EFFECTS OF LERCANIDIPINE VERSUS AMLODIPINE IN HYPERTENSIVE PATIENTS WITH CEREBRAL ISCHEMIC STROKE

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Aims: To evaluate the effect of the drugs in terms of ambulatory BP (ABPM) and clinical reductions, as well as analysing their effect on some variables such as BP morning surge, trough-peak ratio and smoothness index, which have been shown to be predictive of cardiovascular and cerebrovascular risk. **Patients and Methods:** 140 patients who had an ischemic stroke with hypertension during the acute phase (in first 7 days) were evaluated for inclusion. Inclusion criteria were the following: a mean 24 hours ambulatory BP >130/80 mmHg (measured on the first day after the diagnosis of stroke) and if the patients who had a clinical BP≥ 180/105mm Hg were taken the antihypertensive drugs (lercanidipine or amlodipine) after taking the machine of ABPM. The patients with clinical BP <180/105 mmHg were followed for a 6 days observation period and taking the antihypertensive drugs (lercanidipine or amlodipine) at seventh day. We evaluated drug efficacy by using clinical BP, 24h ambulatory BP, average day and night BP, the rate of responder and normalized patients; trough/peak ratio (T/P) and smoothness index (SI); and early morning BP surge rate (MBPS). All data were analysed with SPSS 20 software.We used χ^2 test to compare 2 rates and t-test to compare 2 means value. Statistical significant level was usedwith p value: 0.05, 0.01, 0.001. **Results:** Trough/peak ratio and smoothness index of lercanidipine, in patients with ischemic stroke and hypertension, after the 4-week treatment rise in a statistically significant way, although they remain lower than the readings found in the group treated with amlodipine (T/P = 0.61 for SBP and = 0.52 for DBP versus 0.75 for SBP and 0.73 for DBP; SI = 0.79 for SBP and = 0.57 for DBP versus 1.22 for SBP and 1.0 for DBP). Lercanidipine may be associated with a lower incidence of peripheral oedema than are older dihydropyridine CCBs. Our study showed that the rate of patients suffering adverse events in the amlodipine treated group was significantly higher compared to the lercanidipine treated group (p = 0.0379 and p = 0.0253 respectively). **Conclusion:** This study shows that lercanidipine is an effective drug in ambulatory 24h and clinical BP reduction. The efficacy shown by lercanidipine is similar to amlodipine's and showing a lower rate of adverse events when compared to amlodipine. It is concluded that lercanidipine can be an adequate choice when treating hypertensive patients with stroke.

Key words: *Cardiovascular, hypertensive, lercanidipine.*

1. INTRODUCTION

Antihypertensive treatment can dramatically reduce the number of recurrent strokes, as well as the risk for other associated cardiac events, for patients with a history of stroke or TIA[1,2].

For instance, an analysis of 61 prospective observational studies, involving almost one million individuals, explored the relationship between blood pressure (BP) levels, 12,000 strokes and 34,000 ischemic heart disease events over an average timeframe of 13.2 years. This analysis demonstrated that, in patients aged 40–69 years, each difference of 20 mmHg in usual SBP (or, approximately equivalently,

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10 mmHg in usual DBP) is associated with more than a twofold difference in the stroke death rate, and with twofold differences in the death rates from IHD and from other vascular causes[3]. It has been suggested that the early initiation of antihypertensive treatment, starting on day 1 following the stroke, can reduce cumulative mortality and other cardiovascular events at a 1-year follow-up[4].

Some meta-analyses suggest that agents like calcium channel blockers (CCBs) may have some additional advantage in preventing strokes, although it is not clear whether this can be ascribed to a specific protective effect or to a slightly better BP control, which is often achieved with patients treated with CCBs[5-8]. A meta-analysis of three studies (ALLHAT, JMIC-B, STOP-H2), comparing ACE inhibitors with calcium-channel blockers (CCBs), showed that ACE inhibitors were associated with a higher incidence of stroke (RR 1.14, 95% CI 1.02 to 1.28). Also, based on the results of the two studies reporting stroke as an outcome (ASCOT, ELSA), CCBs were associated with a reduced incidence of stroke (RR 0.77, 95% CI 0.67 to 0.88)[1].

