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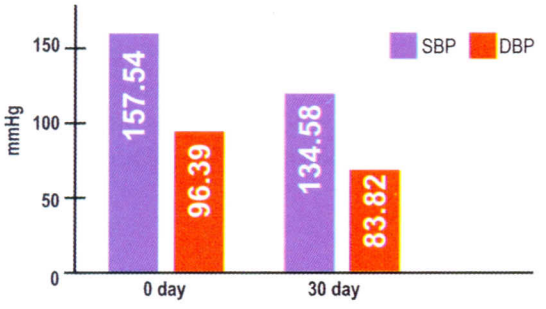

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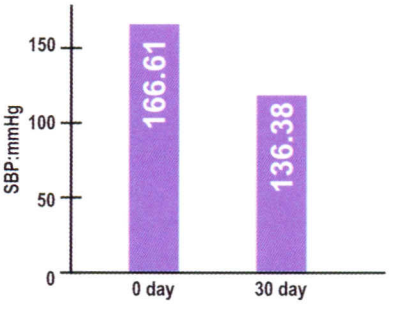

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Combination therapy with a Diuretic and S(-)Amlodipine in the Treatment of hypertension: The D-STAR Trial

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ABSTRACT

Introduction: Hypertension, being a multifactorial disease, is well managed by using fixed dose combination of antihypertensive agents.

Aim: To assess the safety and clinical efficacy of the fixed dose combination of S(-)Amlodipine and Hydrochlorothiazide (ESLO-D) in patients with hypertension.

Materials & Methods: Seventy four practicing physicians throughout India collaborated in the recruitment of 145 hypertensive patients, over a period of eight months. These patients were administered fixed dose combination of 2.5mg S(-)Amlodipine and 12.5mg Hydrochlorothiazide (ESLO-D). They were observed for adverse events and changes in their blood pressure and heart rate over a period of four weeks.

Results: Significant decrease in systolic blood pressure, diastolic blood pressure and heart rate by a mean of 22.95 ± 11.77 mmHg, 12.57 ± 8.62 mmHg and 5.84 ± 6.69 beats/min respectively were observed after treatment with the fixed dose combination of S(-) Amlodipine and hydrochlorothiazide (ESLO-D) for 4 weeks. The JNC VII recommended target blood pressure goal of < 140/90 mmHg was achieved in 80% of the patients while 67.74% of them achieved the target heart rate goal of < 83 beats/min at the end of 4 weeks. The combination also decreased systolic blood pressure by 18% among patients with isolated systolic hypertension. The therapy was found to be well tolerated by the study population.

Conclusion: These findings provide further evidence of the role of fixed dose combination therapy with S(-)Amlodipine and hydrochlorothiazide (ESLO-D) in the management of hypertension, including isolated systolic hypertension.

Key words: Hypertension, S(-)Amlodipine, Hydrochlorothiazide, fixed dose combination, blood pressure

INTRODUCTION

Hypertension is a major risk factor for both cardiovascular (CV) and cerebrovascular morbidity and mortality, contributing to approximately 50% of all CV events.[1] The guideline for the management of hypertension published by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) recommends a target blood pressure of <140/90mm Hg for all patients with hypertension. The use of a combination of antihypertensive agents to manage these patients is recommended by these JNC VII guidelines.[2] Moreover, the clinical guidelines on antihypertensive treatment of the World Health Organization-International Society of Hypertension in 1999 and the European Society of Hypertension and the European Society of Cardiology in 2003 both recommended calcium channel blockers (CCBs) as first-line antihypertensive drugs and emphasized their capacity to be used in combination with most of the other antihypertensive drug classes, including thiazide diuretics, to better achieve blood pressure goals.[3,4]

A 35-40% reduction in stroke and more than 50% reduction in heart failure and reductions in CVD related death rates are attributed to the use of antihypertensive agents including beta-blockers, Calcium channel blockers, diuretics and ACE inhibitors.[1] Thus, the goal of decreasing morbidity and mortality related to cardiovascular issues by preventing end-organ damage is established by these agents.[1]

A widely used group of antihypertensives are the CCBs which have been extensively proven to be effective and safe in lowering the blood pressure and reducing the long term CV risks

in a wide range of patients.[1] Amlodipine is a long-acting CCB with excellent antihypertensive and anti-anginal activities.[5,6] Its therapeutically active enantiomer, S(-)Amlodipine, brings about smoother and non-fluctuating reductions in blood pressure as well as demonstrates safety and predictability of response at half the dose of the racemate.[7,8]

