A Pilot Study Compare the Efficacy of Amlodipine and Captopril in the Treatment for Hypertensive Urgency in Emergency Department and Primary Care Clinic Hospital Universiti Sains Malaysia

by

DR. CHIA BOON YANG

Dissertation submitted in partial fulfillment of the requirement for the degree of Master of Medicine (Emergency Medicine)

UNIVERSITI SAINS MALAYSIA
2008

ACKNOWLEDGEMENT

This dissertation is not an individual effort but with the contribution and cooperation of many people. I would like to take this opportunity to thank those who are involved.

First of all, I wish to thank Dr Nik Hisamuddin Nik Abdul Rahman, Emergency Physician and Head of Department, Emergency Department (ED), Hospital Universiti Sains Malaysia (HUSM), who is also my co-supervisor, for his guidance throughout my residence in HUSM and his kindness to allow this study to be carried out in the ED, HUSM.

I also wish to thank my supervisor, Dr Suhairi Ibrahim, Internal Medicine Physician in Cardiology Unit, Medical Department, HUSM, for his guidance and advice from the preparation of the proposal, the methodology of the study, to the write up of the dissertation. Not forgetting Dr Mohd Rahim Sulong and Dr Kamarul Imran for their help in the statistical analysis and data interpretation.

Similar appreciation goes to all medical officers, sisters, staff nurses, medical assistants and hospital attendants at the ED and KRK HUSM for their kind cooperation. Gratitude and thanks are also extended to all patients who are willingly consented to be part of this study. The same appreciation is extended to all my teachers whose guidance, advice and suggestions had been so valuable in the completion of this dissertation.

To my former supervisor, Dr Idzwan Zakaria, Emergency Physician, thank you for the full support given for the study and has been so helpful in carrying out the study.

I would like to take this opportunity to thank those who have help in the process to complete this dissertation, either directly or indirectly. I also want to thank my family who has been very supportive and encouraging in my career.

TABLE OF CONTENT

LIST OF TABLE

LIST OF FIGURE

LIST OF ABBREVIATION

ED	=	**Emergency Department**
HUSM	=	**Hospital Universiti Sains Malaysia**
KRK	=	**Primary Care Clinic (*Klinik Rawatan Keluarga*)**
BP	=	**Blood pressure**
SBP	=	**Systolic blood pressure**
DBP	=	**Diastolic blood pressure**
MAP	=	**Mean Arterial Pressure**
PR	=	**Pulse rate**
iqr	=	**Interquartile range**
sd	=	**Standard deviation**
NIBP	=	**Non-invasive blood pressure**

ABSTRAK

Kajian Awal Membanding Keberkesanan *Amlodipine* dan *Captopril* dalam Rawatan *Hypertensive Urgency* di Jabatan Kecemasan dan Klinik Rawatan Keluarga, Hoapital Universiti Sains Malaysia

Objektif

Untuk membanding keberkesanan *amlodipine* dan *captopril* dalam rawatan *hypertensive urgency*.

Kaedah

Ini adalah kajian secara label terbuka dan kawalan rambang prospektif dengan penyelidik akhir tertutup yang diadakan dari Okt 2006-Sept 2007. Pesakit-pesakit berumur 18 tahun ke atas dengan tekanan darah yang tinggi, BP>180/110 mmHg selepas berehat 30 min dimasukkan dalam kajian ini. Mereka yang alahan kepada ubat-ubat kajian, dengan kerosakan organ-organ akhir (penyakit jantung, CVA, CRF), peningkatan tahap gula >20mmol/l, menghamil atau menyusu badan dikecualikan. Pesakit-pesakit dibahagi secara rambang blok kepada kumpulan amlodipine (*amlodipine* 5 mg) dan kumpulan captopril (*captopril* 25 mg). Mesin NIBP yang sama digunakan untuk pengambilan tekanan darah (BP) dan kadar nadi (PR) setiap jam untuk 4 jam, kemudian setiap 4 jam sehingga 16 jam selepas rawatan diberi. Jika tekanan darah yang ditetapkan tidak dicapai pada 4 jam, *chlorothiazide* 250 mg akan diberi.

