An Assessment of the Efficacy of Anti-Hypertensive Drugs Via Supersaturated Design.

Nnoka, Love Cherukei & Eleonu, Blessing Chikaodi
Department of Statistics,
Captain Elechi Amadi Polytechnic, Rumuola
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Abstract
The study investigated the efficacy of ten anti- hypertensive drugs as declared by their users.
The data for this study were sourced through a carefully structured questionnaire and administered to 455 respondents at four strategic locations in Rivers State of Nigeria; (Emohua, Ahoada, Khana and Etche). The variables were separated into "Factors" and "Runs" and two-level supersaturated designs (SSD_s) were considered and coded as -1 and 1 signifying low and high levels respectively. The study also recognized a well-known criterion for evaluating the efficacy of supersaturated design (SSD); $E(S^2)$.
The drugs with equivalent efficacy levels were merged and represented by the higher or lower of them all depending on the case. The repeated or duplicated experimental "Runs" (drugs) were interchanged for "Factors" and were eliminated to allow for only a unique column thereby preserving orthogonality principle. Thus, with the drugs as "Factors" we were able to obtain 4 x 6 design matrix representing 4 "Runs" AND 6 "Factors". The study identified the most "active factor" given the 6 "factors" (the most efficacious) of the drugs.

Keywords: *Runs, Factors, Supersaturated, Anti-hypertensive drugs & Efficacy*

INTRODUCTION

The pressure exerted by the blood in relation to wall of blood vessel is termed Blood Pressure (BP) and it is also referred to as arterial blood pressure. It is one of the vital signs, others include temperature and pulse rate. Blood Pressure varies between Systolic (pumping out) and Diastolic (filling in) pressures at each cardiac event. Blood Pressure refers to the systemic arterial pressure measured at an individual's upper arm and is a measure of the pressure in the brachial artery; the main artery in the upper arm.

In humans, blood pressure is normally expressed in terms of the Systolic pressure over diastolic pressure and is measured in millimeters of mercury(mmHg), for example 110/70. Blood pressure varies in People as well as animals, but always monitored by nervous and endocrine system. It should be noted that when the blood pressure becomes pathologically low, it is termed "hypotension and "hypertension" when it is pathologically high. These two distinct classes have various causes that range from "mild" to "severe**" (American Heart Association 11).**

Hypertension (HTN) or high blood pressure (HBP) is sometimes referred to as arterial hypertension and it is a medical condition in which pressure in the arteries is increased **(Agarwal et al, 2008).** Blood Pressure is read by two measurements namely systolic and diastolic; they depend on whether the heart muscle is contracting (systolic) or relaxed between beats (diastole). This can mean the maximum and minimum pressure respectively. It should be mentioned that the blood pressure of rest is between the range of 100 – 140 mmHg systolic (top reading) and 60 –

90mmHg(diastolic) bottom reading, thus the blood pressure is high when it is at or above 140/90mmHg **(National Committee on Prevention, Evaluation and Treatment of High Blood Pressure).**

It is alarming the rate at which cardiovascular disease is increasing in developing countries. According to the **World Health Organization (2001),** non – communicable disease accounted for 22% of the total deaths in African region in the year 2000, cardiovascular diseases alone accounted for 9.2% of the total deaths, killing more than malaria. Hypertension is a common health problem in developed countries and constitute a strong risk factor for cardiovascular disease (Ogah **et al,1979).** The relationship between blood pressure and the risk of cardiovascular disease is continuous and consistent as well as independent of any other risk factor **(Klabunde Richard, 2005).** The higher the blood pressure, the greater the chance of heart attack, kidney failure, heart failure and stroke. Hypertension strains the heart thus is a principal risk factor for cerebrovascular accident or disease or stroke **(WHO, 2001).**

Kearney et al, (2020) attributed 75% deaths in Sub-Sahara Africa to hypertension and several studies showed that if uncontrolled would lead to immediate end organ damage and more premature deaths.