However, to our knowledge direct comparisons between two CCBs in hypertensive patients with previous stroke are still scant. Our study evaluates the effects of two different CCBs, lercanidipine and amlodipine, in hypertensive patients with cerebral ischemic stroke.

We evaluate the effect of the drugs in terms of ambulatory BP (ABPM) and clinical reductions, as well as analysing their effect on some variables such as BP morning surge, trough-peak ratio and smoothness index, which have been shown to be predictive of cardiovascular and cerebrovascular risk.

2. PATIENTS AND METHODS

2.1. Study population

Patients were recruited from May 2009 to July 2012 at Stroke Unit of Neurological Department of General Hospital in Nghe An Province and at Cardiovascular Center of Hue Central Hospital of Vietnam.

One hundred and forty patients who had an ischemic stroke with hypertension during the acute phase (in the first 7 days) were evaluated for inclusion. All these patients gave their informed consent to the study.

Inclusion criteria were the following: a mean 24 hours ambulatory BP >130/80 mmHg (measured on the first day after the diagnosis of stroke) and if the patients who had a clinical BP≥ 180/105mmHg were taken the antihypertensive drugs (lercanidipine or amlodipine) after taking the machine of ABPM. The patients with clinical BP ≤ 180/105 mmHg were followed for a 6 days observation period and taking the antihypertensive drugs (lercanidipine or amlodipine) at the seventh day. During the observation period, patients were treated if their clinical BP became ≥ 180/105 mmHg. Exclusion criteria were: secondary hypertension, BP ≥ 220/120 mmHg, concomitant vascular diseases (e.g. aorta aneurysm, heart attack, left heart failure due to paroxysmal hypertension, subarachnoid haemorrhage), Glasgow Score=3; haemorrhagic stroke, patients who had a hypertensive reaction to the stroke in the acute phase, contraindications to lercanidipine and amlodipine, limb oedema, atrial fibrillation, local allergy and allergy to the sphygmomanometer's cuff, arm size too small to perform precise measurements.

2.2. Study design

This was an open label, controlled, randomized, parallel groups study.

Eligible subjects underwent the clinical BP measurement and the 24-hour ambulatory BP monitoring (ABPM) during the acute phase of ischemic stroke. Subjects who met the eligibility criteria were randomized to a 4-week treatment period.

These subject (32 patients were enrolled the first daywith BP >180/105mmHg and 72 patients during and after the 6 days observation period) were randomly assigned, in a 1:1 ratio, to either an oral treatment with lercanidipine 20 mg/day or amlodipine 10 mg/day. Patients were assigned to one of the two groups according to a randomization list created through a block randomization (block size 8).

The flow chart of the study is described in figure 1.