Keputusan

28 orang pesakit menyertai kajian dengan 18 orang dalam kumpulan amlodipine dan 10 orang dalam kumpulan captopril. Mean umur adalah 60.2 tahun (sd 13.02) untuk kumpulan amlodipine dan 45.0 tahun (sd 14.73) untuk kumpulan captopril, p=0.046. Mean SBP semasa kemasukan adalah 206.9 mmHg (sd 27.16) untuk kumpulan amlodipine berbanding dengan 198.4 mmHg (sd 14.32) untuk kumpulan captopril, p=0.487. Perbezaan SBP pada jam pertama adalah ketara secara statistik dengan p=0.004. SBP menurun secara perlahan-lahan antara jam ke-2 dan jam ke-16 dengan perbezaan tidak ketara. Perbezaan DBP semasa kemasukan adalah ketara (p=0.009) dengan mean pada 112.4 mmHg (sd 9.47) untuk kumpulan amodipine berbanding 124.2 mmHg (sd 10.17) untuk kumpulan captopril. Akan tetapi, perbezaan DBP sepanjang kajian adalah tidak ketara. Mean MAP semasa kemasukan adalah 143.9 mmHg (sd 9.27) untuk kumpulan amlodipine berbanding dengan kumpulan captopril pada 148.9 mmHg (sd 7.75), p=0.137. Perbezaan dalam MAP dan PR antara kumpulan adalah tidak ketara.

Kesimpulan

Amlodipine adalah setanding dengan *captopril* untuk rawatan *Hypertensive urgency*

Kata kunci:

Hypertensive urgency; Jabatan kecemasan; *Amlodipine*; *Captopril*

ABSTRACT

A Pilot Study Compare the Efficacy of Amlodipine and Captopril in the Treatment for Hypertensive Urgency in Emergency Department and Primary Care Clinic Hospital Universiti Sains Malaysia

Objective

To compare the efficacy of amlodipine and captopril in the treatment for hypertensive urgency.

Methodology

This is an open labeled randomized prospective control study with blinded end point conducted from Oct 2006-Sept 2007. Patient aged >18-year-old with persistent elevated BP>180/110 mmHg after 30 min bed rest was included in the study. Patient who allergic to study drugs, with target organ damage (acute coronary syndrome, CVA, CRF), elevated blood sugar >20mmol/l, pregnancy or breast feeding was excluded. Patients were randomized using block randomization into amlodipine group (Amlodipine 5 mg) and captopril group (Captopril 25 mg). Single NIBP machine was used to monitor BP and PR hourly for 4 hours, subsequently 4 hourly until 16^{th} hour of medication. If target BP not achieved at 4^{th} hour of medication, Chlorothiazide 250 mg was added.

Result

28 patients enrolled in the study, 18 patients in amlodipine group and 10 patients in captopril group. Mean age for amlodipine group was 60.2 years old (sd 13.02) and 45.0 years old (sd 14.73) for captopril group, p=0.046. Mean SBP on admission was 206.9

mmHg (sd 27.16) for amlodipine group compared to 198.4 mmHg (sd 14.32) for captopril group, p=0.487. SBP at 1st hour was significantly difference with p=0.004. The SBP reduced gradually from 2nd to 16th hour, with no significant difference. DBP on admission was significantly difference (p=0.009) with mean at 112.4 mmHg (sd 9.47) in amlodipine group and 124.2 mmHg (sd 10.17) in captopril group. However, the differences in DBP were not significant throughout the study. The mean MAP on admission was 143.9 mmHg (sd 9.27) in amlodipine group compared to 148.9 mmHg (sd 7.75) in captopril group, p=0.137. The differences in MAP and PR between study groups were not significant.

Conclusion

Amlodipine is comparable to captopril in the treatment of hypertension urgency.

Key words

Hypertensive urgency; Emergency department; Amlodipine; Captopril

1. INTRODUCTION/LITERATURE REVIEW

Hypertension is a major public health problem (Ministry of Health *et al.*, 2002). It is an established risk factor for cardiovascular disease (Hansson *et al.*, 1998). It has high prevalence worldwide with approximately 1 billion individuals are hypertensive, 30% of them are not aware of their hypertension (Chobanian *et al.*, 2003). It is more common in the older age group and more common in men as compared to women (Aggarwal and Khan, 2006).

In Malaysia, the prevalence of hypertension for the population over the age of 30 was 33%. Only 23% of the them were on treatment and 6% had controlled hypertension (Lim and Morad, 2004). However, in Kelantan, the overall prevalence of hypertension was 13.9%, and the prevalence is likely to increase in the near future (Mafauzy *et al.*, 2003).

1.1 DEFINITION OF HYPERTENSION AND HYPERTENSIVE CRISIS

Hypertension is classified into pre-hypertension, stage 1 and stage II hypertension. Table 1.1 showed the blood pressure (BP) range in the classes based on the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report (Chobanian *et al.*, 2003).