S(-)Amlodipine may display a synergistic interaction with diuretics that may maximize anti-hypertensive action and clinical safety. CCBs are helpful in inactivating the calcium channels in the resistance vessels thereby leading to reduced afterload, while the exact mechanism for the hypotensive effects of diuretics is poorly understood. Thiazide diuretics, in particular, inhibit the sodium and chloride reabsorption in the kidney tubules and produce a corresponding increase in potassium excretion. Thus, their hypotensive effect is probably in part due to the decrease in peripheral resistance.[9] The combined effect of these different modalities leads to substantial decrease in blood pressure. Moreover, owing to the presence of a diuretic in the combination, the incidence of peripheral edema would also be lower than that seen with CCB monotherapy. Thus, the combined therapy with a CCB and diuretic will have beneficial effects on the treatment of hypertensive patients.[10-13]

The present clinical study is a post marketing surveillance carried out to evaluate the safety and efficacy of the fixed dose combination of S(-)Amlodipine with Hydrochlorothiazide (ESLO-D) in the treatment of hypertension.

MATERIALS & METHODS

This post marketing surveillance study was an open, uncontrolled, prospective, observational study.

A. Patients

Physicians throughout India were invited to participate in the study. More than seventy Indian physicians recruited patients, with a target number of 2 patients per physician from August 2009 to March 2010. The criterion for including patients (aged > 18yrs) in the study was the diagnosis of hypertension according to the JNC VII guidelines[2], necessitating the administration of a combination therapy.

B. Study design

The patients were evaluated for occurrence of an adverse reaction and efficacy at the end of four weeks of therapy. Depending on the severity of hypertension and the physician's judgment, the patients received therapy with a low dose combination of S(-) Amlodipine 2.5mg and Hydrochlorothiazide 12.5mg (ESLO-D) once a day for a period of four weeks, and followed up on the 30th day.

A standardized Case Report Form (CRF) was provided to the physicians wherein the data of each patient was documented and the completed CRF was sent to the Zuventus Healthcare Ltd for analysis.

C. Assessments

At baseline, the patient's demographic details, current medical diagnosis, presence of co-morbid conditions and the use of concomitant therapeutic agents were documented.

The patients were evaluated at baseline and at the end of week 4 for changes in the sitting blood pressure and heart rate. The presence or absence of clinical symptoms (dyspnea and palpitation) was also evaluated.

The physicians were required to rate the overall efficacy of the study medication at the end of the study on a four point scale (excellent, good, satisfactory and poor).

Patient's spontaneous reports of adverse events, whether related to the therapy or unrelated, were recorded. In accordance with the normal prescribing practice, dosage adjustments were effected by the physician, if required.

D. Statistical analysis

The changes in blood pressure and heart rate were analyzed by taking into account the mean change from baseline to the end of the study. Similarly, the trend in symptom resolution was also analyzed taking into account the decrease from baseline to the end of therapy. These data were analyzed descriptively and statistically using the Student's paired T-test or Fischer's test (as applicable) with the statistical software WINPEPI 9.9, where *p* value of less than 0.05 was considered as statistically significant.

RESULTS

Study population

Data corresponding to a total of 161 patients was obtained from 74 different practitioners, of which 145 patients with valid entry data were included for efficacy and safety analysis.

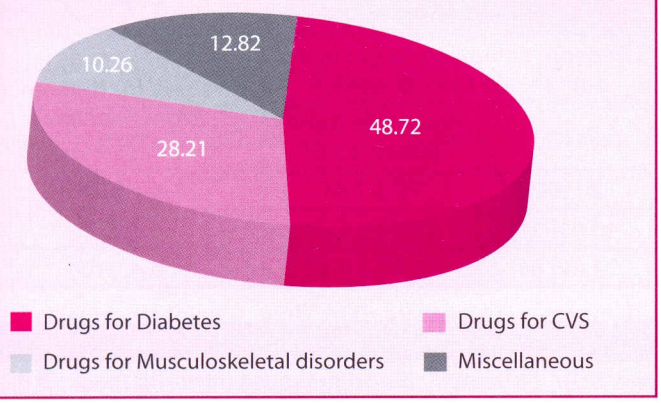
Demographic profile

The demographic data of the patients included for analysis are provided in Table 1. Of the study population, 31.03% of the patients also reported having other illness including diabetes (42.22%), cardiovascular disorders (17.77%) and gastrointestinal disorders (13.33%).

