EVALUATION OF BLOOD PRESSURE LOWERING EFFICACY OF SUSTAINED RELEASE : INDAPAMIDE FORMULATION OVER BANGLADESHI HYPERTENSIVE PATIENT

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Summary

The use of thiazide-type-diuretic is recommended in different guidelines to treat hypertensive patients. Indapamide SR provides powerful BP control without disturbing electrolyte parameters. The aim of this study was to evaluate Indapamide SR for Bangladeshi hypertensive patients in terms of BP reduction efficacy as well as no adverse effect on serum electrolytes. 46 hypertensive patients with age ? 18 without any renal or hepatic disease were enrolled in the study. Indapamide SR initiated for the newly diagnosed hypertensive patients (46%) and in some cases added (54%), where they were uncontrolled on previous antihypertensive medications. Six months later their BP reduction was evaluated by taking the average of three consecutive clinic BP recordings during the visit. At the same time their serum sodium and potassium level was compared with the standard range. The analysis was carried out on all patients,both new & previously uncontrolled patients. The previously uncontrolled group was also further evaluated. The overall BP reduction with Indapamide SR after 6 months was -21.9 /-17.7 mmHg from the average baseline BP (p< 0.0001). SD for final SBP and DBP average was ±11 and ±6 mmHg respectively. The average sodium and potassium level at serum was found to be 139.04 ± 2.79 mEq/L and 3.93 ± 0.31mEq/L respectively which was within the normal range. In the subgroup analysis, BP reduction was as follows- New patients: -21.8/17.7 mmHg; Previously Uncontrolled patients: -22.1/17.7 mmHg; Uncontrolled on monotherapy: -25.7/17.1 mmHg & Uncontrolled on Combination therapy: -16.3/18.8 mmHg. The electrolyte parameter among all the subgroup was found to be within the standard range. This observational study suggest that Indapamide SR provides powerful BP reductions both in new and uncontrolled patients without disturbing serum sodium and potassium level. Matching other evidences and guideline recommendations, we may consider Indapamide SR as a choice of drug in our clinical practice.

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Key words

Hypertension; indapamide SR; thiazide-type-diuretic; blood pressure

Introduction

Hypertension or high blood pressure remains one of the major public health concerns [1] due to the well-established relationship between BP and the risk of cardiovascular disease [2]. Whatever, hypertension is considered as one of the most preventable cause of unwanted morbidity and mortality in the developed as well as developing countries [3]. Currently several guidelines like British guideline [4] and JNC-7 guideline [5] for hypertension management are available worldwide, those recommend <140/90 mmHg as the target BP in most patients, and for the patients with other complications like diabetes mellitus (DM) or chronic kidney disease (CKD), the recommended target line for the BP is <130/80 mmHg [3,4,5]. Although a lot of medications e.g. diuretics, beta-blocker, calcium-channel blocker, ACE inhibitor, Angiotensin receptor blocker & Direct renin inhibitor are available worldwide as well as in Bangladesh, guideline recommendations strongly indicate using of thiazide-type-diuretics as first line (stage-1) and add on with other agents for stage-2 patients [5]. In different studies worldwide, the use of Indapamide SR in terms of BP reduction, cardiovascular protection and other benefits are well proven [6-18].

In Bangladesh, Indapamide SR has been introduced in 2001 [19]. Now, there are several generic versions of the molecule available in Bangladesh [19]. There are controversies regarding the performance of generic version of a molecule and a research brand [20,21,22]. This observational study was undertaken with the aim to identify whether the sustained release formulation of Indapamide is efficacious in clinical practice to control BP to the patients those are newly diagnosed or those are uncontrolled with other available conventional medications available in the market. At the same time, the laboratory parameters specifically serum sodium and potassium level was checked whether they have been altered from the standard range or not.