Table 1.1: BP Classification (adapted from JNC 7, Chobanian *et al.*, 2003)

BP Class	SBP, mm Hg	DBP, mm Hg
Normal	< 120	< 80
Pre-hypertension	121–139	80–89
Stage I	140–159	90–99
Stage II	≥ 160	≥ 100

Hypertensive crisis is defined as severely elevated BP, with systolic blood pressure (SBP) ≥ 180 mmHg and/or diastolic blood pressure (DBP) ≥ 110 mmHg (Flanigan and Vitberg, 2006, Varon and Marik, 2003). It is classified into hypertensive urgency and hypertensive emergency. Hypertensive urgency is the patients with severely elevated BP without target organ damage (Cherney and Straus, 2002). It is more common than hypertensive emergency, account for about 60% of the hypertensive crises (Martin *et al.*, 2004). Hypertensive emergency are those patients with elevated BP with acute target organ damage. It accounts for one third of hypertensive crisis (Cherney and Straus, 2002).

The target organs damage might involve the heart, brain or kidney. The manifestation involved the heart includes acute left ventricular dysfunction, acute pulmonary edema, myocardial ischemia or infarction. The patients might present with hypertensive encephalopathy, cerebro-vascular accident, either ischemia or haemorrhage if the brain was involved. The kidney complication included proteinuria and acute renal failure. Table 1.2 list the target organ damage seen in hypertensive emergency (Aggarwal and Khan, 2006).

The presence of the acute target organ damage differentiate between the patient with hypertensive emergency and hypertensive urgency, not depending on the absolute level of the BP (Varon and Marik, 2003).

Table 1.2: Target organ damage in hypertension (adapted from Aggarwal and Khan, 2006)

Target organ damage
Acute neurologic syndromes Hypertensive encephalopathy Cerebral infarction Subarachnoid hemorrhage Intracranial hemorrhage
Myocardial ischemia and infarction Acute left ventricular dysfunction Acute pulmonary edema Aortic dissection Retinopathy Renal insufficiency

1.2 PREVALENCE OF HYPERTENSIVE CRISIS

About 1% of the hypertensive patients will develop acute elevated BP at some point in their life time (Varon and Marik, 2003). Hypertensive emergency and urgency account for about 3% of all emergency room visits (Cherney and Straus, 2002).

Hypertension-related Emergency Department (ED) visits account for 25% of all acute medical emergencies in busy urban areas in United State (Gilmore *et al.*, 2005). There are more patients found to have elevated BP when they presented with unrelated complaint.

1.3 PATHOPHYSIOLOGY

The primary pathophysiologic abnormality of hypertensive crisis is the alteration of the autoregulation (Elliott, 2001). Autoregulation occurs in the cardiac, cerebral and renal vascular bed. There would be mechanical stress on vessels wall when BP elevated. The blood vessels respond to increase BP by vasoconstriction, thus supporting the vascular endothelium and minimizing acute injury (Gilmore *et al.*, 2005). This autoregulation mechanism will help to maintain constant blood flow to the organs during fluctuations in BP (Gifford, 1991). Chronic hypertension, cerebral vascular disease, and aging tend to impair normal cerebral autoregulation. There will be right shift of the autoregulation curve in chronic hypertensive to maintain normal perfusion in important organs, (Elliott, 2001) as shown in Figure 1.1.

When severe acute elevation of BP, there will be overwhelm of the autoregulation leading to vasodilatation. The sheer forces from the pressure transmitted to the endothelium. The endothelial injury leads to the release of inflammatory mediators, such as nitric oxide under influence of substance P and acetylcholine, cytokines and monocyte chemotatic protein 1. The mediators causing loss of endothelial function which lead to increase endothelial permeability, inhibit local endothelial fibrinolytic activity and activate the coagulation cascade. Platelet aggregation on the damaged endothelium may promote further inflammation, thrombosis, and vasoconstriction (Vaughan and Delanty,

2000). The resulting ischaemia prompts further inflammation and completing the vicious cycle (Varon and Marik, 2000). Renin–angiotensin–aldosterone system is being postulated to be involved (Stewart *et al.*, 2006).