Table 1. Demographic profile of study population

Patients receiving ESLO-D (N=145)	
Sex	(N%)
Male	81 (55.86)
Female	64 (44.14)
Age (yrs), mean (± SD)	55.24 ± 9.96
Stage of Hypertension (n, %)	
Prehypertension	6 (4.14)
Stage I	47 (32.41)
Stage II	92 (63.45)
Duration of Hypertension (yrs), mean (± SD)	4.39 ± 3.79

Figure 1. Concomitant medications used by patients



Concomitant medications

Of the 145 patients evaluable, 73.10% of the patients (106/145) were administered only **ESLO-D** therapy. The remaining 25.33% of the patients (39/154) received other concomitant medications seen in Fig.1.

Efficacy

Overall trend in blood pressure and heart rate control

ESLO-D was associated with significant reduction in blood pressure (systolic and diastolic) as well as heart rate as seen in Table 2. This combination therapy significantly reduced the systolic and diastolic blood pressure by a mean of 22.95 ± 11.77 mmHg & 12.57 ± 8.62 mmHg (p<0.01) after 4 weeks of therapy. Similarly, heart rate was decreased by a mean of 5.84 ± 6.69 beats/min (p<0.01) at the end of therapy.

Achievement of JNC target blood pressure (≤ 140/90 mm Hg)

The treatment goal for individuals with hypertension and no other compelling condition is < 140/90 mmHg according to JNC 7. [2] This goal was achieved by 80% [95%CI: 72.6-86.2] of the population at the end of 4 weeks of therapy with **ESLO-D**. The mean blood pressure of these patients at the end of 4 weeks was 130.83 ± 8.32/ 83.19 ± 6.45 mmHg. Among the 20% of the patients who did not achieve the treatment goal, the mean baseline blood pressure of 172.52 ± 14.77/ 97.51 ± 10.93 mmHg reduced to 150.62 ± 9.16/ 86.48 ± 7.91 mmHg at the end of 4 weeks of therapy (p<0.01).

Subgroup analysis to determine the effect of the severity of hypertension on the achievement of JNC Target blood pressure found that 94.28% of the patients with Stage I hypertension and 70.65% of the patients with Stage II hypertension (Table 3) achieved the JNC target goal (p<0.01).

Achievement of target heart rate (< 83 beats/min)

According to the Framingham Heart study, [2] an ideal heart rate should be <83 beats/min since a higher heart rate is associated with a substantially higher risk of death from a cardiovascular event as compared to that associated with lower heart rate levels. Hence, achieving a target heart rate of <83 beats/min is considered as another therapy goal.

Among the current study population, 42.75% (62/145) of the patients had a baseline heart rate more than 83 beats/min, with a mean of 91.77 ± 7.63 beats/min. The target heart rate was achieved by 67.74% of this subgroup at the end of 4 weeks therapy with

Table 2. Overall trends in blood pressure and heart rate

	Baseline (Mean ± SD)	Week 4 (Mean ± SD)	Δ [95% CI]	p
Systolic Blood Pressure (SBP) (mmHg)	157.54 ± 15.39	134.58 ± 11.44	22.95 ± 11.77 [19.83-26.09]	P<0.01
Diastolic Blood Pressure (DBP) (mmHg)	96.39 ± 10.10	83.82 ± 6.88	12.57 ± 8.62 [10.57-14.57]	P<0.01
Heart Rate (Beats/min)	83.41 ± 9.31	77.56 ± 6.48	5.84 ± 6.69 [3.99-7.70]	P<0.01

Table 3. Trends in the achievement of target blood pressure

Severity of Hypertension	Parameter	Baseline	Week 4
Achievement of JNC Target BP of ≤140/90 mmHg			
Prehypertension (N=6)	SBP (mm Hg), Mean (± SD)	130	119* ± 10.09
	DBP (mm Hg), Mean (± SD)	89.16 ± 6.65	83.16 ± 4.66
	Patients with SBP/DBP ≤ 140/90mm Hg (n, %)	2 (33.33)	6 (100.0)
Stage I (N=47)	SBP (mm Hg), Mean (± SD)	145.96 ± 6.82	127.09* ± 6.76
	DBP (mm Hg), Mean (± SD)	93.51 ± 8.09	81.2* ± 8.13
	Patients with SBP/DBP ≤ 140/90mm Hg (n, %)	12 (25.53)	45 (95.74*)
Stage II (N=92)	SBP (mm Hg), Mean (± SD)	161.41 ± 11.1	134.06* ± 6.27
	DBP (mm Hg), Mean (± SD)	98.55 ± 10.61	84.51* ± 4.84
	Patients with SBP/DBP ≤ 140/90mm Hg (n, %)	0 (0.0)	65 (70.65*)

