in the occurrence of side effects between olmesartan / amlodipine/HCTZ – telmisartan / amlodipine (p=0.857) and telmisartan / HCTZ –telmisartan / amlodipine (p=0.040).

The adverse effects were classified according to system organ class, the most commonly observed adverse reactions being general disorders and administration site conditions (12 patients), followed by nervous system and cardiac disorders (6 patients each).

Eleven side effects were assessed for causality, and 4 were probable and the rest possible. Apart from some of the limitations encountered during the study, it definitely provides a perspective of side effects profile of anti-hypertensive FDCs. The findings of the study will need to be revalidated using larger sample size and longer follow up to derive a stronger conclusion.

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CONCLUSION:

The solitary reason for promoting FDCs is its fewer side effects compared to monotherapy. But it doesn't mean that FDCs have no side effects. During clinical trials, only a little of side effect profile is studied during the limited time period. More over it is to be noted that most of manufacturing and research companies neither perform adequate Periodic Safety Update Reports (PSURs) nor there are sufficient literature regarding side effects of FDCs in the well known abstracting and indexing services.

The present study been monocentered, involving limited sample size and study period, inadequate follow up, and the real influence and outcome of FDCs with regard to side effects were also not fully established. The present study could serve as a frame work upon which further studies can be done over a longer duration and including all available FDCs in the Indian market to screen the side effects of FDCs.

As a clinical pharmacist, continued pharmacovigilence can be encouraged to monitor the side effects and thereby reduce the enormity of this problem.

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AUTHORS CONTRIBUTION:

All authors have contributed equally in initiating, processing and in bringing out the study.

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