

Original Research Article

Preference and practice of Indian physicians towards the use of vasodilator di-hydralazine in the management of resistant hypertension

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Received: 12 October 2020

Accepted: 07 November 2020

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ABSTRACT

Background: The treatment modalities of resistant hypertension (RH) remain a clinical challenge, often requiring secondary/add-on drugs with first-line therapy to control blood pressure (BP). This study was conducted to explore and understand the preferences and practices of Indian physicians towards the use of vasodilator (especially di-hydralazine) in the management of RH.

Methods: This was a cross-sectional, observational, web-based physician survey. The study included cardiologist, nephrologist and consultant physicians from different geographical regions of India. A web-based physician survey questionnaire (PSQ) was created in google forms and the link was circulated to the physicians. Responses obtained were analysed.

Results: A total of 457 physicians participated in this survey. In majority of the physicians, vasodilators were the treatment choice as secondary or add-on drugs with first line therapy to control BP in RH; especially hydralazine/di-hydralazine preferred the most. Majority of the physicians preferred to combine vasodilator with beta blocker and diuretic in patients with uncontrolled and RH. Cardiac failure, followed by chronic kidney disease (CKD), diabetes, dyslipidaemia, hypertensive emergency and angina were the common patient profile in RH in which majority physicians prescribed vasodilator (di-hydralazine). Majority of the physicians rated vasodilator di-hydralazine as “good-very good” in terms of efficacy, safety, tolerability, patient compliance and patient satisfaction in RH.

Conclusions: Overall, vasodilators (hydrazinophthalazine derivatives) are preferred as add-on drugs along with first-line drugs in RH. Physician’s opinion towards the use of di-hydralazine was positive. Di-hydralazine may be preferred as an add-on therapeutic option to control BP in RH, however randomized clinical trials are needed for recommendation in cardio-renal medicine.

Keywords: RH, Di-hydralazine, Hydrazinophthalazine, Physician survey

INTRODUCTION

Hypertension is the world's leading risk factor for cardiovascular disease (CVD), stroke, disability, and death.¹ Hypertension and its complications are responsible for approximately 9.4 million deaths worldwide every year and are expected to rise to 1.56 billion by 2025.^{2,3} Hypertension is a rising issue in India and resulted in 1.63 million deaths in India in the year 2016 alone.²

A meta-analysis found that fewer than 20% of patients with hypertension in India had their blood pressure (BP) under control/target goal.⁴ At the other end of the BP control spectrum are patients with hypertension who suffer from RH, which is not well controlled despite multiple drugs.

RH is defined as the BP of a hypertensive patient that remains elevated above goal despite the concurrent use of 3 antihypertensive agents of different classes, commonly including a long-acting calcium channel blocker (CCB), a blocker of the renin-angiotensin system (angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB), and a diuretic.¹ The identification and treatment RH is urgently needed because they are more prone for target-organ damage and related complications.⁵

Although clinical guidelines have suggested these groups of drugs as conventional first line agents to control blood pressure in RH, there are subsets of patients for whom the target BP goal is achieved through combination of secondary or add-on drugs.⁶

The treatment of RH patients also depends on several clinical and laboratory criteria, with the presence of comorbid diseases and advanced age often complicating the therapy.¹ Therefore, the approach, preference and treatment pattern of RH could vary among Indian physicians depending upon the patient profile. There is inadequate data on the physician's opinion on the selection pattern of first-line and alternative add-on drugs, including vasodilator di-hydralazine in the management of RH in daily practice in Indian setting.

Di-hydralazine is a hydrazinophthalazines-derivate with similar biological activity of hydralazine and is often considered interchangeable. It is an arterial vasodilator and has been utilized in the treatment of hypertension and heart failure.⁷ Since it is nearly 70 years old (long standing) molecule, there is a lack of evidence in literature especially with regard to randomized control trials (RCT) compared to newer drugs. There are also no data on the utilization practice and perspective of the physicians regarding efficacy, tolerability, patient compliance and satisfaction with di-hydralazine in RH. Therefore, this survey was conducted to understand the preferences and practices of Indian physicians towards

the use of vasodilator (with emphasis on di-hydralazine) in the management of RH.