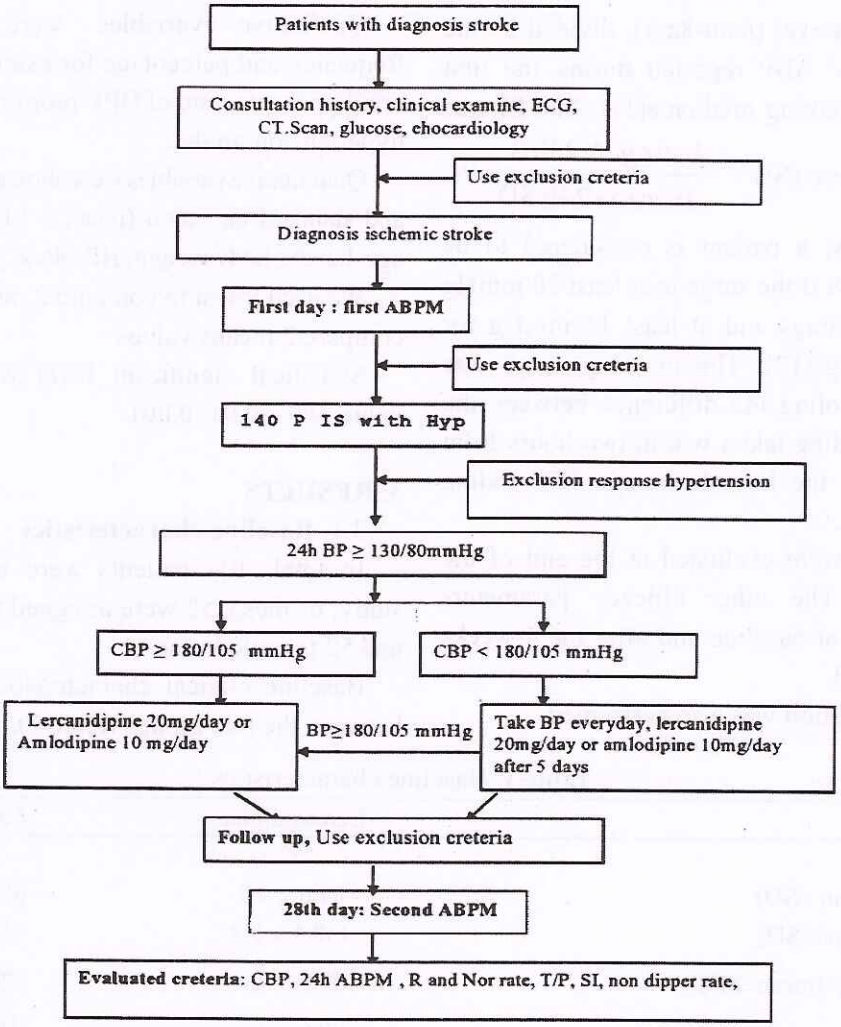

Diagram 1: Diagram of study design

P = Patient, IS = Ischemic Stroke, Hyp = Hypertension, CBP = Clinical Blood Pressure
R = Response, Nor = Normalization, T/P = trough/peak, SI = Smoothness Index

All subjects were assessed by two times of measurements, the first time: an ambulatory BP monitoring during 24h (24hABPM) and clinical BP measurement during the acute phase, and the second time at the end of the 4 week treatment period. ABPM was performed with reading every 30 minutes during the daytime (from 6 a.m. to 10 p.m.) and hourly during the night (10 p.m. to 6 a.m.). Those patients from with less than 70% of either awake or asleep valid BP reading were excluded from the statistical analyses.

Clinical BP was measured by doctor after resting no less than 5 minutes in a sitting position. The doctor measured directly 2 times in machine of ABPM and took the mean value of 2 measurement times. Grades of hypertension were classed by WHO/ISH 2003(Grade I: 140-159/90-99mmHg; Grade II: 160-179/100-109mmHg; Grade III: ≥180/110mmHg).

2.3. Study variables

We evaluated drug efficacy using clinical BP, 24h ambulatory BP, average day and night BP, the rate of responder and normalized patients; trough/peak ratio (T/P) and smoothness index (SI); and early morning BP surge rate (MBPS).

Response was defined as a 24h average BP reduction ≥15mmHg for SBP or ≥10 mmHg for DBP[9,10]. Patients were considered normalized when mean 24h BP was <130/80 or mean daily BP <135/85 mmHg[9].

For clinic BP, response was defined as BP reduction≥ 20/10mmHg and normalization when

BP was < 140/90mmHg[11]. T/ P was the lowest mean of ΔBP at the end of the last two hours of the treatment interval (6am-8am) divided by the highest mean of ΔBP reported during the first 2-8 hours after taking medicine[11]. The SI was defined as follows: $(SI) = \frac{Average\Delta\ 24hB}{Average\ 24h\ SD}$ [11]

In this study, a patient is considered to be having an MBPS if the surge is at least 20 mmHg for systolic readings and at least 15 mmHg for diastolic readings[12]. The morning surge was calculated by noting the difference between the average BP reading taken within two hours from awakening and the lowest average BP reading during the night.

