MANAGEMENT OF HYPERTENSION- INSIGHTS INTO REAL-WORLD CLINICAL PRACTICE FOR DIFFERENTIAL USAGE OF CALCIUM CHANNEL BLOCKERS (CCBS)

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ABSTRACT

BACKGROUND

Calcium channel blockers (CCB) like amlodipine, S (-) amlodipine and cilnidipine, etc. have established place in the treatment of hypertension (HTN). As perceived by most of the physicians, they have comparative antihypertensive efficacy. However, available evidences suggest varied differences in incidence of pedal oedema.

Aim- This survey was planned to understand real-world clinical practice pattern of Indian physicians for usage of various antihypertensive agents with emphasis on CCBs and whether differential incidence of oedema with CCBs is encountered in their clinical practice.

MATERIALS AND METHODS

Survey questionnaire consisting of 10 questions about preferred antihypertensive choice for different subsets of patients with HTN and efficacy and safety of S (-) amlodipine was prepared and validated in small group of physicians. Overall, 494 general physicians and cardiologists practising in India were approached for seeking their opinion on usage of various CCBs.

Statistical Analysis- Data were expressed in percentage.

Design**-** Prospective, cross sectional, questionnaire-based survey.

RESULTS

Amongst various anti-hypertensive agents, majority of the physicians preferred CCB as their initial drug of choice for patients with HTN (53.8%), HTN with CKD (41.1%), elderly (55.3%), and young (30.8%) patients. Though amlodipine was preferred by 75.7% physicians, pedal oedema was observed in >10% patients by 40.5% physicians. Most of the physicians rated S (-) amlodipine to have better efficacy (79.4%) and safety profile (88.3%) with decreased incidence of pedal oedema than racemic Amlodipine.

CONCLUSION

Available evidences suggest comparative efficacy of S (-) amlodipine and racemic amlodipine with varied differences in incidence of pedal oedema. However, our survey suggests better efficacy and safety of S (-) amlodipine over racemic amlodipine as opined by most of the physicians of India. The survey findings need to be further evaluated in randomised clinical trials.

KEYWORDS

Hypertension, Calcium Channel Blockers, S-Amlodipine, Pedal Oedema.

HOW TO CITE THIS ARTICLE: Dasbiswas A, Tamboli T, Ingole S, et al. Management of hypertension- Insights into real-world clinical practice for differential usage of calcium channel blockers (CCBs). J. Evid. Based Med. Healthc. 2017; 4(38), 2295-2299. DOI: 10.18410/jebmh/2017/451

BACKGROUND

Hypertension (HTN) is a highly prevalent condition and has become a major cause of concern due to its insidious nature of onset and also due to high rates of mortality and morbidity associated with the condition.[1] A systematic review and meta-analysis stated an overall prevalence of HTN in India to be 29.8%, affecting 33% urban and 25% rural Indians.[2] HTN is attributed as major modifiable risk factor for premature cardiovascular (CV) disease and stroke globally. Effective control of blood pressure (BP) can bring down the dreadful consequences of HTN to a larger extent. Various HTN guidelines have recommended thiazide diuretics, Renin angiotensin system (RAS) blockers (angiotensin converting enzyme (ACE) inhibitors & angiotensin receptor blockers (ARBs)) and calcium channel blockers (CCBs) as first line agents for uncomplicated HTN and recommended preferential use of one agent over the other after careful evaluation of patients for comorbidities.[3,4,5] CCBs like

Financial or Other, Competing Interest:
Emcure Pharmaceuticals Ltd.,
Submission 27-03-2017, Peer Review 05-04-2017,
Acceptance 28-04-2017, Published 10-05-2017.
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DOI: 10.18410/jebmh/2017/451

amlodipine, S (-) amlodipine and cilnidipine are amongst the most commonly used antihypertensive drugs today. Their antihypertensive effect is based on the ability to reduce total peripheral vascular resistance due to inactivation of voltage-dependent calcium channels in smooth muscle tissue of arterial and arteriolar walls. Available evidence suggests that these CCBs have comparative antihypertensive efficacy, but they differ in their tendency to cause peripheral oedema, which can result in dose reduction or drug withdrawal and adversely affect antihypertensive management.[6,7,8]

Amlodipine is a racemic mixture of two isomers i.e. R (+) and S (-) amlodipine existing in a 1:1 ratio, of which the therapeutic effects owing to the calcium channel blocking activity are attributable only to S (-) amlodipine. S (-) amlodipine has been proved as the only active isomer of amlodipine having 1000 times greater affinity for binding to calcium channels when compared to the R (+) isomer.[9] Also, the safety and efficacy of S isomer of amlodipine is proved in various randomised controlled clinical trials including studies in over 5000 Indian hypertensive patients. These studies have shown that the overall incidence of pedal oedema with S (-) amlodipine is as low as 1.56%.[10] Because of these benefits, S (-) amlodipine has also been recommended as an ideal therapy for switching from conventional racemic amlodipine for patients developing peripheral oedema.[11]

However, there are differences amongst physicians in having preferences for various antihypertensive drug classes as first line agents in hypertensive patients with or without comorbidities. Also choice amongst various CCBs differs. Therefore, this survey was planned to understand the real-world clinical practice pattern of Indian physicians for usage of various antihypertensive agents with emphasis on CCBs and whether differential incidence of oedema with CCBs is encountered in their clinical practice.

