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Management of Acute Hypertensive Crises: Comparing the Efficacy and Safety of Different Antihypertensive Agents in the Acute (Emergency) Management of Hypertensive Crises

**Dr. Danish Mand¹, Dr. Anees Shakoor², Dr. Basit Amin³, Dr. Ishfaq Ahmad Mohmand⁴,
Dr. Amir Ali Khan⁵, Dr. Zubair Ahmad⁶, Dr. Shahid Sarwar⁷, Dr. Samandar Khan
Babar⁸, Dr. Qazi Muhammad Safwan⁹**

¹Senior Medical Officer, Karnal Sher Khan Cadet College, Swabi Pakistan

²PGR- General Medicine, Saidu Group of Teaching Hospital, Saidu Sharif Swat Pakistan

³PGR-Nephrology, Institute of Kidney Disease Hayatabad Medical Complex, Peshawar Pakistan

⁴Senior House Officer, Mayo Hospital/King Edward Medical University, Lahore Pakistan

⁵MBBS MRCP (UK), Medical Officer, BHU Fazalabad, Swabi Pakistan

⁶Resident Physician Internal Medicine, Hayatabad Medical Complex/Khyber Girls Medical College, Peshawar Pakistan

⁷PGR General Medicine, MTI HMC, Peshawar Pakistan

⁸Resident Physician Internal Medicine, Hayatabad Medical Complex, Peshawar Pakistan

⁹Resident Physician Internal Medicine Hayatabad Medical Complex, Peshawar Pakistan

***Corresponding author:** Dr Zubair Ahmad; Email: dr.zubair1193@gmail.com

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Abstract

Hypertensive crises therefore are defined as major medical complications that manifest by sharp elevations of blood pressure that actually precipitate acute target organ dysfunction. So, it is necessary to manage the disease and its consequences in a proper and timely manner. There are many antihypertensive agents for acutely managing hypertensive patients, however, there is no clear consensus regarding the ideal choice of drug, its efficacy or the safety in specific settings.

The objective of this study was to evaluate the effectiveness and side effects of three widely prescribed ANT agents; labetalol, nitroglycerin and Hydralazine in the management of hypertensive emergency in emergency department of Hayatabad Medical Complex Peshawar.

In the next prospective, noninterventional study, patient data were collected from patients with hypertensive crisis from January 2022 to June 2023 which included 450 patients. One of the three antihypertensive agents was given to the patients depending on the assessment. The main dependent factor was the change in the systolic and diastolic blood pressure after the use of the study massage within half an hour. Secondary objectives were side effects and receiving the goal blood pressure. Data analyses used were ANOVA and t-test and the alpha level of significance set at 0. 05 considered statistically significant.

Because of its efficacy in achieving target pressure in shortest time than any drug in the three arms of the study, the mean reduction of systolic and diastolic blood pressure was also the highest for Labetalol within 30 minutes being 40 /20 mmHg respectively. Moderate effectiveness was observed in nitroglycerin and least effectiveness was found in hydralazine with mean systolic reduction of about 30mmHg. Finally, on the comparison of substantial side effects, it was shown that Labetalol has the slightest percentages of the effect (Only 5% of the patients complained of dizziness) while hydralazine revealed the highest percentages of effect (Twelve percent of the patients indicated tachycardia).

In hypertensive emergency, the ideal drug revealed to be labetalol as it did not cause significant complications. These results attest for its utilization in the first line of management in the emergency department with nitroglycerin and hydrohalotized as second line drugs.

Keywords: Hypertensive crisis, labetalol, antihypertensive drugs, emergency medicine, blood pressure.