METHODS

This was a cross-sectional, observational, web-based physician survey conducted in cardiologist, nephrologist and consultant physicians from different geographical regions of India. The survey was carried out in the month of May 2020. The sampling method was convenient sample. The study included cardiologist, nephrologist and consultant physicians with at least 1 year of experience of treating RH.

A database of the consulting physicians, cardiologists and nephrologists was prepared. A web-based PSQ was created in google form with incorporation of informed consent at the beginning of the survey. The web-link of the PSQ was circulated to the physicians via telephonic communication and email. Physicians who agreed to and clicked the online consent were allowed further to participate in this web-based physician survey. The PSQ had questions on the physician's drug preferences and practices in RH with multiple choice options, Likert scale and open-ended questions to answer for response.

Data was analysed in the statistical package for the social sciences version 20. Descriptive statistics were presented using means and standard deviation for continuous variables, frequencies, and percentages for categorical variables.

RESULTS

A total of 457 physicians participated in this survey. The mean age of the participating physicians was 48.8 ± 10.1 years. The male participants were 423 (92.6%) and the female participants were 34 (7.4%). The total mean clinical experience of the physicians was 19.6 ± 9 years with a mean experience of 16.3 ± 10 years in treating RH (Table 1). The specialty of the consultants who participated in this survey was general medicine (53.4%), followed by cardiology (32.8%), nephrology (9.2%) and others (4.6%).

In this study, the prevalence of RH among hypertensive patients encountered by the physicians in their clinical practice ranged from 1 to 50%, with majority reporting up to 30% in patients. The majority of RH patients treated by physicians in practice were between age group of 50 to 65 years followed by 35 to 50 years and over 65 years.

Diabetes, followed by CKD, obesity, dyslipidaemia, and congestive heart failure were the most common comorbidities/concomitant diseases often seen/encountered by physicians in RH patients. On subgroup analysis, CKD/renal parenchyma disease was the most common concomitant disease followed by

diabetes encountered in RH by nephrologist and cardiologist (Table 2).

Majority of the physicians normally considered clinical judgment followed by laboratory parameters, clinical outcome measure/targets and comorbid conditions as criteria while deciding on treatment for patient with RH.

In this study, majority of the physicians preferred ARB, diuretics, ACE-I and CCB as First-line therapy. While in majority of the physicians, vasodilators were the treatment choice for secondary or add-on drugs with first line therapy to control BP in RH, especially hydralazine/di-hydralazine (Figure 1).

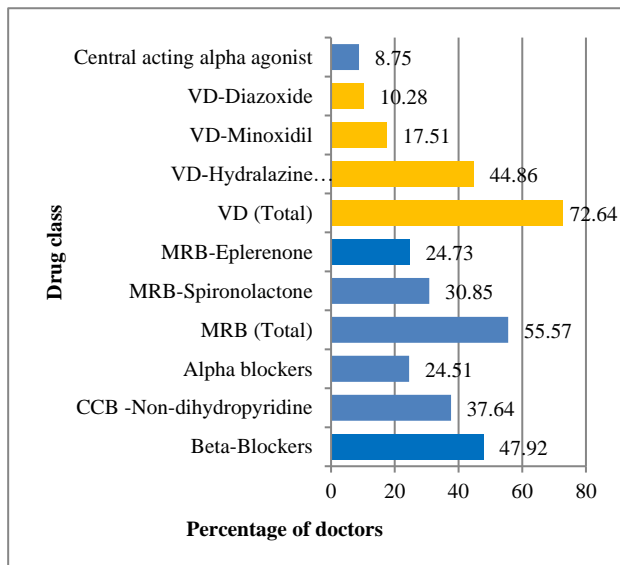


Figure 1: Physician's choice of treatment for secondary or add-on drugs adopted with first line therapy to control BP in RH.