Materials and methods

This was an observational clinical study which was conducted mainly in out-patient clinic. The patients were recruited at Uttara Adhunik Medical College,

Uttara, Dhaka, the capital city of Bangladesh and followed up by the investigators. The study duration was 24 weeks, i.e. 6 months for each patient enrolled in the study. The primary objective of the study was to assess the efficacy of the once daily Indapamide SR on the newly diagnosed hypertensive patients as well as patients uncontrolled with other agents. Additional objective also was to evaluate whether the serum potassium and sodium level after the six-months duration of the study remained within the standard reference range or not. We used the research brand of Indapamide SR named "Natrilix SR" 1.5 mg tablet.

Patients

Men or women ≥18 yrs old were eligible if they were hypertensive, either taking no antihypertensive medication or remained uncontrolled even after taking medication. Pregnant or lactating female or those known to have allergy to the studied medication was not enrolled in the study. Those, who have been enrolled, had given their consent before entering into the study.

Exclusion Criteria

Hypertension due to any known secondary cause was excluded. Patients with severe renal disease, hepatic impairment, malnourished patients, and patients with known electrolyte imbalance, a history of myocardial infarction or cerebral stroke within the preceding 6 months, heart failure, orthostatic hypotension & severe concomitant disease were also considered for exclusion.

Study design

After successful inclusion, three consecutive BP readings were taken for each patient at the 1st visit. BP was recorded by common clinical BP measuring approach since ABPM was not possible. The readings were taken from the same arm by the investigator himself/herself using mercury sphygmomanometer at the sitting condition and each recording was separated by one minute interval. The three recordings were averaged to get the mean baseline sitting SBP and DBP.

Other information e.g. age, gender, weight, associated disease and concomitant medication histories were collected at the 1st visit prior to inclusion in the study.

The patients those were hypertensive but taking no other medication were given once daily Indapamide SR, and those uncontrolled with other agents, indapamide SR once daily was added with the existing medication. Patients are also advised to modify life styles like doing exercise, avoiding excessive salt with food and junk foods, taking plenty of water etc. where applicable.

After six months, at the end of the study, the BP measurement for each patient was completed in the same way of 1st visit. Additionally to confirm the electrolyte level, serum potassium and serum sodium level was assessed for each patient and compared with the standard reference range.

Data analysis

Analysis was done in intent-to-treat population. The patients who has been enrolled in the study and counted for the sitting baseline SBP and DBP with the completion of the study after 6 months of once daily intake of indapamide SR are considered as intent-to-treat population. The study was considered statistically significant if the p-value is found to be lower than 0.05. Chi-square test was performed to find the significance of the study in overall studied patient population as well as in several sub-groups like newly diagnosed hypertensive and uncontrolled hypertensive patients. The uncontrolled group was further analyzed on the basis whether they are uncontrolled with one agent or more than one agent. Both the BP reduction and the electrolyte parameters are analyzed in all groups and sub-groups.

Results

A total of 46 patients were enrolled in this study. Among them 22 were newly diagnosed and 24 were uncontrolled patients. Among these total 46 patients, 25 were male and 21 were female. Finally the data were analyzed for 39 patients since 5 patients did not returned in the final follow up visit after 6 month of the enrolment and one patient was discontinued from the study because of hyponatraemia who was actually taking the generic version of the drug. There may be other reasons of developing hyponatraemia. The patient was excluded from the study as he was not taking the research brand of the preparation.

Baseline characteristics

Mean age of the patients (n=39) was 48 years (±14) and among them 22 were male (56%) and 17 were female (44%). Total 18 patients were newly diagnosed (46%) and 21 patients were uncontrolled with existing medications (54%). The average initial or baseline SBP was 159 mmHg (±15) and for the DBP it was 98 mmHg (±7).