MATERIALS AND METHODS

This was a prospective, cross sectional, questionnaire-based survey of physicians and cardiologists across different geographic areas in India conducted over a period of 4 months from June to September, 2016. Survey questionnaire was prepared consisting of 10 questions related to management of hypertension in real world clinical settings to analyse the approach of Indian practitioners for management of hypertension. The questions were pertaining to goal BP followed in their practice; initial antihypertensive of choice; preferred antihypertensive of choice in different subsets of patients like essential HTN with diabetes, HTN with chronic kidney disease (CKD), elderly hypertensives, young hypertensives and isolated systolic HTN; preferred CCB, occurrence of pedal oedema with amlodipine and cilnidipine, efficacy and safety of S (-) amlodipine compared to racemic amlodipine, BP level to start dual antihypertensive therapy and the preferred ARB of choice to combine with S (-) amlodipine. The questionnaire was then validated in small group of physicians. Overall, 494 general physicians and cardiologists practising in India were approached for seeking their opinion. The completed questionnaires were collected and analysed. Number of responses to each question was categorised and percentages for all the responses were calculated. Missing data was not considered for calculating percentages. Data were expressed in percentage.

RESULTS

A total of 494 physicians and cardiologists who were managing a considerable percentage of newly diagnosed as well as uncontrolled hypertensive patients in routine clinical practice completed the survey questionnaire. In patients with HTN without comorbidities, majority of the physicians followed the goal BP of 130/80 mmHg (45.5%) followed by target BP of <140/90 mmHg by 41.9% physicians. In hypertensive patients with diabetes or chronic kidney disease (CKD), majority of physicians preferred to set a goal of <130/80 mmHg (42.9% and 35% respectively). Goal BP of <140/90 mmHg in hypertensive diabetic and CKD patients was followed by 21.5% and 25.7% physicians respectively. Overall, CCBs were the most preferred antihypertensive of choice for initiating therapy in hypertensive patients by 61.3% physicians followed by ARBs (19.2%). Most of the physicians preferred CCB as their initial antihypertensive of choice for patients with HTN without comorbidities (53.8%), HTN with CKD (41.1%), elderly hypertensive (55.3%), patients with isolated systolic HTN (46.2%) and young hypertensive patients (30.8%) (Figure 1), whereas ARBs were the preferred choice in diabetic patients with hypertension (49.6%).

Out of amlodipine and cilnidipine, though amlodipine was preferred by 75.7% physicians, pedal oedema was observed in >10% of patients by 40.5% physicians (Figure 2). Pedal oedema was observed even with use of cilnidipine by 33.2% of physicians. Most of the physicians rated S (-) amlodipine to have better efficacy (79.4%) and safety profile (88.3%) with decreased incidence of pedal oedema than racemic amlodipine (Figure 3). More than half of the physicians (51.4%) preferred to start dual anti-hypertensive therapy when BP level was >160/100 mmHg, and telmisartan was the most preferred agent for addition to S (-) amlodipine, according to 71.9% of physicians.

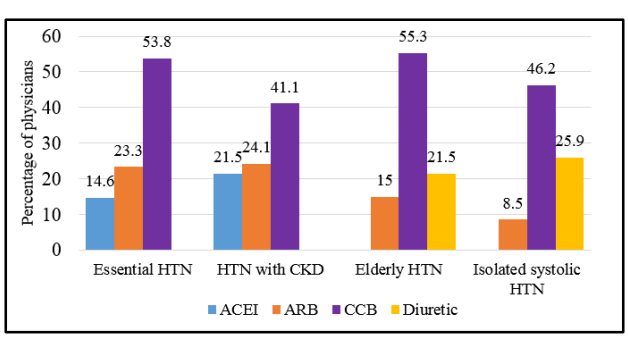

Figure 1. Preferred First Line Hypertensive

*3 most preferred agents for different subsets of patients with hypertension.