VD-Vasodilator, MRB- Mineralocorticoid receptor blockers, CCB-Calcium channel blocker.

The common parameters considered by majority of physicians while prescribing vasodilator to patient with RH was uncontrolled BP (despite first-line drugs or their combination) followed by patient comorbidities, contraindications and intolerance to first line drugs, refractory cases, emergency situation, advancing age and pregnancy (Table 3).

In this study, among the various class of vasodilators "hydralazine/di-hydralazine" was the preferred vasodilator by majority of the physicians for their routine practice (Figure 2). Majority of the physicians preferred to combine vasodilator with beta blocker and diuretic in patients with uncontrolled and RH.

The common advantages of vasodilator (di-hydralazine) over potassium sparing diuretics (PSD)/mineralocorticoid receptor blockers (MRB) considered by majority of the physicians was high efficacy followed by lack of incidence of hypokalaemia, lack of incidence of breast

tenderness/gynaecomastia and safer during pregnancy (Figure 3).

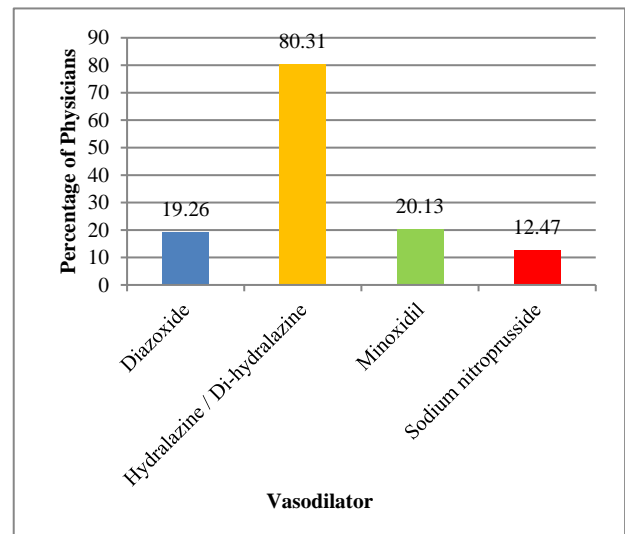


Figure 2: Physician-based vasodilators routinely prescribed to treat RH.

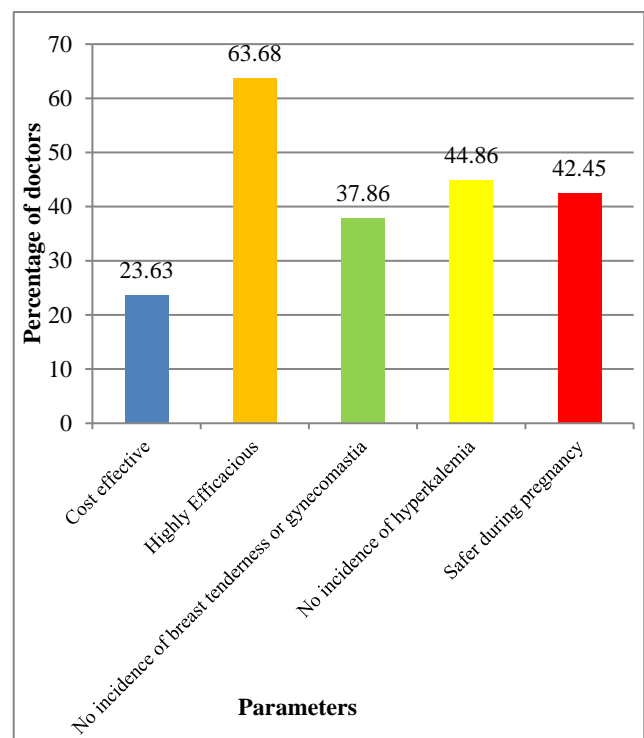


Figure 3: Physician's opinion-advantages of vasodilator (di-hydralazine) over PSD/MRB.