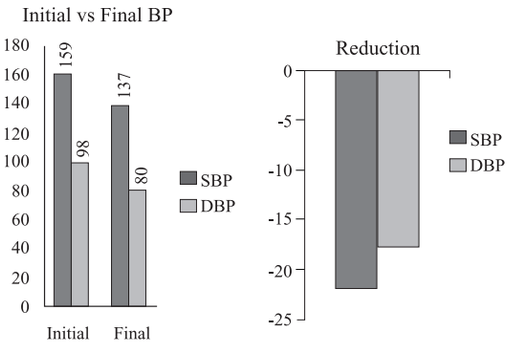
Table I : Baseline patient information

Characteristics	Patients prescribed indapamide SR (n=39)
Male (%)	22 (56%)
Female (%)	17 (44%)
Age in years (mean ± SD)	48 ± 14
Newly diagnosed hypertensives (%)	18 (46%)
Uncontrolled hypertensives (%)	21 (54%)
Blood Pressure in mmHg	
SBP (mean ± SD)	159 ± 15
DBP (mean ± SD)	98 ± 7

SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure

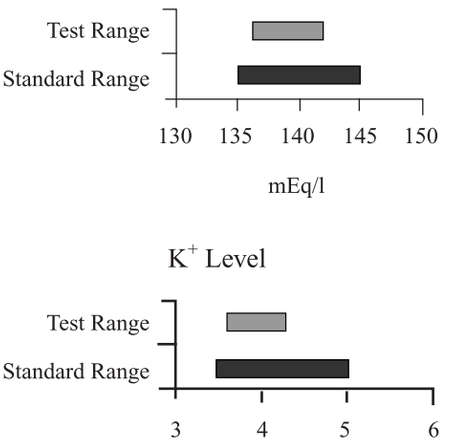
Reductions in overall Blood Pressure

In the overall population, the mean BP was reduced significantly ($p<0.001$) from 159/98 mmHg at baseline to 137/80 mmHg by week 24. SD for final SBP and DBP average was ±11 and ±6 mmHg respectively. The overall BP reduction at week 24 was -21.9 /-17.7 mmHg. (Table-II)



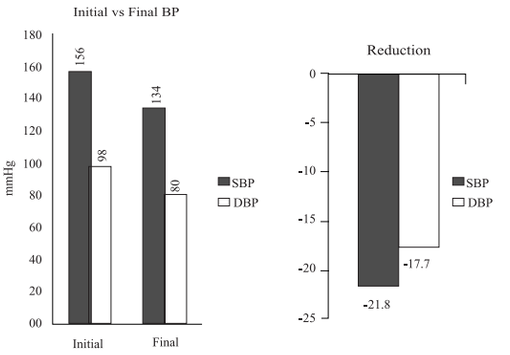
Electrolyte parameters in overall patients

At the end of the study, the average serum sodium and potassium level was found to be 139.04 ± 2.79 mEq/L and 3.93 ± 0.31mEq/L respectively. The standard reference ranges for sodium and potassium level are 135-145 mEq/L and 3.5 to 5 mEq/L respectively. The end result was within the range and hence there was no event of electrolyte imbalance. (Table-II)



Reductions in Blood Pressure among newly diagnosed patients

In the newly diagnosed patient population (n=18), the no. of male was 9(50%) and female was 9 (50%). Their mean age was 45 years (SD = ±14). The mean BP in this newly diagnosed patient group was reduced significantly ($p<0.001$) from 156/98 mmHg at baseline (SD= ±13/±6) to 134/80 mmHg by week 24 (SD= ±9/±5). The BP reduction among this group at week 24 was -21.8 /-17.7 mmHg. (Table-III)

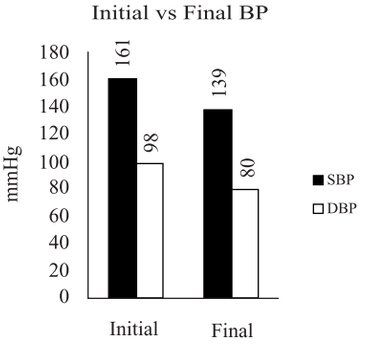


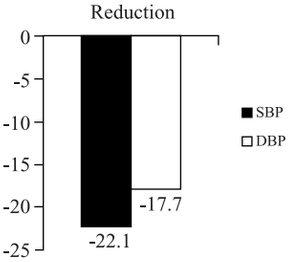
Electrolyte parameters in newly diagnosed patients