Hypertension in adults has a high impact on the national economy and on the quality of life of individuals with important implication on resource expenditure. With hypertension, too much force is exerted on the arteries as blood is pumped through and subsequently destroys not only the blood vessels but the organs that receive the stress **(Lawrence et al, 1996)**

The world's population with uncontrolled hypertension reduced drastically between 1980 and 2008 but rose again from 2008 and is still rising as a result of aging, population growth. Until recently, hypertension was mainly associated with more affluent regions of the world, however, the condition is increasing and spreading in low and middle-income countries ($LMIC_S$)

However, identification of the modifiable risk factors of hypertension would help reduce the incidence and hitherto the prevalence of hypertension. It would also help decrease the mortality and morbidity in middle – aged and older persons, subsequently lead to a better quality of life **(Pickering, 1972)**

Recognizing the several classes of blood pressure medication can also help put a check on hypertension but it surprising that not all anti-hypertensive drugs produce the desired result and this is the purpose for this research. It is more surprising that sometimes the least- priced drug has more efficacy than the high-priced ones **(Fretheim & Oxman ,2005)**

DATA COLLECTION

In this study, a well structured questionnaire was designed and completed by 455 respondents who were hypertensive patients though stable as a result of their placement on one of the anti-hypertensive drugs or combination of any two of the drugs. The questionnaire was used to obtain information on socio-demographic variables, lifestyle habits, comorbid condition, family history of hypertension, and diabetes and number of anti-hypertensive drugs' prescription and their effectiveness.

The respondents were either residents or indigenes of the following four Local Government Areas of Rivers State (Emohua, Ahoada, Khana and Etche).

TEN ANTI –HYPERTENSIVE DRUGS THAT WERE CONSIDERED ARE AS FOLLOW:

BUMETANIDE: A brand of Diuretics. It can be used alone for the treatment of mild hypertension and can sometimes be combined with other high blood pressure medication.

Bumetanide increases urination which serves as a means of lowering the amount of sodium and fluid in the body thus helping to lower blood pressure by lowering blood volume.

BISOPROLOL: This is a form of beta-blockers. It lowers blood pressure by acting directly on the heart and reducing heart rate and the force of heart pumping thereby reducing blood volume. Its side effects include skin reaction, dizziness, fatigue and sometimes fainting.

ESMOLOL: This is a brand of beta – blockers and so behaves like Bisoprolol.

LISINOPRIL: Lisinopril is a form of Angiotensin – Converting Enzyme (ACE) is a hormone in the body that causes blood vessels to narrow and subsequently lowers blood pressure.

LOSARTAN: A form of angiotensin 11 receptor blockers (ARB), the hormone narrows blood vessels and also prevent angiotensin from binding to receptors on the blood vessels thus lowering blood pressure.

AMLODIPINE: Amlodipine is a Calcium channel Blocker (CCB) that increases the strength and force of contraction in the heart including blood vessels. Its side effects include; dizziness, heartburn nausea, flushing and sometimes ankle swelling.

DOXAZOSIN: This is one of the brands of Alpha – blockers. It aids in dilation of blood vessels thus lowering blood pressure. It can be used also in the treatment of Prostate enlargement in men. Its side effects are; headache, increased heart rate and nausea.

ALDOMET: It is a brand of alpha -2 receptor agonist (Methyldopa) and of the oldest blood pressure medications that is still in circulation. Aldomet works in the central nervous system to lower blood pressure. Its side effects are; dry mouth, local skin reaction, drowsiness, inability to fall asleep, stuffy nose and depression.

MINOXIDIL: Minoxidil makes the blood pressure to fall by relaxing the artery wall muscles. They are usually combined with other anti –hypertensive drug for better result. The side effects are drowsiness and heartburn.

VALSARTAN: This is the same brand with losartan and behaves same as it.

METHODOLOGY

We employed the method of supersaturated design matrix in our analysis. A supersaturated design is a fractional factorial design in which the number of factors m exceeds the number of runs n and if $m \geq n-1$ then such a design is said to be supersaturated **(Bashir,2003).** The construction method for improved supersaturated and Orthogonal designs were proposed by **(Wang & Wu ,1991).** Apart from the saturated and unsaturated design matrix, the study was limited to supersaturated design matrix where the "factors" in the design could exist in one of two states (levels) at a time in a particular "experimental run". One - way ANOVA was used to determine if there was a significant difference in the means efficacy of the drugs throughout the four study sites. Our factors were divided into four "levels". two major variables were used namely the Localities or study sites (independent) and Drug (dependent).