The six most common patients' profiles of RH in which majority physicians preferred vasodilator (di-hydralazine) were cardiac failure, followed by CKD, diabetes, dyslipidaemia, hypertensive emergency and angina (Table 4).

Majority of the physicians rated vasodilator (di-hydralazine) as "good-very good" in terms of efficacy,

safety, tolerability, patient compliance and patient satisfaction (Figure 4).

In this study, majority of the physicians rated effectiveness of vasodilator (di-hydralazine) as “good-very good” in the management of RH.

The most common benefits considered by majority of the physicians while prescribing vasodilator (d-hydralazine) was effectiveness in achieving recommended BP targets followed by reduced systemic vascular resistance, improved cardiac function and reduced risk for CVS events, improved renal function/perfusion and reduced nitrate tolerance (Table 5).

According to majority of physicians, the incidence of severe hypotension and tachycardia with vasodilator di-hydralazine in RH patients in their clinical practice was less than 20% (Figure 5).

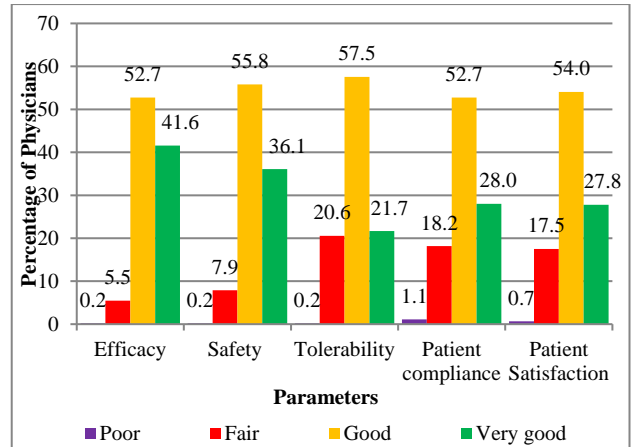


Figure 4: Physician ratings for di-hydralazine based on: efficacy, safety tolerability, patient compliance and patient satisfaction.

Table 1: General characteristics of the physicians.

Characteristics		Value	Percentage (%)
Total physicians (N)		457	100
Age (year) (Mean ± SD)		48.8±10.1	
Total clinical experience (Year) (Mean ± SD)		19.6±9.8	
Clinical experience in treating RH (Year) (Mean ± SD)		16.3±10.6	
Gender-wise	Male	423	92.6
	Female	34	7.4
Specialty-wise	General medicine	244	53.4
	Cardiology	150	32.8
	Nephrology	42	9.2
	Others	21	4.6
State -wise	Maharashtra	52	11.4
	West Bengal	49	10.7
	Gujarat	21	4.6
	Uttar Pradesh	56	12.3
	National capital territory of Delhi	13	2.8
	Tamil Nadu	77	16.8
	Odisha	21	4.6
	Bihar	26	5.7
	Karnataka	25	5.5
	Andhra Pradesh	43	9.4
	Jharkhand	23	5.0
	Telangana	9	2.0
	Goa	2	0.4
	Assam	3	0.7
	Kerala	35	7.7
	Madhya Pradesh	2	0.4

Table 2: Physician-based concomitant illness commonly associated with RH.

Concomitant illness commonly associated with RH in practice		Overall physicians (%)	General medicine (%)	Cardiology (%)	Nephrology (%)
Comorbidities/ Concomitant illness commonly	Diabetes	62.80	69.67	53.33	42.86
	CKD/renal parenchyma disease	60.18	57.79	59.33	80.95
	Congestive heart failure	33.04	31.97	40.00	23.81

Continued.