* Changes are statistically significant (p<0.01)

Table 4. Trends in the achievement of target heart rate

Achievement of target heart rate of <83 beats/min (N=145)					
Stage of hypertension	Patients with heart rate of >83 bpm at baseline		Patients achieving target heart rate of <83 bpm at week 4		p-values for difference from baseline
	N (%)	Heart rate (bpm) (mean ± SD)	N (%)	Heart rate (bpm) (mean ± SD)	
Pre-hypertension (N=6)	2 (33.33)	87 ± 1.41	2 (100)	79 ± 1.41	p > 0.05
Stage I (N=47)	17(36.17)	88.76 ± 6.82	16 (94.11)	76.94 ± 4.24	p < 0.05
Stage II (N=92)	43 (46.73)	93.37 ± 7.72	24 (55.81)	76.91 ± 3.47	p < 0.05

Table 5. Effect on isolated systolic hypertensive patients

	Systolic blood pressure (mm Hg) (mean ± SD)	Diastolic blood pressure (mm Hg) (mean ± SD)
Effect on overall blood pressure reduction (N=13)		
Baseline	166.61 ± 13.76	78.62 ± 8.12
Week 4 (n=13)	136.38 ± 13.36	77.84 ± 4.43
Achievement of JNC target BP of <140/90 mm Hg (N=13)		
Baseline	166.61 ± 13.76	78.62 ± 8.12
Week 4 (n=7)	126.85 ± 3.43	78.85 ± 1.95

ESLO-D ($p<0.01$). The mean heart rate of these patients at the end of therapy was 81 ± 7.13 beats/min.

Subgroup analysis also revealed that 94.11% of patients with Stage I hypertension and 55.81% of those with Stage II hypertension (Table 4) achieved this target at the end of therapy with ESLO-D ($p<0.01$).

Subgroup analysis: Isolated systolic hypertension (ISH)

Considering that the average age of the study population is 55yrs, a subgroup analysis was carried out on the subgroup of patients with isolated systolic blood pressure (ISH). Patients with systolic blood pressure above 140 mmHg together with diastolic blood pressure (DBP) below 90 mmHg[14] were considered for this analysis.

It was found that 8.9% of the study population showed the presence of isolated systolic hypertension, with baseline mean blood pressure of 167/79 mmHg. The administration of ESLO-D resulted in an overall reduction in the mean systolic blood pressure by 18.14%. Moreover, 53.84% of these patients achieved the JNC VII target at the end of week 4 of therapy (Table 5).

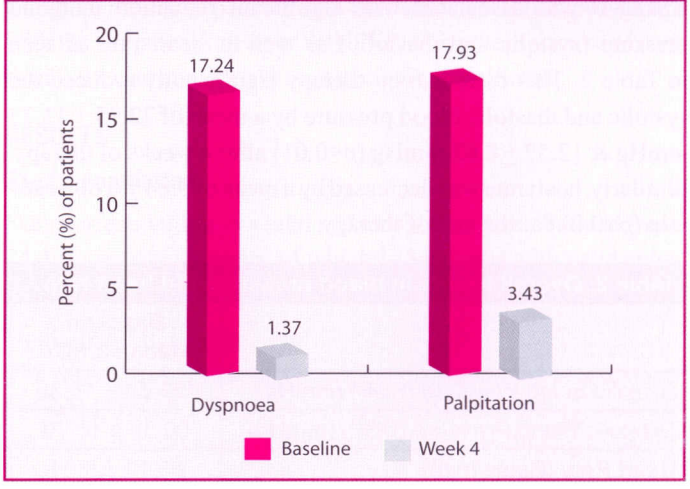
Symptom resolution

Symptoms associated with hypertension, mainly dyspnea (N=25) and palpitation (N=26), were followed throughout the study duration. An overall significant improvement in dyspnea and palpitation by 92.0% and 80.76% respectively was found ($p<0.01$). The trend in symptom resolution during the study period is seen in Fig 2.

Safety

ESLO-D was found to be well tolerated in this study population with 96.55% of the patients not reporting any adverse events including ankle edema or facial flushing throughout the treatment

Figure 2. Trends in symptom resolution



period. Of the remaining patients, headache (n=3), dryness of mouth (n=2) and peripheral edema (n=1) were the commonly reported adverse events.