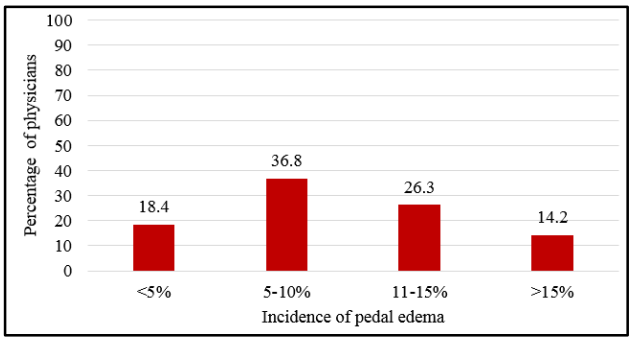

Figure 2. Response of Physicians on Incidence of Oedema with Amlodipine

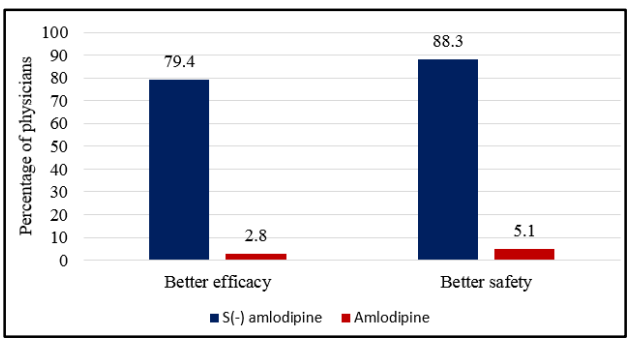

Figure 3. Response of Physicians on Safety and Efficacy of S (-) Amlodipine

DISCUSSION

In the light of recent recommendations by JNC-8 and other clinical practice guidelines for hypertension, it is of utmost importance to understand the preferences of physicians for managing HTN with available classes of pharmacological agents. This cross-sectional survey on prescribing trends and differential usage of CCBs provides useful information on physicians' preferences for the management of patients with HTN and preferential use of various CCBs. BP goals for hypertensive patients with and without compelling indication have been largely affected by many conflicting results from randomised-controlled trials and observational studies in the last decade and also because of updated hypertension guidelines. Our study findings demonstrate that irrespective of comorbidities, similar BP goal of 130/80 mmHg was followed by most of the physicians across all the groups like essential HTN without comorbidities, HTN with diabetes and HTN with CKD. BP goals of 130/80 mmHg followed by most of the practitioners in this survey for uncomplicated HTN is lower than what is recommended by JNC-7 Guidelines (<140/90 mmHg), JNC-8 Guidelines (<140/90 mmHg for <60 years of age and <150/90 mmHg for >60 years of age) and ESH/ESC 2013 Guidelines (<140/90 mmHg).[3,4,5] However, remaining 41.9% physicians' decision to follow a BP goal of <140/90 mmHg for uncomplicated HTN largely appears to be as per these recommendations. Following the JNC7 guidelines, for patients with DM & CKD, Indian practitioners appear to set a slightly lower BP goal than that recommended by JNC-8 and ESH/ESC Guidelines (<140/90 mmHg).[3,4,5]

It has been observed in previous studies that presence of the comorbidities increase risk of cardiovascular (CV) events in patient of HTN, which might be reason of the strict goal BP followed by the physicians in these conditions.[12,13] A recent systematic review by Emdin et al, and another review by Rosendorff C et al have also suggested that, in diabetic patients, lowering systolic BP by 10 mmHg was significantly associated with lower mortality risk, CV events, Coronary Heart Disease (CHD), stroke, albuminuria and retinopathy and hence, a lower BP goal (compared to recommended goal of<140/90 mmHg) may be appropriate in patients with diabetes.[14,15] However, there is still a discrepancy regarding benefits of additional BP lowering to 130/80 mmHg in CKD. Additional BP lowering to 130/80 mmHg have not shown to provide significant CV or renal benefits when compared to goal of <140/90 mmHg in previous studies.[16,17] However, lowering BP to <130/80 mmHg in patients with proteinuria of more than 300 to 1000 mg/day have been shown to be beneficial in a study done by Upadhyay et al.[17]

Though JNC-8 and ESH/ESC guidelines recommended thiazide diuretics, ACE inhibitors, ARB or CCB as initial drug of choice used in hypertension without comorbidities, individual preference over one agent is not given. Guidelines recommend RAS blockers as the agents of choice in HTN with CKD and HTN with DM. However, in this survey, CCBs emerged as the first choice of majority of the physicians followed by ARBs in uncomplicated HTN, HTN with CKD, HTN in elderly and young patients and isolated systolic HTN. This decision is well supported by various controlled clinical trials which established the superiority of amlodipine compared with other antihypertensive drugs in reducing BP variability with possible prevention of CV events.[18]