Concomitant illness commonly associated with RH in practice	Overall physicians (%)	General medicine (%)	Cardiology (%)	Nephrology (%)
associated				
Dyslipidaemia	39.82	44.67	37.33	16.67
Ischemic heart diseases	23.63	22.95	29.33	7.14
Obstructive sleep apnoea	19.26	21.72	13.33	19.05
Obesity	45.73	47.54	44.67	28.57
Primary aldosteronism	8.10	8.20	6.67	9.52
Renal artery stenosis	22.10	18.03	26.67	35.71
Stable angina	15.10	15.98	16.67	4.76
Pheochromocytoma	7.22	6.56	5.33	14.29

Table 3: Parameter considered by physicians while prescribing vasodilator to patients with RH.

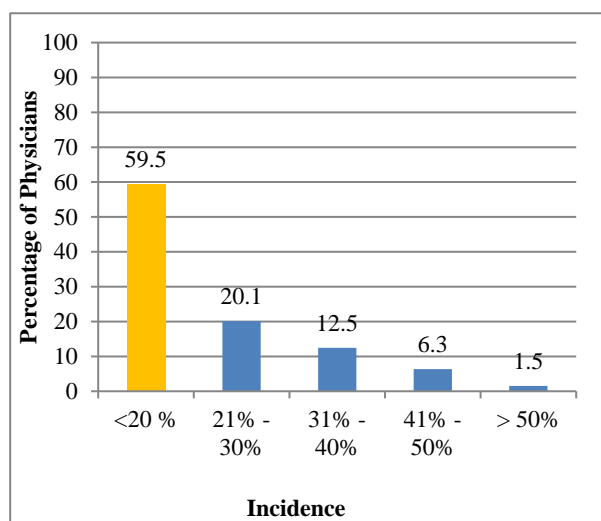
Parameters considered while prescribing vasodilators to patients with RH	Overall physicians (%)	General medicine (%)	Cardiology (%)	Nephrology (%)
Parameters				
Advancing age (Year)	19.47	19.67	18.67	9.52
Contraindications to 1 st line drugs	32.17	29.92	36.67	23.81
Emergency situations	16.85	16.80	14.67	23.81
High risk patients	29.54	29.51	29.33	21.43
Intolerant to first line drugs	32.39	31.97	33.33	28.57
Patients with comorbidities	47.05	45.49	48.00	45.24
Pregnancy	14.44	14.75	15.33	11.90
Refractory cases	30.20	31.15	29.33	21.43
Uncontrolled BP despite first-line drugs or their combination	67.18	68.85	61.33	71.43
Rescue drug	6.56	6.15	6.67	7.14

Table 4: Patient profile wherein physician preferred di-hydralazine.

Patient profile wherein physician preferred di-hydralazine	Overall physicians (%)	General medicine (%)	Cardiology (%)	Nephrology (%)
RH with heart failure				
Yes	81.40	81.97	82.00	76.19
No	10.50	9.43	10.00	16.67
Can't say	8.10	8.61	8.00	7.14
RH with CKD				
Yes	78.56	77.87	77.33	80.95
No	11.16	12.30	11.33	4.76
Can't say	10.28	9.84	11.33	14.29
RH with angina				
Yes	52.95	50.41	56.00	47.62
No	25.82	25.41	26.00	33.33
Can't say	21.23	24.18	18.00	19.05
RH with diabetes				
Yes	74.62	77.46	70.00	69.05
No	13.57	11.07	16.67	19.05
Can't say	11.82	11.48	13.33	11.90
RH with COPD/asthma				
Yes	37.20	37.70	40.67	21.43
No	31.51	31.15	29.33	40.48
Can't say	31.29	31.15	30.00	38.10
RH with dyslipidaemia				
Yes	63.02	65.57	56.67	64.29
No	19.91	18.44	24.00	19.05
Can't say	17.07	15.98	19.33	16.67
RH with atrial fibrillation				
Yes	38.07	36.48	41.33	38.10
No	26.04	26.23	26.00	28.57
Can't say	35.89	37.30	32.67	33.33
Hypertensive emergency				
Yes	61.49	60.25	62.67	66.67
No	20.79	20.90	20.67	19.05
Can't say	17.72	18.85	16.67	14.29

Table 5: Benefits considered by physician while prescribing di-hydralazine.