At the end of the study among the newly diagnosed patients, the average serum sodium and potassium level was found to be 138.85 ± 2.76 mEq/L and 3.89 ± 0.32mEq/L respectively. The standard reference ranges for sodium and potassium level are 135-145 mEq/L and 3.5 to 5 mEq/L respectively. The end result was within the range and hence there were no events of electrolyte imbalance. (Table-III)

Reductions in Blood Pressure among uncontrolled patients

In the uncontrolled patient population (n=21), the no. of male was 13 (62%) and female was 8 (38%). Their mean age was 50 years (SD = ±14). The mean BP in this uncontrolled patient group was reduced significantly ($p<0.001$) from 161/98 mmHg at baseline (SD= ±16/±8) to 139/80 mmHg by week 24 (SD= ±11/±6). The BP reduction among this group at week 24 was -22.1 /-17.7 mmHg.





Electrolyte parameters in uncontrolled patients

At the end of the study among the uncontrolled patients, the average serum sodium and potassium level was found to be 139.19 ± 2.87 mEq/L and 3.96 ± 0.30mEq/L respectively. The standard reference ranges for sodium and potassium level are 135-145 mEq/L and 3.5 to 5 mEq/L respectively. The end result was within the range and hence there were no events of electrolyte imbalance.

Reductions in Blood Pressure among monotherapy uncontrolled patients

In the uncontrolled patient population (n=13), the no. of male was 8 (61%) and female was 5 (39%). Number of monotherapy uncontrolled patients were as follows- Atenolol uncontrolled=3 (23%), Losartan uncontrolled =6 (46%), Lacidipine uncontrolled = 2 (15%), Amlodipine uncontrolled = 1 (8%) and Ramipril uncontrolled = 1 (8%). Their mean age was 51 years (SD = ±15). The mean BP in this monotherapy uncontrolled patient group was reduced significantly ($p<0.001$) from 167/96 mmHg at baseline (SD= ±14/±9) to 141/79 mmHg by week 24 (SD= ±12/±7). The BP reduction among this group at week 24 was -25.7 /-17.1 mmHg.

Electrolyte parameters in monotherapy uncontrolled patients

At the end of the study among the monotherapy uncontrolled patients, the average serum sodium and potassium level was found to be 139.04 ± 2.31 mEq/L and 3.98 ± 0.34 mEq/L respectively. The standard reference ranges for sodium and potassium level are 135-145 mEq/L and 3.5 to 5 mEq/L respectively. The end result was within the range and hence there were no events of electrolyte imbalance.

Reductions in Blood Pressure among combination uncontrolled patients

In the uncontrolled patient population (n=8), the no. of male was 5 (63%) and female was 3 (38%). Number of combination uncontrolled patients were as follows- Atenolol+ Amlodipine uncontrolled=2 (25%), Atenolol+ Amlodipine + Losartan uncontrolled =1 (12%), Amlodipine + Valsartan uncontrolled = 2 (25%) and Amlodipine + Olmesartan uncontrolled = 3 (38%). Their mean age was 48years (SD = ±11). The mean BP in this combination uncontrolled patient group was reduced significantly ($p<0.001$) from 153/101 mmHg at baseline (SD= ±17/±4) to 136/83 mmHg by week 24 (SD= ±11/±4). The BP reduction among this group at week 24 was -16.3 /-18.8 mmHg.

Electrolyte parameters in combination uncontrolled patients

At the end of the study among the combination uncontrolled patients, the average serum sodium and potassium level was found to be 139.44 ± 3.77 mEq/L and 3.93 ± 0.23 mEq/L respectively. The standard reference ranges for sodium and potassium level are 135-145 mEq/L and 3.5 to 5 mEq/L respectively. The end result was within the range and hence there were no events of electrolyte imbalance.