Introduction

Hypertensive crisis are defined as acute sharp rises in blood pressure and reaching 180/120 mm Hg and are related to acute target organ dysfunction (Pinto, 2007). These crises are typically classified into two categories: has differentiated between two forms of hypertensive related conditions; these are, hypertensive urgency and hypertensive emergency. Hypertensive urgency describes conditions in which the blood pressure is very high but the target organs are not acutely compromised whereas hypertensive emergency involves increased blood pressure and damage to

vital organs like the heart, kidney, brain or the eyes (Panza et al., 2018). Unless urgency is done, hypertensive emergencies results to serious complications like stroke, myocardial infarction, acute heart failure or renal failure (Aggarwal et al., 2020).

Hypertensive crisis is less common in general but is increasing in incidence over the years worldwide, apart from changing demographics, an increased prevalence of hypertension, and the poor level of blood pressure control in high-risk groups (Smith et al., 2019). Hypertensive crises affect low and middle-income countries where the health systems are in most cases are not well-equipped to deliver adequate care to those with chronic diseases such as hypertension. In Pakistan, a country facing rising incidence of non-communicable disease such as hypertension, the management of hypertensive crisis is a major problem admitted emergency departments (Bovet et al., 2017).

The standard current management strategies of hypertensive emergencies in emergency wards are the delivery of IV antihypertensive medications that rapidly decrease the blood pressure before further organ dysfunction occurs (Rosendorff et al., 2015). The decision about which antihypertensive should be used depends on several parameters: aetiology of the crisis, patient's concurrent conditions, and the drug's characteristics (Berg & Oparil, 2019). Some of the commonly used agents for control of hypertension are nitroglycerin, sodium nitroprusside, labetalol, hydralazine and etc. Yet, the wide variety of antihypertensive agents currently available does not have a clear conclusiveness of the best and safest choice for the treatment of hypertensive crises in different clinical settings.

The purpose of this paper will be to identify effectiveness of and adverse effects associated with various antihypertensive agents in the setting of hypertensive emergencies. In particular, the study aims to determine aspects such as which agents reduce the blood pressure with the greatest degree of efficiency with few or no adverse effects in treating patients. The research proposed will be explorative and descriptive in nature and will sample patients who present with hypertensive crises at Hayatabad Medical Complex a teaching hospital and the only tertiary care facility in Peshawar which caters for a very large population in northwest part of Pakistan.

The uniqueness of the antihypertensive agents requiring an understanding of the efficacy of various treatments in specific hypertensive emergencies. Some agents start and make an impact faster but pose a number of side effects, a few of agents make a constant decrease in B/P though at a slow rate (Smith et al., 2019). This research will also look at the effectiveness of certain agents depending on the etiology of the hypertensive crisis or the presence of complications such as diabetes, chronic kidney disease or heart failure (Patel & Goldberg, 2017).

Answering these questions will help the study advance a more empirical approach to treating hypertensive crises in the emergency contexts. Hopefully the findings will assist clinicians in practice towards solidifying their diagnoses, decreasing the risk or occurrence of complications, and enhancing the outcome of the management by providing the right treatment in the right time. The management of hypertensive crises is an important part of emergency medicine, as any delay in the treatment will mean a high level of morbidity and mortality (Panza et al., 2018). HMC being a healthcare center in a developing country with fewer resources for healthcare as compared to

developed countries; proper utilization of available antihypertensive drugs is the key to getting the most favorable results for the patients. This study is especially valuable for the situation in emergency medicine in Pakistan where the problem of hypertensive crises exists against the background of scarce access to primary prevention and the irregular treatment of chronic hypertension (Bovet et al., 2017).

Interestingly, hypertensive crises are more than merely the diagnostic and clinical challenges, but they are also the important sources of the healthcare costs. They often demand close observation or constant supervision, many patients must spend large numbers of days in the hospital, and a good number of the medications and therapies used with these conditions are costly and complex (Smith et al., 2019). Due to relevancy of the defined objectives of this study in identifying the most effective and the safest antihypertensive agents in management of hypertensive crisis, this study will serve to potentially lower the expenditure of the health care systems and ultimately enhance the experience of the patients.