Benefits considered the most, while prescribing di-hydralazine		Overall physicians (%)	General medicine (%)	Cardiology (%)	Nephrology (%)
Benefits	Effective in achieving recommended BP treatment targets	67.40	68.03	68.00	54.76
	Reduces systemic vascular resistance	66.30	69.67	64.00	57.14
	Improves cardiac function and reduces risk for cardiovascular events	50.33	50.82	50.67	45.24
	Improves renal function/perfusion	37.64	38.52	36.67	33.33
	Reduces nitrate tolerance	21.88	22.54	21.33	11.90
	Cost effective drug	26.91	29.51	21.33	26.19

**Figure 5: Physician based incidence of severe hypotension and tachycardia with di-hydralazine in practice in management of RH.**

DISCUSSION

The scenario of treatment modalities of RH remains a clinical challenge in India. The prevalence of RH is on the rise, ranging from 10 to 30%. Despite treatment with effective pharmacological agents and/or interventions, many patients with RH, have persistent symptoms and have refractory uncontrolled blood pressure.⁶

In this study an attempt was made to explore and understand the preference, opinion and practice of Indian physicians towards use of vasodilator (especially di-hydralazine) in the management of RH. Our study findings indicate that vasodilators are the most preferred secondary or add-on drugs used with first-line therapy to control BP, particularly hydralazine/di-hydralazine, which is being preferred by most physicians. The major factors considered by physician for prescribing vasodilators in RH was uncontrolled BP (despite first-line

drugs or their combination) followed by patient comorbidities, contraindications/ intolerance to first line drugs, refractory cases, emergency situation, advancing age and pregnancy.

The hydrazinophthalazine-derivatives, hydralazine and di-hydralazine were discovered in 1950 as potent direct-acting vasodilators which lowered blood pressure and increased renal perfusion. Since then it has been utilized in the treatment of hypertension and heart failure.^{7,8} Often both molecules are considered fully interchangeable with regard to their biological activity.⁷ Although the exact mechanism of action is unknown, the proposed mechanism for the direct arterial vasodilation include inhibition of IP3-induced release of calcium from the sarcoplasmic reticulum and inhibition of myosin phosphorylation in arterial smooth muscle cells.^{9,10} They cause direct relaxation of the arteriolar smooth muscle, which in turn results in lowering the BP and decreasing the peripheral vascular resistance (PVR) with compensatory activation of sympathetic system to cause tachycardia.^{8,9,11,12}

In this study, a significant proportion of physician preferred vasodilators (hydralazine/di-hydralazine) as add-on drugs to control the BP in RH. The characteristics advantage of high efficacy, safer during pregnancy, no risk of hyperkalaemia and lack of incidence gynaecomastia makes them the preferred choice over MRB/PSD, as evident from this study.

Another important aspect of hydralazine/di-hydralazine vasodilators reflected is safety during pregnancy, which is well recognized by majority of the physicians in this survey. For many years, hydralazine has been a therapeutic choice to treat severe hypertension in pregnancy.¹⁴⁻¹⁷ They are recommended in acute-onset, severe hypertension in pregnant women and women in the postpartum period.¹⁸

In this study, among the various class of vasodilators “hydrazinophthalazines-hydralazine/di-hydralazine” were the preferred by majority of the physicians for their routine practice. Majority of the physicians preferred to combine vasodilator with beta blocker and diuretic in patients with uncontrolled and RH. The combination provides synergistic effects with vasodilator enhancing the BP lowering activity, while beta-adrenergic antagonist and thiazide in turn attenuates the vasodilator induced sympathetic tone and sodium retention.¹

The recent American heart association (AHA) scientific statement guidelines for RH has recommended vasodilator as add-on therapy to control BP and to be combined with nitrates in cases of cardiac failure (requiring the use of concomitant beta-blocker and diuretic).¹