T/P and SI were evaluated at the end of the study period. The other efficacy parameters were evaluated at baseline and after the 4-weeks treatment period.

Safety evaluation was also performed.

Statistical analyse

All data were analysed with SPSS 20 software.

Qualitative variables were showed by frequency and percentage for example dipper and nondipper rate, rate of BPs' morning surge, rate of hypertension grade...

Quantitative variables were showed by mean value and standard deviation (mean ± SD), for example: age, height, body weight, BP, blood glucose...

We used χ^2 test to compare 2 rates and t-test to compare 2 means values.

Statistical significant level was usedwith p value: 0.05, 0.01, 0.001.

3. RESULTS

3.1. Baseline characteristics

In total, 104 patients were included in the study; of these, 52 were assigned to lercanidipine and 52 to amlodipine.

Baseline clinical characteristics were similar between the two groups (table 1).

Table 1. Baseline characteristics

	Lercanidipine	Amlodipine
Patients number	52	52
Age (years) (mean ±SD)	64.6 ± 9.7	65.4 ± 10.8
Height (cm) (mean±SD)	158.5 ± 5.8	158.4 ± 6,1
Body weight (kg) (mean±SD)	50.0 ± 9.4	49.0 ± 9.2
BMI	20.6 ± 3.0	19.9 ± 3.0
Severity of hypertension N (%)		
Grade I	19 (36.5%)	19 (36.5%)
Grade II	20 (38.5%)	16 (30.8%)
Grade III	13 (25.0%)	17(32.7%)
Clinical BP (mmHg)		
SBP (mean±SD)	168.9 ± 21.6	167.1 ± 19.9
DPB(mean±SD)	96.2 ± 13.6	97.7 ± 14.5
24h-ABPM (mmHg)		
SBP (mean±SD)	154.4 ± 15.2	156.4 ± 17.6
DBP (mean±SD)	89.9 ± 10.3	90.2 ± 12.8
24h heart rate (beats/m) (mean±SD)	75.3 ± 12.4	75.1 ± 12.2
Blood glucose (mmol/l) (mean±SD)	6.59 ± 2.62	6.05 ± 2.04
Diabetes mellitus N (%)	2 (3.8%)	6 (11.5%)

(NS = Not significant)

3.2. Efficacy parameters

Clinical BP

Lercanidipine significantly reduced the mean clinical SBP/DBP from 168.9±21.6/96.2±13.6 mmHg to 147.1±22.0/87.1±14.0 mmHg (p<0.001 for SBP and <0.01 for DBP). Amlodipine significantly reduced the clinical SBP/DBP from 167.1±19.9/97.8±14.5 mmHg to 143.3±21.9/82.8 ± 14.1 mmHg (p <0.001 for both comparisons) (table 2).

Table 2. Clinical BP for before and after treatment in lercanidipine and amlodipine

BP (mmHg)	Lercanidipine (1)				Amlodipine (2)			
	Baseline	AT	Δ	p	Baseline	AT	Δ	P
SBP	168.9 ± 21.6	147.1 ± 22.0	21.8 ± 21.2	<0.001	167.1± 19.9	143.3 ± 21.9	23.8 ± 24.5	<0.001
p(Δ) 1-2	0,657							
DBP	96.2 ± 13.6	87.1 ± 14.0	8.9 ± 14.0	<0.01	97.8 ± 14.5	82.8 ± 14.1	14.6 ± 18.3	<0.001
p(Δ) 1-2	0.0774							

AT= After Treatment; Δ = Baseline's BP - ATs'BP

Table 2: *BP Reduction in lercanidipine and amlodipine groups from baseline; 4w: Following a 4-week Treatment).*

Clinical BP/DBP reductions were 21.8±21.2/8.9±14.0 mmHg in the lercanidipine group and 23.8±24.5/14.6±18.3 mmHg in the amlodipine group. The reduction level of 2 groups was not different significantly with p = 0.657 for SBP and p = 0.0774 for DBP.