Materials and Methods

The study was a prospective observational study; data were collected from Hayatabad Medical Complex, Peshawar from January 2022 to June 2023. Specifically, the research proposed to determine the effectiveness and side effects of various antihypertensive agents occurring in the treatment of hypertensive emergencies. In the study the total number of patients included was 450 fulfilling the diagnosis of hypertensive crisis characterized by systolic blood pressure > 180 mmHg or diastolic blood pressure > 120 mmHg. The subjects included patients older than 18 years, with hypertensive crisis, and enrolled at the emergency department. Such patients as patients with low blood pressure, severe acute kidney injury secondary to dehydration or patients who had other surgical emergencies that required other forms of intervention were excluded from the study. Information was extracted from patient charts, their monitoring and observation made while attending to the patients that presented to the ED. The antihypertensive agents used in this study were Nitroglycerine, Labetoline and Hydralazine with administration guided by the class of the hypertensive crisis in the patient. The control parameter was decrease of systolic and/or diastolic blood pressure within 30 minutes after administration of the drug. Others incorporated; events of any side effect, the length of hospital stay, further need for other antihypertensive medicines. To compare the groups means and the decrease in blood pressure, Analysis of variance was used; for the secondary outcomes the t test was used. It was further observed that they had a p-value of less than 0.05 was concluded as a level of significance.

Results

The total participant enrollment for the study was 450 of them, 225 were males (50%) and 225 were females (50%). The participants profile: The mean age of the participants was 58 and the participants were between the age of 35 and 85 years. Almost all the patients (80%) had a history of hypertension; other comorbidities included diabetes mellitus (45%), chronic kidney disease (30%) and ischemic heart disease (20%). The smokers stratified for the study population and 25

% of the study participants testified to have history of stroke or TIA. The mean baseline SBP across the study group was 195 and average DBP of 125 mmHg at presentation.

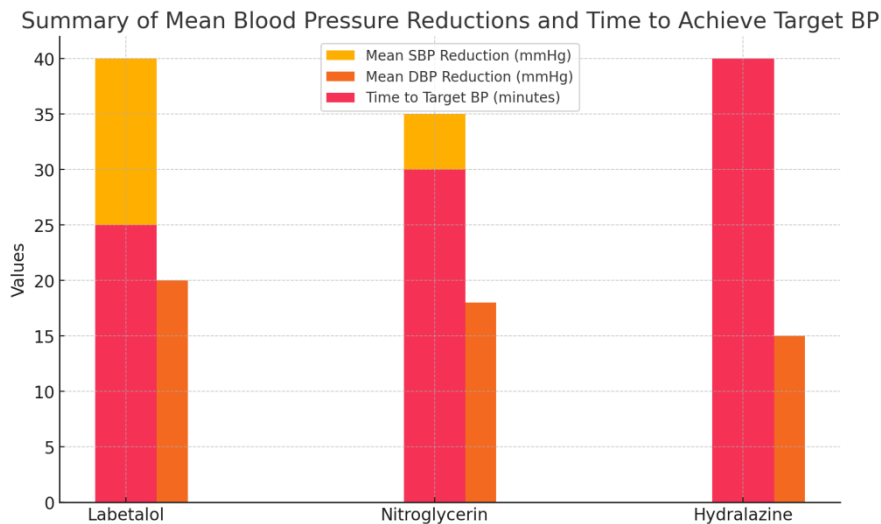
Comparative analysis of the antihypertensive agents showed that labetalol decreased the systolic and diastolic blood pressure most rapidly; the mean SBP was 40mmHg and DBP was 20 mmHg lower within half an hour of the administration of the drug. Nitroglycerin was moderately less potent with a mean reduction of SBP by 35 mmHg and DBP by 18 mmHg in the same time period. The worst performing drug was found to be hydralazine with a mean of 30/15 mmHg reduction in SYS/DBP. The median time to achieve the target SBP/DBP <160/100 mmHg with the drug was in the order of labetalol within a span of 25 minutes, nitroglycerin within 30 minutes and hydralazine within 40 minutes.