The localities were initially considered as "Factors" and the drugs as "Runs" but there after interchanged to suit the principle of orthogonality. This process resulted to feasible approach called the optimal supersaturated design with 4 x 6 matrix signifying 4 runs and 6 factors with drugs as factors and localities as runs and satisfying its condition of number of experimental runs being fewer than the number of factors. The relevance of supersaturated design cannot be

underrated because it is useful in situations where the number of active factors is very small compared to the total number of factors being considered **(Wang &Wu, 2003).** It aids in identifying active factors among a number of factors without requiring much number of experimental runs. It is called optimal supersaturated design because it minimizes cost (or cost effective), it is used when the implementation of experimental runs is costly. The most efficacious drug from the six factors was analyzed using the optimal criterion $E(S^2)$ which is a measure of goodness of fit test and for comparing the performance of supersaturated design.
Mathematically, this optimal criterion can be represented by the formula:

$E(S^2) = \frac{\sum_{i<j} S^2_{ij}}{\binom{m}{2}}$ where ij refers to number of rows in ith and jth column respectively, m denotes number of factors. The lower bound of $E(S^2)$, which is a function of n and m is defined as

$E(S^2) \geq \frac{n^2(m-n+1)}{(m-1)(n-1)}$ $where\ (m \geq n)$

From our chosen 4 x 6 matrix, our n is 4 and m is 6 so the lower bound of $E(S^2)$ becomes

$E(S^2) = \frac{4^2(6-4+1)}{(6-1)(4-1)}$

$E(S^2) = \frac{16(3)}{(5)(3)}$

$E(S^2) = \frac{16}{5}$

$E(S^2) = 3.2$

TABLE 1: RESPONSES FROM THE QUESTIONNAIRE ABOUT THE EFECTTIVENESS OF EACH DRUG

DRUGS	EMOHUA	AHOADA	KHANA	ETCHE
BUMETANIDE	6	7	3	4
BISOPROLOL	8	4	7	3
LISINOPRIL	15	20	27	30
LOSARTAN	10	9	12	12
AMLODIPINE	20	15	24	18
DOXAZOSIN	5	0	0	3
ALDOMET	22	23	20	14
MINOXIDIL	0	1	1	0
ESMOL	12	15	18	10
VALSARTAN	11	20	8	18
TOTAL	109	114	120	112

The zero score could either mean; such drug was not common to them(respondents) or made no impact at all when taken.

TABLE 2: PERCENTAGE REPRESENTATION OF RESPONDENTS' VIEW FOR EACH DRUG

DRUGS	EMOHUA	AHOADA	KHANA	ETCHE	OUTPUT
BUMETANIDE	5.50	6.14	2.50	3.57	17.71
BISOPROLOL	7.34	3.51	5.83	2.68	20.20
LISINOPRIL	13.76	17.54	22.50	26.79	79.76
LOSARTAN	9.17	7.89	10.00	10.71	37.77
AMLODIPINE	18.35	13.16	20.00	16.07	67.58
DOXAZOSIN	4.59	0.00	0.00	2.68	7.27
ALDOMET	20.18	20.18	16.67	12.50	69.53
MINOXIDIL	0.00	0.88	0.83	0	1.71
ESMOLOL	11.01	13.16	15.00	8.93	48.1
VALSARTAN	10.09	17.54	6.67	16.07	50.37
TOTAL	100	100	100	100	

By observing table 2, Lisinopril recorded highest percentage throughout the four study sites.
To compute the design matrix , two values (-1 and 1) were considered as "low" and "high" respectively using 13.16% as our bench mark. Any value less than or equal to 13.16% was regarded as -1 and any above 13.16% was taken to be high and thus represented by 1.