The response rate in the lercanidipine group was 36.5% (n=19), whereas the normalization rate was 30.6% (n=16). In the amlodipine treated group, these figures were 44.2% (n=23) and 36.5% (n=19). The response and the normalization rate of lercanidipine versus amlodipine were not different significantly(p=0.424 and p = 0.533, respectively).

24h ambulatory BP

Following the 4-week treatment, both lercanidipine and amlodipine significantly reduced mean 24h, daytime and night-time BP. (Table 3)

Table 3. 24 h, daytime and nighttime BP reductions with lercanidipine and amlodipine treatment

		Baseline SBP ± SD (mmHg)	4 week SBP ± SD (mmHg)	Baseline DBP (SD) (mmHg)	4-week DBP ± SD (mmHg)	p vs baseline
Lercanidipine (n=52)	24 h mean	154.4±15.2	137.4±17.2	89.9±10.3	81.7±11.0	<0.001
	Day-time	155.9±16.1	137.8±17.2	90.3±11.0	82.1±11.2	<0.001
	Night-time	150.0±16.0	136.3±19.5	87.9±10.3	80.8±12.3	<0.001
Amlodipine (n=52)	24 h mean	156.4±17.6	132.9±14.0	90.2±12.8	77.4±8.8	<0.001
	Day-time	157.3±17.8	133.9±14.7	90.7±12.6	78.0±9.2	<0.001
	Night-time	152.8±19.1	129.2±13.2	88.3±14.6	74.4±9.5	<0.001

The level of BP reduction during the 24h timeframe and the night-time systolic/diastolic blood pressure values in lercanidipine treated patients was significantly lower compared to the amlodipine treated patients (-17.0±8.2/-8.2±8.5mmHg and -13.7±16.2/-7.1±11.8mmHg in the lercanidipine group versus -23.5±17.3/-12.7±10.3mmHg and -23.7±17.4/-13.8 ± 11.6mmHg in the amlodipine group; (p=0.0233 for 24h timeframe SBP, p=0.0168 for 24h timeframe DBP; p = 0.0031 for night-time SBP; and p =0.0043 for night-time DBP).

The response rate in the lercanidipine group was 34.6% (n=18) while the normalization rate was 30.8% (n=16); in the amlodipine group, these figures were 48.1% (n=25) and 44.2% (n=23). The response and normalization rate of 2 drugs were not different significantly (p = 0.163 for response rate and p =0.156 for normalization rate).

Trough/peak ratio and SI

T/P in the lercanidipine group was 0.61 for SBP and 0.52 for DBP; in the amlodipine group it was 0.75 for SBP and 0.73 for DBP. The SI was 0.79 for SBP and 0.57 for DBP in the lercanidipine group; in the amlodipine group, it was 1.22 for SBP and 1.0 for DBP.

Statistical analysis showed that both T/P and SI were higher in the amlodipine group than in the lercanidipine group.

Effects on early morning surge

In the lercanidipine, group the early MBPS rate decreased significantly after the 4-week treatment period when compared to baseline (from 67.3% [n=35] to 11.5% [n=6]; p<0.05).

In amlodipine treated group the rate decreased significantly, from 59.6% (n=31) to 9.6% (n=5) (p<0.001).

The rate of reduction in early MBPS rate did not differ between the two drugs.