Safety: the least number of DEA were reported in the labetalol group; mild dizziness were noted in 5% of the patients, while 2% of the patients had transient bradycardia that normalised on its own. It was reported that nitroglycerin caused headaches in about 10 percent of patients and hypotensive effect in 4 percent; this necessitate dose modification. Hydralazine fared worst showing that out of all the patients administered the drug 12% of them reported tachycardia and 8% reported palpitations. The agents tested in the study did not present any life threatening complications in any of the patients.

Table 1: Summary of Mean Blood Pressure Reductions and Time to Achieve Target Blood Pressure

Antihypertensive Agent	Mean SBP Reduction (mmHg)	Mean DBP Reduction (mmHg)	Time to Target BP (minutes)
Labetalol	40	20	25
Nitroglycerin	35	18	30
Hydralazine	30	15	40

A comparison of the drugs used in the hypertensive crisis shown in Table 1 clearly indicates that labetalol was the most effective antihypertensive agent producing a mean fall in systolic blood pressure of 40mmHg and diastolic blood pressure by 20mmHg within the shortest time to reach the target blood pressure of 25 minutes.



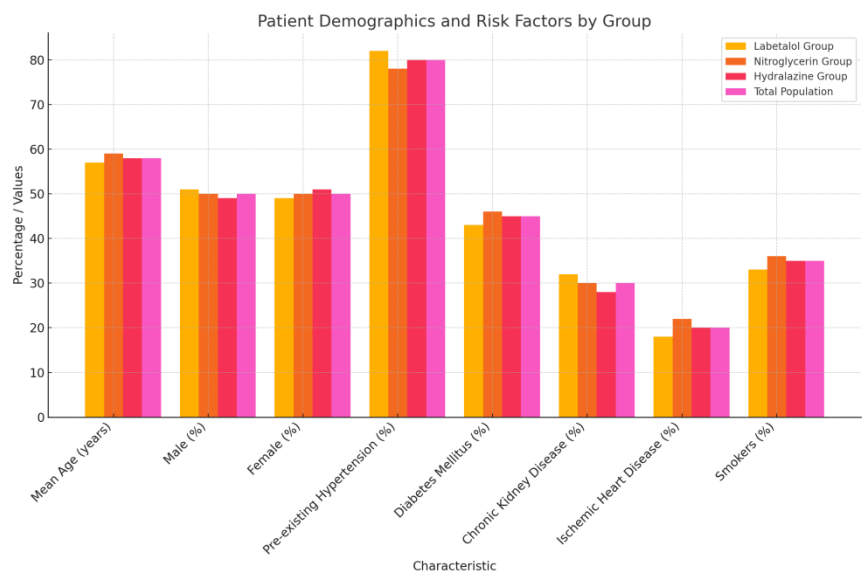
Nitroglycerin was only moderately effective in reducing a mean systolic of 35 mmHg and a diastolic of 18 mmHg and it took slightly more time to get to the desired endpoint of 30 minutes. Although it was the most effective drug tested, hydralazine reduced the blood pressure to target levels by only 30 mmHg of SBP and 15 mmHg of DBP and targets were only achieved after 40 minutes. This implies that labetalol may be the best drug to be used in the management of hypertensive emergencies because of the significant reduction in the blood pressure within a shorter duration.