TABLE 3: FORMATION OF DESIGN MATRIX USING LOCALITIES (STUDY SITES) AS FACTORS AND DRUGS AS EXPERIMENTAL RUNS

DRUGS	FACTORS				OUTPUT
-	EMOHUA	AHOADA	KHANA	ETCHE	-
BUMETANIDE(1)	-1	-1	-1	-1	17.71
BISOPROLOL(2)	-1	-1	-1	-1	20.20
LISINOPRIL(3)	1	1	1	1	79.76
LOSARTAN(4)	-1	-1	-1	-1	37.77
AMLODIPINE(5)	1	-1	1	1	67.58
DOXAZASIN(6)	-1	-1	-1	-1	7.27
ALDOMET(7)	1	1	1	-1	69.53
MINOXIDIL(8)	-1	-1	-1	-1	1.71
ESMOLOL(9)	-1	-1	1	-1	48.10
VALSARTAN(10)	-1	1	-1	1	50.37

Looking at the above table, it was obvious that some drugs have repeated rows (same efficacy level) in some localities. These are ***run 1, run 2, run 4, run 6 and run 8***. We needed to merge and allow one to represent them as shown in table 4. The mean of these drugs will be used as their output and this also implies that the drugs can be used alternatively for the treatment High Blood Pressure. It was also observed that of all these drugs Minoxidil was the least ineffective of them with 1.71 of output.
Lisinopril with highest efficacy can be used without alternative for treatment of hypertension followed by Amlodipine and Aldomet.

TABLE 4: REMOVAL OF REPEATED EXPERIMENTAL RUNS BY MERGING DRUGS WITH EQUAL EFFICACY LEVEL

EXPERIMENTAL RUNS	FACTORS				OUTPUT
-	EMOHUA	AHOADA	KHANA	ETCHE	-
BUMETANIDE/BISOPROLOL/ LOSARTAN/DOXAZASIN/MINOXIDIL(5)	-1	-1	-1	-1	26.21
LISINOPRIL(6)	1	1	1	1	79.76
AMLODIPINE(7)	1	-1	1	1	67.58
ALDOMET(8)	1	1	1	-1	69.53
ESMOLOL(9)	-1	-1	1	-1	48.10
VALSARTAN(10)	-1	1	-1	1	50.37

Table 4 showed the merging of the five equivalent runs, that is to say that drugs with equal efficacy were treated as one drug.

TABLE 5: DESIGN MATRIX OF INTERCHANGING FACTORS FOR RUNS

EXPERIMENTAL RUNS	FACTORS										
-	BUMETANIDE	BISOPROLOL	LISINOPRIL	LOSARTAN	AMLODIPINE	DOXAZASIN	ALDOMET	MINOXIDIL	ESMOLOL	VALSARTAN	OUTPUT
EMOHUA	-1	-1	1	-1	1	-1	1	-1	-1	-1	33.64
AHOADA	-1	-1	1	-1	-1	-1	1	-1	-1	1	35.45
KHANA	-1	-1	1	-1	1	-1	1	-1	1	-1	24.18
ETCHE	-1	-1	1	-1	1	-1	-1	-1	-1	1	28.01

A careful inspection of table 5 showed equality of some columns which violates the principle of orthogonality of design matrix and hence we merged the columns as shown in table 6 below.

TABLE 6: DESIGN MATRIX OF MERGING EQUIVALENT COLUMNS

RUNS	**FACTORS**					
-	LOSARTAN	LISINOPRIL	AMLODIPINE	ALDOMET	ESMOLOL	VALSARTAN
EMOHUA	-1	1	1	1	-1	-1
AHOADA	-1	1	-1	1	-1	1
KHANA	-1	1	1	1	1	-1
ETCHE	-1	1	1	-1	-1	1

By inspecting table 6 above, a unique column was obtained thus satisfying orthogonality.
The table showed a 4 x 6 matrix signifying 4 'runs 'and 6 'factors'. This implies that of the ten anti-hypertensive drugs only four were effective with Lisinopril being the highest of them (most efficacious of the four drugs). The order of their efficacies is Lisinopril, (Amlodipine & Aldomet) and Valsartan

We conducted One –Way ANOVA to see if there was a significant difference in the **means** of the efficacy of the drugs from the four study sites.