The treatment of RH patients depends on several clinical and laboratory criteria with the presence of comorbid diseases and advancing age complicating the therapy in this study, RH with cardiac failure and RH with CKD were the most common patient profile, wherein majority physicians preferred to prescribe vasodilator (di-hydralazine) in combination. Combination of hydralazine and nitrates is well established in CHF and has demonstrated improvement in cardiac function and left ventricular systolic function with a favourable effect on survival.¹⁹⁻²²

The rationale for combination therapy includes balanced vasodilation, with nitrates decreasing preload and hydralazine decreasing afterload predominantly. nitrates help restore calcium (Ca²⁺) cycling and cardiac contractile performance and control superoxide production in cardiomyocytes, whereas hydralazine has antioxidant properties that mitigate nitrate tolerance.¹

Hypertension and CKD are closely interlinked pathophysiologic states. Often patients of CKD require more than 3 drugs to control the BP. Although vasodilators are not preferred as first-line drugs for the treatment of CKD hypertension due to limited evidence, guidelines does suggest that they are secondary add-on drugs to control uncontrolled BP.^{23,24} There is evidence of increased renal blood flow without changes in the glomerular filtration rate with hydrazinophthalazine derivatives.^{25,26,27} Thus preferring the use in renal dysfunction patients with uncontrolled BP, as an add-on drug to improve both cardiovascular and kidney outcomes.

In this study, majority of the physicians rated effectiveness of vasodilator (di-hydralazine) as “good-very good” in the management of RH. Majority of the physicians rated vasodilator (di-hydralazine) as “good-very good” in terms of efficacy, safety, tolerability, patient compliance and patient satisfaction.

The general benefits that most physicians considered while prescribing vasodilator (di-hydralazine) were its efficacy in achieving recommended BP targets followed by reduced systemic vascular resistance, improved cardiac function and reduced risk for CVS events, improved renal function/perfusion and reduced nitrate tolerance. Overall, the physician’s opinion towards the use of di-hydralazine was positive based on their real-world experience in RH. With the use of vasodilator (di-hydralazine), the risk of side effects especially severe hypotension and tachycardia are the concerns of the physician due to its potent pharmacological activity. In this study, most of the physicians observed the incidence of severe hypotension and tachycardia with vasodilator (di-hydralazine), in less than 20% of the RH patients in their clinical practice.

In the practice setting, individual decision making is often required regarding BP targets and drugs with the risks and benefit being taken into account for achieving optimal clinical outcomes in RH. Despite being brought to clinical use in pre-modern clinical trial era, vasodilator-hydrazinophthalazine derivatives has kept its role in clinical practice for over 70 year. Further clinical studies and robust randomized clinical trials are warranted to validate the potential role in different indications for recommendation in cardio-renal medicine.

Overall, we have gained some valuable insight into perspectives and prescribing practices of Indian physicians towards the use of vasodilators (especially di-hydralazine) in RH, but there were some limitations to the study. First, it was a cross-sectional online survey and the responses were subjective. Second, the study participation was limited sample of physicians and therefore our results may not be generalized to all physicians. Third, actual prescription pattern monitoring or clinical audit was not performed.

CONCLUSION

Vasodilators (hydrazinophthalazine derivatives) are preferred as add-on drugs along with first-line drugs in RH. Physician’s opinion towards the use of di-hydralazine was positive. Di-hydralazine may be preferred as an add-on therapeutic option to control BP in RH, however randomized clinical trials are needed for recommendation in cardio-renal medicine.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Pradeep Jadhav for assistance in writing the manuscript and the study physicians for their participation and co-operation in the survey.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Kahale P, Biswas PK, George S, Sree RPC, Singh P, Nag SK, Roy S. Preference and practice of Indian physicians towards the use of vasodilator di-hydralazine in the management of resistant hypertension. *Int J Adv Med* 2020;7:1781-8.