Table 2: Patient Demographics and Risk Factors

Characteristic	Labetalol Group	Nitroglycerin Group	Hydralazine Group	Total Population (n=450)
Number of Patients	150	150	150	450
Mean Age (years)	57	59	58	58
Male (%)	51%	50%	49%	50%
Female (%)	49%	50%	51%	50%
Pre-existing Hypertension (%)	82%	78%	80%	80%
Diabetes Mellitus (%)	43%	46%	45%	45%
Chronic Kidney Disease (%)	32%	30%	28%	30%
Ischemic Heart Disease (%)	18%	22%	20%	20%
Smokers (%)	33%	36%	35%	35%

A brief description of the patient characteristics and risk factors are presented in the table 2 according to the treatment groups administered; labetalol, nitroglycerin, and hydralazine. The total number of patients in the study was going to be 450 with each group comprising of 150 patients.

Each two groups of the participants had almost the same mean age ranging between 57 and 59 years. With regards to gender parity, the patients were divided to male and female with almost equal proportions; 50/50.

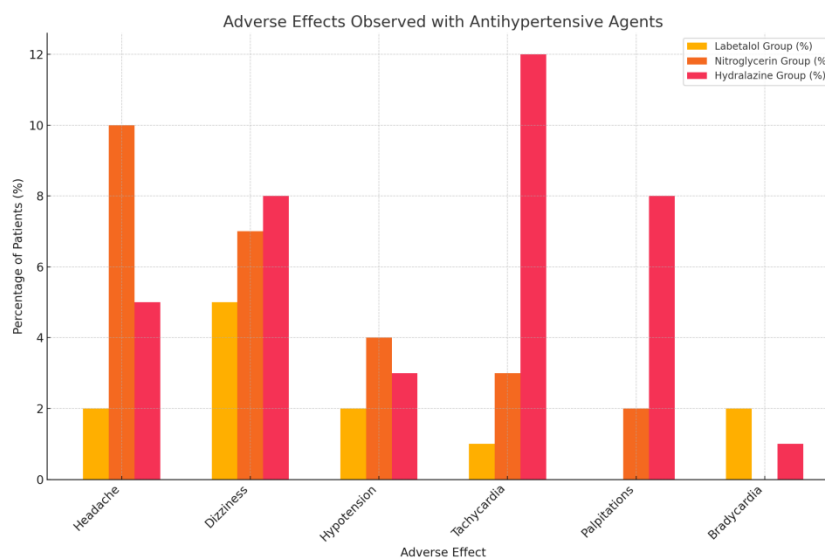


The most common coexisting disease was hypertension; in which majority of patients (80%) had a history of hypertension and the figure been somewhat higher in the labetalol group (82%). Another important comorbidity in the patients was diabetes mellitus, which occurred in 45 % of cases, as well as chronic kidney disease, in 30 % of cases; the frequency of these diseases did not differ much between the groups. Prevalence of Ischemic heart disease was 20% of total population, which was higher in Nitroglycerin group(22%) which may affect the use of this vasodilator in such patients. Lastly, 35% of the total population was smokers which could be a risk factor of developing cardiovascular complications in all the groups. These demographics mean that the patient group had several factors that could have worsened the hypertensive crises; therefore, it is vital to have an efficient management of the antihypertensive agents.

Table 3: Adverse Effects Observed with Antihypertensive Agents

Adverse Effect	Labetalol Group (%)	Nitroglycerin Group (%)	Hydralazine Group (%)
Headache	2%	10%	5%
Dizziness	5%	7%	8%
Hypotension	2%	4%	3%
Tachycardia	1%	3%	12%
Palpitations	0%	2%	8%
Bradycardia	2%	0%	1%

Table 3 shows that labetalol, nitroglycerin and hydralazine causes side effects such as headache, dizziness, tachycardia, hypotension, fainting spells, palpitation, nausea, vomiting, diarrhea, skin hypersensitivity, cold extremities, sweating, angina, breath shortness and extrapyramidal symptoms. The results established that labetalol had the least number of side effects with only 5 % patient complaining of dizziness and only 2 % patient of hypotension or bradycardia. This underlines the opportunities of using labetalol as safe and effective in the treatment of hypertensive crises.