TABLE 7: RESULT OF ANOVA

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
EMOHUA	10	109	10.9	45.65556
AHOADA	10	114	11.4	69.6
KHANA	10	120	12	95.11111
ETCHE	10	112	11.2	85.28889

ANOVA

Source of Variation	*SS*	*Df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	6.475	3	2.158333	0.029201	0.993158	2.866266
Within Groups	2660.9	36	73.91389			
Total	2667.375	39				

The p-value of 0.993 indicated the non-rejection of the null hypothesis that the means of the drug efficacies are the same at 0.05 significance level.

FIGURE 1: RESPONDENTS VIEW FOR EACH DRUG'S EFFICACY IN ALL THE STUDY SITES

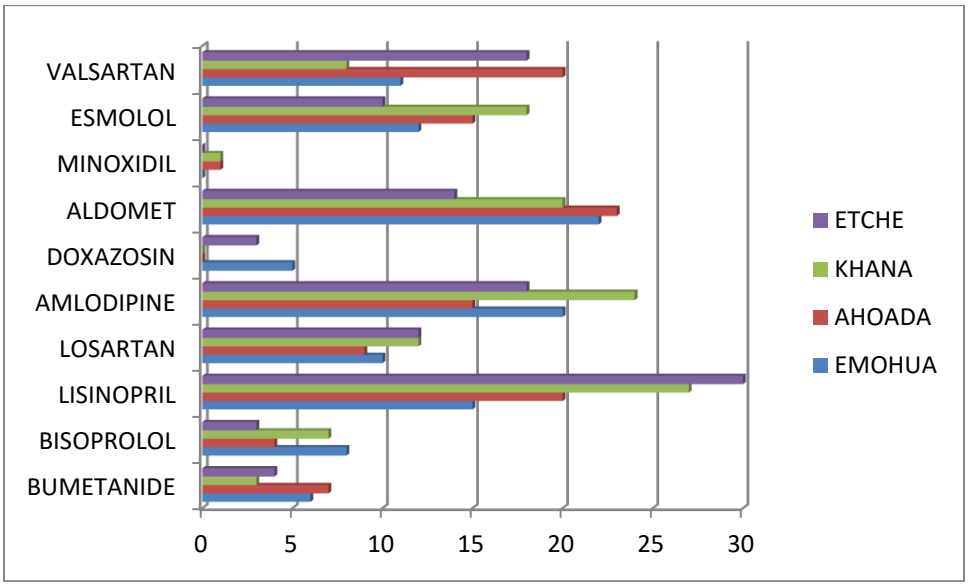


FIGURE 2: RESPONDENTS VIEWS ON THE DRUGS' EFFECTIVENESS IN EMOHUA

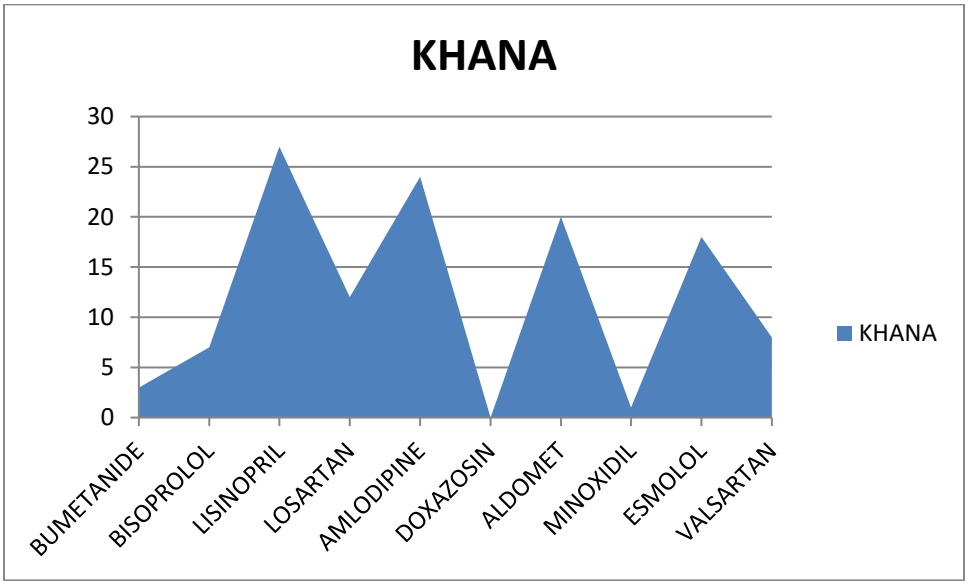


FIGURE 3: RESPONDENTS VIEWS ON THE DRUGS' EFFICACY IN ETCHE

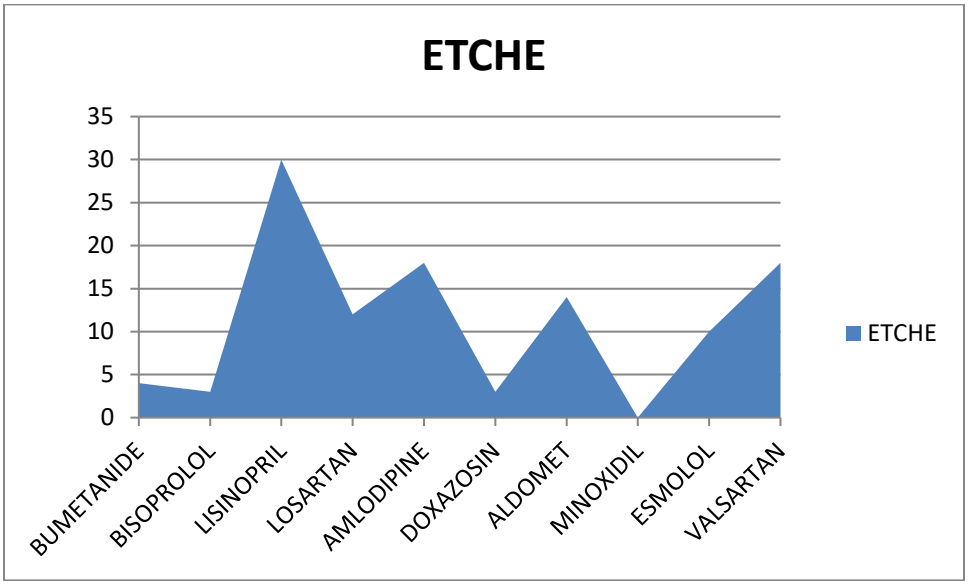


FIGURE 4: RESPONDENTS VIEW ABOUT THE DRUGS EFFECTIVENESS IN EMOHUA

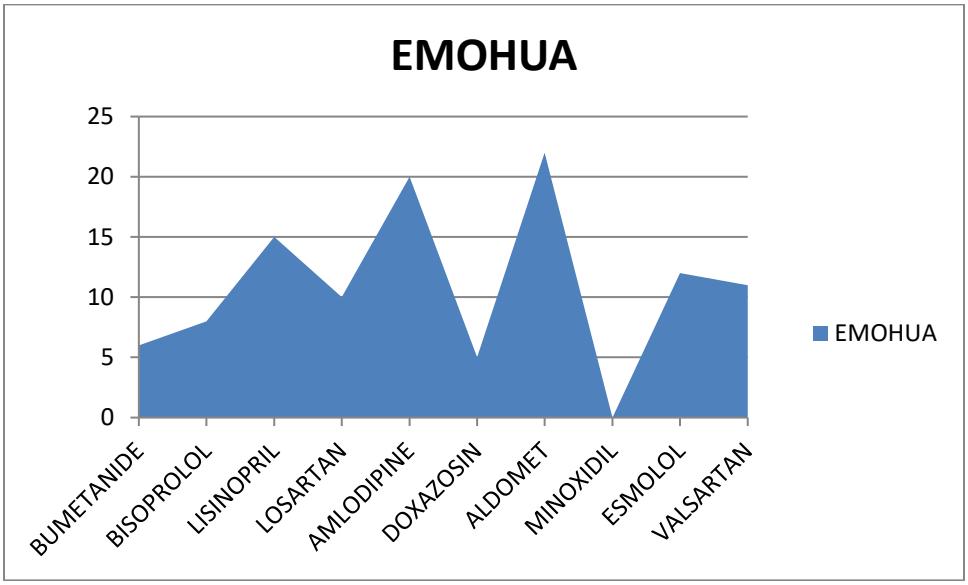