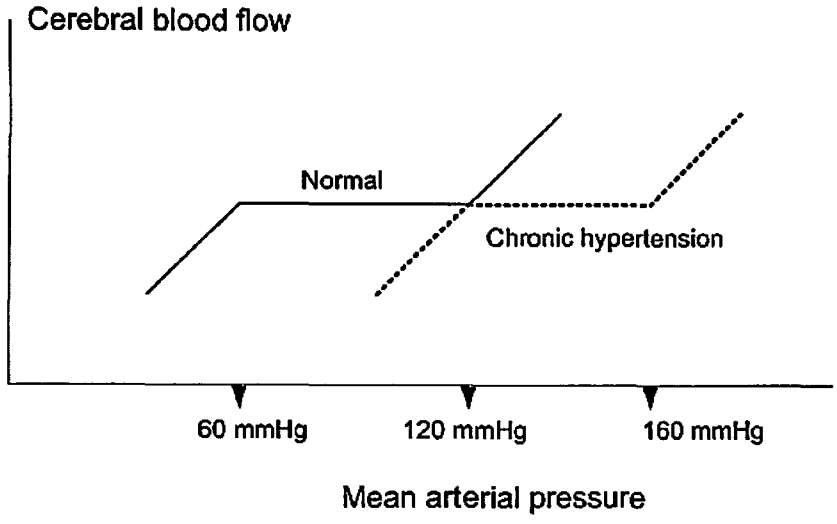

Figure 1.1: Cerebral autoregulation in normatensive and chronically hypertensive patient (adapted from Varon and Marik, 2003)

1.4 CAUSES OF HYPERTENSIVE CRISIS

The most common cause of hypertensive crisis is an abrupt rise in BP of chronic hypertensive patients. Defaulted medication and follow up therefore is the main reason for patients to develop hypertensive crisis. Half of the patients with hypertensive crisis will already have a diagnosis of essential hypertension (Stewart *et al.*, 2006).

1.5 TREATMENT OF HYPERTENSIVE URGENCY

Hypertensive urgency should be treated with oral antihypertensive agent to achieved BP reduction in 24-48 hours (Grossman *et al.*, 1998). They do not require hospitalization (Chobanian *et al.*, 2003). However, they require combination oral medication and monitoring. This will limit and prevent further end organ damage as most patients will have rightward shift of the autoregulation curve (Aggarwal and Khan, 2006, Varon and Marik, 2003). Often the urgency is more in the mind of the treating physician than in the body of the patient (Flanigan and Vitberg, 2006).

Medications recommended include nifedipine, captopril and labetolol (Ministry of Health *et al.*, 2002). Nifedipine is a short acting calcium antagonist, has been used widely to reduce the BP rapidly (Varon and Marik, 2000). It is recommended as first line agents for hypertensive urgency and emergency because of peripheral arteriolar bed selectivity (Kanneganti and Halpern, 1996). However, its uses was strongly condemned because it may precipitate cerebral, renal and myocardial ischaemia (Cherney and Straus, 2002). Nifedipine and other dihydropyridines increase heart rate which is particularly detrimental in patients with ischaemic heart disease (Grossman *et al.*, 1998). The clinicians were reminded of the fact that use of short-acting dihydropyridine agents may be associated with increased cardiac event rates in patients with ischemic heart disease and hypertension (Gibson and Boden, 1996). Patient treated with nifedipine also found to have transient cerebrovascular ischaemic attack (Sanchez *et al.*, 1999). Thus the used of nifedipine should be discouraged (Varon and Marik, 2003).

1.5.1 Captopril

Captopril is a short acting angiotensin-converting enzyme (ACE) inhibitor. It is used in the treatment of hypertension, congestive heart failure, diabetic and/or hypertensive nephropathy with albuminuria (Massana *et al.*, 1997, Fischler and Follath, 1999). In patients with mild or moderate essential hypertension, titrated low doses of captopril used alone or in conjunction with a diuretic are similar in efficacy to usual doses of diuretics, beta-adrenoceptor blocking drugs or the other ACE inhibitor (Brogden *et al.*, 1988).

The bioavailability of captopril is more than 60% and the half-life is one hour (Fischler and Follath, 1999). Administration orally will have the BP reduction range from 60-120 min with median of 90 min (McElnay *et al.*, 1996).

Captopril was used in the treatment for hypertensive emergencies and was found to have significantly reduced the BP at 50 min. It is effective and safely lowers BP in hypertensive emergencies (Angeli *et al.*, 1991). Another study also recommended captopril as one of the first line agents to be used for hypertensive urgency (Komsuoglu *et al.*, 1991).

Captopril should be avoided in patients with bilateral renal artery stenosis or unilateral renal artery stenosis in patients with a solitary kidney (Wu and Chanmugam, 2004). The dosage of the ACE inhibitors should be adjusted according to renal function rather than age, the dose captopril may need to be reduced, depending on renal function (Grossman *et al.*, 1998). Captopril is both metabolized and excreted through the kidney unchanged. The duration of ACE inhibition after administration of any of the ACE

inhibitors is prolonged in proportion to the degree of renal impairment (Piepho and Fendler, 1991).