In hypertensive patients with DM, it is recommended that individual drug choice takes comorbidities into account e.g. RAS blockers to be preferred in diabetic hypertensive patients with CKD. Though RAS blockers were preferred for diabetic hypertensive patients according to the recommendations, CCBs were the preferred choice in hypertensive patients with CKD, which differed from the JNC7, JNC8 and ESH/ESC guidelines.[3,4,5]

Amongst the CCBs, considering the global acceptance since original approval of amlodipine, it was the preferred agent of choice amongst the surveyed physicians, which may be because of its unique pharmacokinetic characteristics (e.g., slow time-to-effect and a long t1/2) along with high degree of specificity for vascular smooth muscle, global approval of amlodipine than cilnidipine, amlodipine is in clinical practice since >2 decades compared to cilnidipine, more robust CV outcome data with amlodipine than cilnidipine, and similar effects on urinary albumin to creatinine [Cr] ratio (UACR) in hypertensive patients with diabetic microalbuminuria.[19] However, the major limitation with use of amlodipine is the higher incidence of pedal oedema, which is a common adverse effect shared by dihydropyridine CCBs.[20] This was further confirmed in our study where about two-third of physicians observed pedal oedema with amlodipine in their >10% patients. Pedal oedema has also been of concern with newer CCB like cilnidipine; one–third of the physicians observed pedal oedema even with use of cilnidipine. In a study by Fogari et

al, pedal oedema was observed in 34.4% patients treated with amlodipine, which is obviously a matter of concern as data suggest that withdrawal from therapy increases as incidence of pedal oedema increases.[21,22]

It has been observed that amlodipine is a racemic mixture of R and S enantiomers, of which R (+) amlodipine is the inactive isomer not only lacking in the calcium-channel blocking property, but also decreasing the activity of postural vasopressor reflex, thereby increasing the capillary osmotic pressure without increasing the oncotic pressure, resulting in exudation of fluid into surrounding tissues.[23,24] Hence, when a racemic amlodipine containing the R isomer of amlodipine is used, it leads to increased incidence of oedema due to concentration-dependent kinin-mediated mechanism of nitric oxide release.[24] On the contrary, S (-) enantiomer of amlodipine doesn't promote peripheral vasodilatation or alter the postural vasopressor reflex, and prevents excessive release of nitric oxide.[24] These properties of S (-) amlodipine result in decreased incidence of peripheral oedema, due to negative effect of sinistrorotatory enantiomer on precapillary vasodilatation. Overall, incidence of pedal oedema observed with S (-) amlodipine in various studies ranges from 0.75% to 1.93% which is far less than oedema observed with racemic amlodipine. Also, the higher incidence of side effects because of the vasodilatory action of amlodipine are avoided because of the higher potency of S (-) amlodipine requiring half the dose for similar efficacy when compared with racemic amlodipine. The above advantages justify the choice of physicians in our study who preferred using S (-) amlodipine over racemic amlodipine because of its better efficacy and safety with decreased incidence of pedal oedema.[9,23,25]

Dual antihypertensive therapy was started by most of the physicians when the BP was >160/100 mmHg, which was well in accordance with the JNC 8 guidelines.[4] Monotherapy for the treatment of HTN has shown to achieve the desired BP goals in only one third of patients, and hence combination therapy is essential for reduction in the risk of adverse vascular outcome by effective achievement of BP goals in majority of hypertensive patients, especially stage 2 HTN.[26,27] For combination with S (-) amlodipine, telmisartan was the preferred agent of choice by the physicians. The rationale for combining agents which block the renin-angiotensin-aldosterone system (RAAS) and CCB is well established, and addition of an angiotensin receptor blocker (ARB) to CCB monotherapy has shown to ameliorate oedema by reducing the capillary bed pressure owing to its venodilatory action along with arteriolar dilatation.[28,29] The choice of physicians can further be supported by a study which has demonstrated that the FDC of S (-) amlodipine besylate and telmisartan tablet offers an effective and safe option in patients who require combination therapy.[29]

Our study has certain limitations being a cross sectional survey with subjective responses; the actual prescription patterns were not tracked and analysed based on BP cut-off values, comparative efficacy in reducing BP and actual incidence of oedema.

CONCLUSION

Most of the physicians follow the recommended guidelines for goal BP and choice of antihypertensive in various comorbid conditions in patients with hypertension. S (-) amlodipine is a more efficacious and safer option with lesser incidence of pedal oedema when compared to racemic amlodipine as opined by most of the physicians of India. However, this needs to be further evaluated in randomised clinical trials.

ACKNOWLEDGEMENT

We would like to thank all the participants who provided their valuable inputs for completion of this study.

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