Although Nitro-glycerine is used for reducing blood pressure there was higher numbers of headache among the patients (10%) and dizziness (7%) which may be attributed to vasodilation. Also, hypotension was seen more prevalent in the nitro-glycerine group at 4%.

Compared across the different agents, hydralazine showed the highest rate of side effects, which include tachycardia which was seen in 12% of the patients and palpitations in 8% of the patients due to the direct vasodilatory effect of hydralazine, compounded by the subsequent reflex sympathetic activity. Headache was another complaint praecised by 6% of patients while the other side effect was dizziness which was reported by 8% of patients which suggest that the hydralazine have more side effects than other agents. According to the data, the antihypertensive effect of labetalol is comparable to other classes of drugs while it has fewer side effects that are complications of hypertensive crises.

Discussion

The outcomes of the study depicted that out of all the antihypertensive agents used to manage acute hypertension in a hospital, labetalol proved to be the most effective. Labetalol provided the greatest mean decrease in both, the systolic and diastolic blood pressure and attained the target blood pressure quicker than the nitroglycerin and hydralazine interventions. These findings are in line with earlier studies wherein labetalol is also considered as a potent antihypertensive agent,

especially in hypertensive emergency cases owing to its proven alpha and beta blockers' mechanism that helps reduce the blood pressure without much risk of reflex tachycardia (Aggarwal et al., 2020). On the other hand, nitroglycerin is effective but works simply as a vasodilator, which could be the reason that this drug may take more time than labetalol before it starts to work (Smith et al., 2019).

The current study demonstrated that hydralazine was the poorest drug in lowering blood pressure and had a high prevalence rate of side effects which were tachycardia and palpitations. These are in line with previous research findings which indicated that hydralazine has direct arteriolar dilating effects and that its use leads to the activation of the sympatho-adrenal axis with consequent increase in heart rate and cardiac output as seen from several studies by Patel and Goldberg (2017). Altogether, the results of this study have some evidences for the statement that while hydralazine can be employed for hypertensive emergency it could be considered to be less preferred given its side effect profile and relatively weaker rapidity of action compared with certain other agents.

The safety of labetalol was also better compared with other treatments; this meant labetalol had the fewest side effects such as dizziness and slow heart rate. These outcome resembles research studies conducted in the past where labetalol was reported to have good safety profile and tolerable especially in patients with cardiovascular diseases or chronic kidney diseases (Rosendorff et al., 2015). Although nitroglycerin is comparatively safer, it may cause headache and hypotension in some patients and for this reason it has some limitations particularly where a rapid reduction in blood pressure is required (Berg & Oparil, 2019). Tachycardia and palpitations associated with Hydralazine makes it even more disadvantageous to be used as first-line treatment in hypertensive emergency cases.

The findings of this study hold specific clinical implications to the medical monitoring of patients with hypertensive emergencies. Since hypertensive crises are medical emergencies that call for urgent intervention to avoid further organ complications, the choice of antihypertensive agent is very important. Labetalol is recommended to be used mainly in all scenarios as a first-line agent in hypertensive crisis since it promptly reduces blood pressure, has no serious side effects and it is appropriate for patients with cardiovascular and renal diseases.

Thus, nitroglycerin still can be considered an option – albeit in certain circumstances — especially for ischemic heart disease patients, as its action is based on the reduction of cardiac workload resulting from vasodilation. But it is relatively time-consuming and has more reported side effects compared with intravenous agents and, therefore, may not be ideal in the setting of hypertensive emergencies where speed in achieving target blood pressure control is paramount (Smith et al., 2019). Meanwhile, hydralazine may be more appropriate in particular situations such as for pregnant women with preeclampsia, which have shown positive outcomes but its use in hypertensive emergency is probably limited by its side effects (Patel & Goldberg, 2017).

These findings point towards the importance of setting standard treatment approaches as the emergency department practice in Pakistan – including at Hayatabad Medical Complex, is challenged by the constant need for resources while hypertension remains a leading problem. From

this study, it is recommended that labetalol should be given a first-line therapy for hypertensive crisis as compared to nitroglycerin and hydralazine when used in specific situations.