Discussion

Prevalence of hypertension in Bangladesh is growing [23]. Socioeconomic status of the people of the country is not like the people from developed countries. Food habit, life-style and other non-clinical practices are not very popular in Bangladesh. Therefore, they are vulnerable to be hypertensive very soon. Most of them become diagnosed at the advanced stages of hypertension and therefore uncontrolled.

The use of thiazide-type-diuretic for treating hypertension is well established in the guideline recommendations of JNC-VII [1,5] & BHS-NICE [4]. Moreover, the BP reduction efficacy of Indapamide SR as monotherapy was proven in a meta-analysis of 19 drugs [9]. In that meta-analysis, results of 80 randomized trials have been observed (n=10818), and it has been found that Indapamide SR provides highest BP reduction as monotherapy. There was even a BP reduction of 34/12 mmHg in ARGUS study where the population number of the study was 1277 [7]. This was also for newly diagnosed patients. Now if we consider uncontrolled patients, NATIVE and ARGUS-2 study is there. NATIVE study showed a BP reduction of 33/19 mmHg, where all the patients were uncontrolled [6]. Most importantly, the study was conducted in Pakistan, a subcontinental country where we can assume similar physiology of the population as with ours. ARGUS-2 study was conducted in Russia where indapamide SR reduces BP by 28/14 mmHg [8]. Most of the patients of that study were also uncontrolled with different monotherapy.

For any diuretic agent, the electrolyte parameters as well as metabolic parameters are considered as important issues. Fortunately, indapamide SR in different studies have shown to be neutral, i.e., it does not alter the electrolyte and metabolic parameters of the patients. In HYVET study-the largest morbidity-mortality trial (n=3845) of indapamide SR, there were no metabolic change. Another study performed by Ambrosioni and Luigi Malin with indapamide SR, no change of electrolyte and metabolic parameters found [13].

This may be because of the molecular mechanism of the indapamide which is different from other diuretics. Beside of its diuretic action, Indapamide is supposed to have a vasorelaxant action that may contribute its anti-hypertensive action [18].

This observational study was done on Bangladeshi patients with the aim to assess the effectiveness of the research brand Indapamide SR to reduce the blood pressure in daily practice, as well as to find out if there is any incidence of electrolyte imbalance. Since the study shows that it is effective in reducing BP in newly diagnosed patients as monotherapy even in combination therapy those were uncontrolled with other agents. The once daily dosage regimen was also convenient for the patients, and since the electrolyte parameter was within the range, it may be safe for the patients with hypertension. Despite the difficulties of performing studies in Bangladesh as the patients sometimes are indifferent about the importance of coming in the follow-up visit, this study was successful in terms of observing the efficacy. Further study may be needed to find out comparison of efficacy with others agents in Bangladeshi patients.

Although the study was successfully completed, there were some limitations of our study. One of the most important limitations of our study was the absence of control group. Since, it was observational, and the patients were intent-to-treat population, the control group set up was omitted. But the presence of control group analysis could be a more rational way to assess efficacy. Another one is the absence of baseline electrolyte parameters. Unfortunately the socioeconomic conditions of the patients were unfavorable to do a baseline electrolyte check up. But use of the baseline parameter could be more conclusive. The baseline and final BP measurements were done with normal clinical BP measurement approach. Use of ABPM could be useful to assess the efficacy more clearly.

Conclusion

Lots of studies were performed on Indapamide SR worldwide and this study reflects the same thing that has been revealed from other studies. This study suggests that Indapamide SR is a powerful antihypertensive agent that can be used in our daily clinical practice since both new and uncontrolled patients are available in our country. At the same time undisturbed electrolyte parameter confers one of the important benefits of of Indapamide SR.

Disclosure

All the authors declare no competing interest.

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