More in detail, lercanidipine reduced SBP/DBP morning surge from 41.4±14.4/27.7±7.8 mmHg to 37.3±10.9/21.7±6.7mmHg (p<0.01 for SBP and p<0.001 for DBP). Amlodipine reduced significantly SBP morning surge from 42.9 ± 13.5 to 35.8 ± 10.8 mmHg (p <0.01). As for DBP the reduction was not significantly from 24.4 ± 9.4 mmHg to 22.8 ± 3.4 mmHg (p>0.05).

Safety

Table 3 shows the rate of adverse events. The number of patients suffering adverse events in the lercanidipine group was significantly lower when compared with the amlodipine group (3 [5.7%] vs 10 [19.2%]; p=0.03); a similar finding was reported for the number of adverse events (5 vs 15; p=0.02).

Table 4. Adverse events with lercanidipine and amlodipine

Adverse Event	Lercanidipine		Amlodipine		p value
	n	%	n	%	
Patients with AE	3	5.7	10	19.2	0.03
Flushing	3	5.7	8	15.4	0.11
Ankle oedema	2	3.8	4	7.7	0.66
Headache	0	0.0	2	3.8	(-)
Dizziness	0	0.0	1	1.9	(-)
Total Side Effects(F+ Ao+ H + D)	5	9.6	15	28.8	0.02
Flushing and Ankle oedema/Patient	2	3.8	5	9.6	0.42
Flushing + A oedema + Headache/Patient	0	0.0	2	3.8	(-)
≥2 Adverse events	2	3.8	7	13.6	0.14

4. DISCUSSION

The use of antihypertensive treatment during the acute phase of stroke is still being discussed. Following a stroke, even minor changes in BP may be associated with alterations in cerebral perfusion pressure, which may in turn affect the ability of damaged neurones to survive[13]. However, evidence suggests that the early initiation of an antihypertensive treatment following an ischaemic stroke can improve prognosis. In our study we only enrolled patients with clinical BP >180/105 mmHg during the acute phase of the stroke. Patients with lower BP values were followed up for 6 days before the beginning of the study treatment.

Despite Guidelines state that treatment can be based on any antihypertensive drug, since it is the reduction in BP that decreases the risk of events, some recent meta-analyses suggest that CCBs may provide some additional advantage in preventing stroke[14].

In our study, we compared lercanidipine and amlodipine, currently the most widely prescribed antihypertensive agents[15], in their efficacy on clinical and ambulatory BP reductions as well as a number of other clinical parameters.

Various previous trials have shown lercanidipine to be effective in reducing BP and to have a good tolerability profile compared to other CCBs.

In two large, non-blind, non-comparative studies involving approximately 16,000 patients with mild/moderate hypertension, SBP and DBP were significantly reduced after a 12 week treatment with lercanidipine 10-20 mg/day. Furthermore, in the largest study 64% of patients were responders after 12 weeks of treatment and an additional 32% had their BP normalized. In comparative trials lercanidipine 10-20 mg/day was as effective as nifedipine slow release (SR) 20-40 mg twice daily, amlodipine 10 mg/day, felodipine 10-20 mg/day, nifedipine gastrointestinal therapeutic system (GITS) 30-60 mg once daily or verapamil SR

240 mg/day in reducing SBP and DBP in patients with mild/moderate hypertension after 2-16 weeks of treatment [16].

Goda et al[17], conducted a randomized clinical trial in 202 mild to moderate hypertensive patients treated with lercanidipine 10mg or amlodipine 5mg with a 28 week follow up. The results showed that both lercanidipine and amlodipine decreased BP during treatment and that the group treated with lercanidipine had a higher response rate versus the amlodipine treated group (after 2 weeks: 53% compared with 34%, p <0.001 and after 12 weeks it was 93.9% compared with 87.4%, p = 0.03) and a higher normalization rate (<140/90 mmHg) after 12 weeks (68% vs 56%, p <0.01).

Our study showed that following the 4-week treatment of hypertensive patients with ischemic stroke, lercanidipine was as effective as amlodipine in reducing mean clinical systolic and diastolic BP. Even if our study does not show a statistically significant difference in terms of responder and normalisation rates when comparing the two drugs, it does show a high rate with both drugs.