DISCUSSION

The current study demonstrates the anti-hypertensive activity of the fixed low dose combination of S(-)Amlodipine and Hydrochlorothiazide (ESLO-D). The blood pressure was adequately controlled with a statistically significant reduction in the mean blood pressure of all the patients who successfully completed the month long therapy. The heart rate and various associated symptoms were also well managed on the administration of this combination.

It becomes necessary to administer a combination of two drugs with different but complementary modes of activity to

achieve an effective control of blood pressure, owing to the fact that hypertension is a multi-factorial disease. According to the guidelines for the management of hypertension, the combined treatment of long-acting CCBs and diuretics is recommended.[2-4] It is believed that the addition of a diuretic agent to an existing therapy regimen would enhance the efficacy of that agent and generally, a diuretic will be a component of combination therapy.[3,4,9] The combination of a diuretic (hydrochlorothiazide) with a CCB (S-amlodipine) has a dual effect: the combination increases antihypertensive efficacy and also reduces the side-effects associated with individual drugs, especially with CCBs.[9-13] The efficacy and safety of combining hydrochlorothiazide with amlodipine has already been demonstrated in controlled studies.[11-13]

An average reduction of 23/13 mmHg obtained with ESLO-D after one month therapy is better than or similar to that observed in previous studies with the individual drugs or similar combinations.[11,12,15] Further, the JNC VII goal of attaining a blood pressure < 140/90 mmHg was achieved by 80% of the patients at the end of therapy. This reduction in blood pressure may result in subsequently decreased risks of CVD and stroke.[2] This combination was also found to be equally effective in controlling blood pressure in patients with Stage I as well as Stage II hypertension. Similarly, the significant reduction of heart rate by an average of 9 beats/min helped 80.69% of the patients achieve a target heart rate of < 83 beats/min. This, in turn, translates into a lower risk of death from a cardiovascular event.[2]

Another interesting finding of this study is that the administration of ESLO-D among patients with ISH results in clinically significant control of systolic blood pressure. It is well known that ISH is an important cardiovascular risk factor and the results of the Systolic Hypertension in the Elderly Program (SHEP) have shown that its treatment can lead to a favorable outcome. It has also been established that diuretics and their combinations are the first line therapy for these patients.[14] In the current study, an average decrease in systolic blood pressure by

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Dr. AN Pandey	UP
Dr. A Sachdeva	Delhi
Dr. A Biswas	Delhi
Dr. A Verma	Delhi
Dr. A Chatterjee	West Bengal
Dr. AK Chakraborti	West Bengal
Dr. B.L.Kantroo	Delhi
Dr. B.P.Dutta	West Bengal
Dr. B.P.Singh	Bihar
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Dr. V Rana	Delhi
Dr. Y.S.Goel	Delhi

about 18% was seen on the administration of ESLO-D in patients with ISH. Thus, a fixed dose combination of hydrochlorothiazide and S(-)Amlodipine can be effectively used in patients diagnosed with ISH, especially the geriatrics.

The tolerability of the medication is also an important aspect while dealing with the pharmacological treatment of hypertension.[16] It is believed that an additive hypotensive effect with reduced side-effect profile than individual monotherapy is achieved with low dose combination drugs, like ESLO-D owing to the presence of sub-maximum doses of the individual components.[17] The present study helps to substantiate this pharmacological rational to some extent. The few stray cases of adverse experiences reported with ESLO-D were similar to those reported in earlier studies.

Adverse events reported in clinical studies with combination therapy with CCBs and diuretics as a component, range between 33.2-50%.[11-15] The incidence of adverse events reported with ESLO-D in this study was 3.55%. Peripheral edema is a very common adverse event with CCBs, and in case of racemic amlodipine, the incidence ranges from 20 to 30.6%.[18,19] However, it has also been proven that adverse events, especially edema, occur less frequently with S-amlodipine, and presence of a diuretic as part of the combination, thereby contributing to more expressed, positive clinical dynamic of the state of patients receiving this drug.[20] In the present study also, edema was found to occur in just one patient receiving the combination therapy.

There are a number of advantages including improved efficacy, enhanced responder rates, fewer adverse reactions and increased cost effectiveness when low dose combination therapy are used.[17] The current post-marketing surveillance study of ESLO-D helps substantiate this claim. Thus, this combination has been found to bring about normalization of blood pressure, without compromising the safety, in a large population of hypertensive patients. Thus, it can be concluded that this combination is a valuable therapeutic option for the treatment of mild to moderate hypertension.

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