Common adverse effects of captopril are hypotension, cough, hyperkalaemia and renal failure (Benowitz, 1995). Cough is an infrequent but troublesome effect resulting from ACE inhibition (Brogden *et al.*, 1988). Chinese experienced more cough than Caucasians (Ding *et al.*, 2000). Less frequent adverse effects are angioedema, bone marrow suppression and also fetal damage. Thus, it is contraindicated in pregnancy (Fischler and Follath, 1999). The use of generally lower dosages of captopril in patients with normal or slightly impaired renal function has resulted in a generally low incidence of rash, proteinuria, neutropenia and symptomatic hypotension (Brogden *et al.*, 1988).

1.5.2 Amlodipine

Amlodipine is a dihydropyridine calcium channel antagonist and is prescribed for the management of hypertension. It is a long acting calcium channel blocker because of slow elimination (Park *et al.*, 2006). The elimination-half-life is 30 hours on the average (van Zwieten, 1994).

The pKa value of amlodipine is 8.7, thus it remained in ionized form in physiological pH (Rameis, 1993). This helps in almost complete absorption of amlodipine. The onset is gradual with peak plasma drug concentration occurs 6-8 hours after oral administration (van Zwieten, 1994).

After single doses, blood pressure decreases gradually over 4-8 hours, the maximum decrease of blood pressure of 18 mmHg at 6 hours (Di Filippo *et al.*, 2005). Daily doses of 5-10 mg amlodipine led to a statistically significant decrease in systolic and diastolic blood pressure (-30.5/-20.7 mmHg) while there was no substantial influence

on heart rate or decrease in efficacy (Habeler *et al.*, 1992). However, recent study found that there is an increased in heart rate, which were more pronounced in women (Abad-Santos *et al.*, 2005). Discontinuation treatment results in a slow return of blood pressure to baseline over 7-10 days, with no evidence of a 'rebound' effect (Abernethy, 1992). Thus, there will be lower risk of target organ damage in severely elevated BP.

Amlodipine has low incidence of adverse effects headache, flushing, tachycardia, perimalleolar oedema, vertigo and insomnia (Zicha, 1996, Waeber *et al.*, 1992). It has advantages in the treatment of hypertension, especially in terms of the low incidence of acute side effects and daily dose regime, which may ultimately translate into improved patient compliance (Waeber *et al.*, 1992).

1.5.3 Chlorothiazide

Chlorothiazide is a thiazide diuretic, in which increase the excretion of water by inhibiting the reabsorption of sodium and chloride ions at the distal convoluted tubule. It is indicated for the treatment of hypertension therapy (Ives and Warnock, 1995).

Oral diuretics are amongst the most widely used drugs in clinical practice today (Lant, 1986). The clinical use of diuretics often involves concurrent administration with other drugs. Thiazide-type diuretics are superior in preventing one or more major forms of CVD and are less expensive. They should be preferred for first-step antihypertensive therapy (ALLHAT Collaborative Research Group, 2002).

The dosage regimens for thiazide diuretics must be individually titrated in the elderly patient, since the elimination decreased concurrently with decreased renal function, as indicated by compromised creatinine clearance (Piepho and Fendler, 1991).

The side effects of chlorothiazide include orthostatic hypotension, dizziness and/or syncope. It also has potential fluid and electrolyte disturbances, such as hypokalaemia or hyponatremia. Hypokalemia is one of the most common adverse effects and can lead to cardiac arrhythmias. It also has the effect on blood sugar, lead to hyperglycemia. The other side effects include hyperuricemia and hyperlipidemia. Patients may develop fatigue, weakness and paresthesias (Ives and Warnock, 1995).

1.6 RATIONALE

In Emergency Department, Hospital Universiti Sains Malaysia (ED HUSM), patients with hypertensive urgency will be given a stat dose of oral antihypertensive agent and will be admitted in the observation ward for BP monitoring. One of the oral antihypertensive agents being used is amlodipine. Amlodipine was chosen because of the good safety profile and least side effects. Previous study using lacidipine, a long acting calcium channel blocker, is more effective than nifedipine in controlling and maintaining the BP (Sanchez *et al.*, 1999). Extrapolating from that study, amlodipine, was chosen as the treatment for hypertensive urgency. Besides, amlodipine is also easily available in ED HUSM. Captopril was not used in ED HUSM, because worried of acute renal failure.

If the target BP is not achieved after 2-4 hours, the patients will be referred to the medical team for further control of BP and admission. If the target BP is achieved, patients will be discharged with the medication and will be given an appointment to be reviewed by Primary Care Clinic (KRK) in 3-7 days.