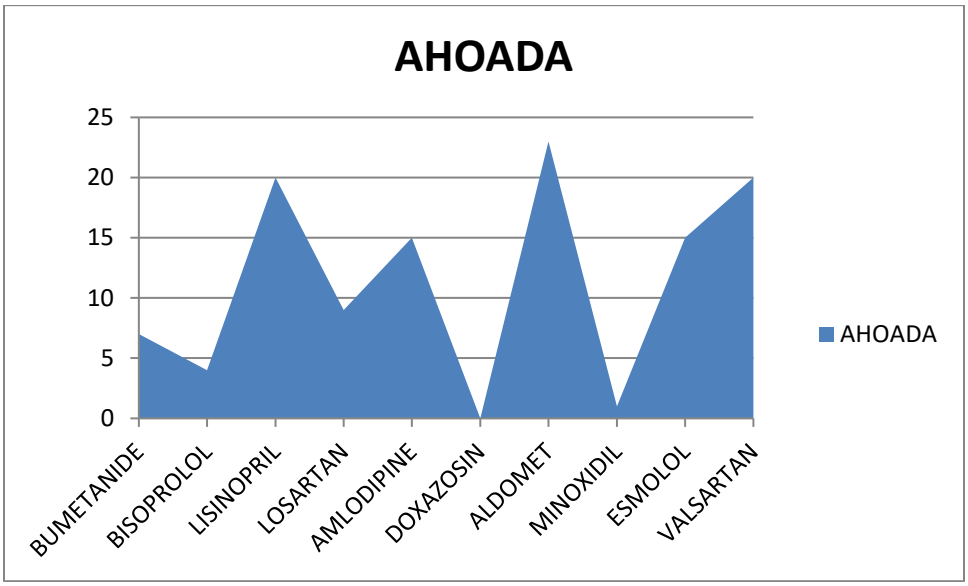


FIGURE 5: RESPONDENTS VIEW ON THE EFFECTIVENESS OF DRUGS IN AHOADA



CONCLUSION

The study has reliably identified four effective anti-hypertensive drugs in the following order; Lisinopril, (Amlodipine & Adolmet) and Valsartan. It should be mentioned here that of these four, Lisinopril was the most efficacious in the treatment of high blood pressure otherwise known as hypertension.

Amlodipine & Aldomet had the same efficacy level and should be used alternatively for the treatment of hypertension while Lisinopril and Valsartan should not be used as alternatives.

The other six drugs which were considered ineffective in the treatment of hypertension are in their order of less effectiveness; Esmolol, Losartan, Bisoprolol, Bumetanide, Doxazosin, Minoxidil. The non or less effectiveness of the anti-hypertensive drugs as shown via supersaturated design could be attributed to either of the followings:

High salt intake, concomitant medication, poor adherence to the antihypertensive drugs, other comorbidities etc

RECOMMENDATION

The following recommendations were made based on the result analysis:

- Lisinopril as the most effective anti-hypertensive medication among the ten that were examined should receive more popularity in terms of prescription
- In the identification of active factors where there are more' factors' than 'runs' the method of Supersaturated design should be employed because of its low cost effectiveness.
- Hypertensive patients should be more open to their physicians so as to disclose any existing comorbidity and concomitant drug use if any to avoid poor performance of the anti-hypertensive medication.

- A special test to be conducted on a patient to know the type of anti-hypertensive medication that will be best tailored to the patient's need so as to avoid random treatment.

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