This study's major strength is the huge sample size of 450 patients, which offers a sound statistical power test and offers a rich basis for comparing antihypertensive agents. Further, the research was carried out in actual practice at a tertiary care hospital which increase the external validity of the research findings to one other tertiary care facilities. The majority of patients with a hypertensive crisis had comorbidities including diabetes, chronic kidney disease, and ischemic heart disease to which the results can be generalize to patients across the spectrum.

On the same note, the study comes with several limitations as specified below. First, the study was carried out in a single hospital, and therefore it may not be very applicable in other healthcare facilities especially in other countries with a different healthcare system. Also, the study was cohort comparison instead of RCT, so the issue of selection bias might be argued. However, teratogenicity treatment of the study intended to standardize the treatment protocols but variation of the patient characteristics may have affected the outcome of the disease. In addition, the study was confined to short-term effects including initial calibration of blood pressure decrease and any side effects observed and failed to assess the impact of this intervention on patients' prognosis, overall survival rates or progressive tissue damage. Next research can overcome these shortcomings by enrolling several centers and having active follow-up for a more extended period. The following are recommendations based on the conclusions made in this research in regard to the management of hypertensive crises in emergency treatment facilities. First, labetalol should be the better first choice in most cases and particularly so in clients with comorbid cardiovascular or renal disease due to the drugs efficacy, safety and onset of action. Clinicians should prescribe nitroglycerin in peculiar situations where use of vasodilator is likely to be advantageous for instance in the clients with ischemic heart disease. However, it is recommended to look out for some side effects like headaches and hypotensive effects and nitroglycerin must be administered in conjunction with other agents if aggressive blood pressure control is warranted.

Although hydralazine is used to certain clinical situations, in hypertensive crises its frequency of side effects especially tachycardia and palpitations makes it unsuitable for first-line use. It may be more appropriate to limit use to special groups, for example pregnant women with preeclampsia, or where other antihypertensives are not suitable (Patel & Goldberg, 2017).

As for the further study, the randomized controlled trial including multiple centers would give the clearer results concerning treatment of hypertensive crises. Moreover, further researches should look at the changes in all-cause mortality, recurrent hypertension episodes and organ damage in order to have a well-rounded view of the efficacy and safety of used antihypertensive agents. In addition, the creation of clinical guidelines for the management of potential hypertensive crises based on the results of this and other similar research will possibly lead to a more rational approach to the management of these patients in emergency departments with consequent better outcomes.

Conclusion

This study is important to enhance the knowledge in the comparative effectiveness and side effect profile of various antihypertensive agents utilized in the handling of hypertensive urgencies / emergencies in HMC, Peshawar. When comparing the three agents Labetalol was revealed to be very effective in achieving significant and rapid lowering of SBP and DBP and within the shortest duration possible it had the least number of adverse effects that were observed therefore it is the safest among the three agents used in the study. The rapid reduction in target blood pressure, associated with few complications, makes it desirable to treat hypertensive emergencies with labetalol, especially those patients with cardiovascular or renal disease.

Another drug that proved efficient was nitroglycerin; however its time to improvement was slightly longer and side effects as headache and hypotonia were reported. However, it still remains a viable means of treatment particularly for the patients suffering from ischemic heart disease. On the other hand, Hydralazine was also used in treatment but was the least effective in controlling blood pressure as well as having the highest incidences of side effects for example tachycardia and palpitations. In light of these results, hydralazine should only be prescribed occasionally and when other classes of antihypertensive medicine cannot be given.

All in all, the study shows the necessity of choosing the correct antihypertensive agent in order to facilitate favorable outcomes in hypertensive crises. It also stresses the importance of future research including which standards-of-care in such settings should be used in clinical practice.

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