We know that ambulatory 24h systolic BP is a better predictor than clinical assessment for cardiovascular morbidity and mortality. When clinical BP measurement was compared to ABPM, ambulatory 24h BP was shown as more effective in predicting clinical events[1].

We found that the two drugs reduce ambulatory BP in terms of daytime, night-time and 24h means. When compared, amlodipine reduces 24h ambulatory BP and night-time mean BP more effectively than lercanidipine (23.4 ± 17.3/12.7 ± 10.3 mmHg and 23.7 ± 17.4/13.8 ± 11, 6 mmHg vs 17.0 ± 10.1 mmHg and 8.2 ± 8.5 mmHg, p<0.05). Lercanidipine is as effective as amlodipine in reducing daytime mean BP (p> 0.05).

4.1. Early morning surge, trough/peak ratio and smoothness index

Our study evaluates the early MBPS as an efficacy parameter to test the drug's effect during the first hours of the morning that are well known to be associated with a major risk of cardiovascular and cerebral events.

MPBS is a predictor of subsequent stroke events in elderly hypertensive patients independently of ambulatory BP levels and target organ damage. Controlling the MBPS with antihypertensive medication might improve stroke prognosis[18].

In this study within the group of patients receiving lercanidipine the rate of early morning BP surges decreased significantly after a 4-week treatment period, compared with baseline, from 67.3% (n=35) to 11.5% (n=6) (p <0.05).

Smoothness index (SI) is inversely correlated with BP variability within a 24h timeframe, the higher the index is, the lower BP variability will be.

SI may be a more accurate measurement of smooth blood pressure control under therapy than trough/peak ratio[19].

Our results showed that trough/peak ratio and smoothness index of lercanidipine, in patients with ischemic stroke and hypertension, after the 4-week treatment rise in a statistically significant way, although they remain lower than the readings found in the group treated with amlodipine (T/P = 0.61 for SBP and = 0.52 for DBP versus 0.75 for SBP and 0.73 for DBP; SI = 0.79 for SBP and = 0.57 for DBP versus 1.22 for SBP and1.0 for DBP).

4.2.Side effects of lercanidipine and amlodipine

Results from clinical studies suggest that lercanidipine may be associated with a lower incidence of peripheral oedema than are older dihydropyridine CCBs[20].

Gastone Leonetti et al[21] conducted a multicentre, double blind and parallel group study on 828 elderly hypertensive patients, aged ≥ 60. Patients were randomized to lercanidipine 10mg/day (n = 420), amlodipine 5mg/day (n = 200) or lacidipine 2mg/day (n = 208) (2:1:1 ratio). Results showed that, with similar BP reduction, amlodipine treated patients had significantly higher rates of oedema (19%) compared with lercanidipine treated patients (9%), and of early study discontinuations due to oedema (8.5% vs 2.1%). Similarly, oedema-related symptoms (lower limb swelling and heaviness) occurred significantly more often with amlodipine than with lercanidipine and lacidipine. Most

cases occurred within 6 months. The study concluded that lercanidipine and lacidipine have an antihypertensive effect comparable to amlodipine but a better tolerability profile.

Our study showed that the rate of patients suffering adverse events in the amlodipine treated group was significantly higher compared to the lercanidipine treated group ($p = 0.0379$ and $p = 0.0253$ respectively). During the 4-week treatments no patient in either group had to discontinue the treatment because of side effects.

5. CONCLUSION

This study shows that lercanidipine is an effective drug in ambulatory 24h and clinical BP reduction. The efficacy shown by lercanidipine is similar to amlodipine's.

Lercanidipine is actually superior in terms of tolerability showing a lower rate of adverse events when compared to amlodipine.

It is concluded that lercanidipine can be an adequate choice when treating hypertensive patients with stroke.

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