EVALUATION OF CAPTOPRIL AND NIFEDIPINE IN TREATMENT OF HYPERTENSION SECONDARY TO POST STREPTOCOCCAL ACUTE GLOMERULONEPHRITIS – A RANDOMIZED CONTROL TRIAL

BY

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ABBREVIATIONS

PSAGN:	Post-streptococcal acute glomerulonephritis
BP:	Blood Pressure
SBP:	Systolic Blood Pressure
DBP:	Diastolic Blood Pressure
GAS:	Group A Streptococci
ETB:	Erythrogenic toxin type B
ETBP:	Erythrogenic toxin type B-precursor
ASOT:	Anti-streptolysin O titre
RBC:	Red blood cell

ABSTRACT

ENGLISH VERSION

Introduction

Post-streptococcal Acute Glomerulonephritis (PSAGN) is still common in Malaysia. Hypertension is one of its main complications which can lead to severe morbidity in children. Conventional method in treating hypertension in these patients was to use nifedipine to reduce the blood pressure. Recent study in the pathophysiology of the disease had shown apart from water and sodium retention, inappropriate production of angiotensin II could also contributes to the development of hypertension. Captopril, an angiotensin converting enzyme inhibitor can help to reduce the production of angiotensin II which can cause blood pressure reduction.

Aim

To compare the effectiveness of captopril versus nifedipine in controlling blood pressure in children with PSAGN with hypertension.

Methods

This was a double blinded randomized controlled trial, registered with ANZCTR (Trial No: ACTRN12611000778987) All children admitted to Wad 6 Selatan HUSM diagnosed clinically with PSAGN with hypertension during a one year study period are eligible for the study. Subjects were randomized either to receive nifedipine (control) or captopril (intervention). Outcomes measured are blood pressure changed in the first 4 hours and blood pressure changes until Day 3 of starting the medication, duration of days to achieve blood pressure control, total duration of admission and the need to use additional medication. Blood urea and serum creatinine levels are compared from before starting treatment and at Day 3 after starting treatment.

Results

Out of 40 patients who were recruited and randomized, only 19 from the nifedipine treatment group and 13 from the captopril treatment group completed the study. Both treatment groups had no difference in their baseline data. Nifedipine produces a more significant reduction in SBP and DBP compared to captopril in the first 4 hours of starting treatment (SBP p= 0.001, DBP = 0.016). There was no difference in reduction of SBP and DBP after 8 hours of treatment between the groups (SBP p=0.630, DBP p=0.497). There were no significant differences in the duration of blood pressure normalization (nifedipine: 2.7 days, captopril 2.9 days, p= 0.803) and duration of admission (nifedipine: 6.9 days, captopril: 5.4 days; p=0.183) and the need for additional medication to control the blood pressure (p=0.32) between the groups. Changes of blood urea and serum creatinine levels

were not significant before and after treatment (Blood urea changes, p= 0.564; serum creatinine changes, p= 0.236).

Conclusion

Nifedipine produces more significant blood pressure reduction in SBP and DBP in the first 4 hours of starting treatment.

ABSTRAK

VERSI BAHASA MELAYU

Pengenalan

Keradangan ginjal 'post-streptococcal' (PSAGN) masih menjadi penyakit yang biasa di Malaysia. Hipertensi adalah salah satu komplikasi yang utama yang boleh membawa kepada morbiditi teruk di kalangan kanak-kanak. Kaedah konvensional untuk merawat hipertensi dalam pesakit-pesakit ini adalah dengan menggunakan ubat 'nifedipine' untuk mengurangkan tekanan darah. Kajian terkini dalam patofisiologi penyakit ini telah menunjukkan selain daripada pengekalan air dan natrium, faktor-faktor lain seperti pengeluaran paras angiotensin II juga menyumbang kepada terjadinya hipertensi. 'Captopril', sejenis ubat perencat enzim penukar angiotensin, boleh membantu untuk mengurangkan pengeluaran angiotensin II seterusnya menyebabkan pengurangan hipertensi.

Tujuan

Untuk membandingkan keberkesanan 'captopril' berbanding 'nifedipine' dalam mengawal tekanan darah di kalangan kanak-kanak bermasalah hypertensi disebabkan oleh PSAGN.

Kaedah

Ini adalah suatu ujian acak terkendali (double- blinded randomized controlled trial) berdaftar dengan ANZCTR (No.Pendaftaran: ACTRN12611000778987). Semua kanak-kanak yang dimasukkan ke Wad 6 Selatan HUSM yang didiagnosis secara klinikal dengan PSAGN dengan hipertensi semasa tempoh satu tahun kajian adalah layak untuk menyertai kajian ini. Subjek diambil secara rawak sama ada untuk menerima nifedipine (kawalan) atau captopril (ujian). Hasil diukur daripada perubahan tekanan darah dalam tempoh 4 jam pertama dan diteruskan sehingga hari ke-3 bermula ubat, tempoh hari untuk mencapai tekanan darah yang terkawal, tempoh hari kemasukkan ke hospital dan keperluan untuk menggunakan ubat-ubatan tambahan. Paras urea darah dan paras serum kreatinin dibandingkan dari sebelum memulakan rawatan dan pada hari ke tiga selepas memulakan rawatan.

Keputusan

Daripada 40 pesakit yang telah diambil dan rawak, hanya 19 daripada kumpulan rawatan 'nifedipine' dan 13 dari kumpulan rawatan 'captopril' berjaya menyiapkan kajian ini. Kedua-dua kumpulan rawatan tidak mempunyai perbezaan dalam data asas mereka. 'Nifedipine' menghasilkan pengurangan yang ketara dalam tekanan darah sistolik (SBP) dan tekanan darah diastolik (DBP) berbanding captopril dalam 4 jam pertama rawatan bermula (SBP p = 0.001, DBP p = 0.016). Walau bagaimanapun tiada perbezaan dalam

pengurangan SBP dan DBP selepas 8 jam rawatan dalam setiap kumpulan (SBP p = 0,630, DBP p = 0,497). Terdapat tiada perbezaan yang signifikan dalam tempoh tekanan darah kembali normal (nifedipine: 2.7 hari; captopril 2.9 hari, p = 0.803), dalam tempoh kemasukan hospital (Nifedipine: 6,9 hari, captopril: 5.4 hari; p = 0,183) serta keperluan untuk ubat tambahan dalam mengawal tekanan darah (p = 0.32) diantara kumpulan rawatan. Perubahan paras urea darah dan paras serum kreatinin tidak ketara sebelum dan selepas rawatan (perubahan urea darah, p = 0,564; perubahan serum kreatinin, p = 0,236).

Kesimpulan

Nifedipine menghasilkan tekanan darah yang lebih ketara dalam pengurangan SBP dan DBP dalam 4 jam pertama memulakan rawatan.

INTRODUCTION

Post-streptococcal Acute Glomerulonephritis (PSAGN) is one of the known complications associated with Group A *streptococcus* (GAS) infection. Group A Streptococci (GAS) or the scientific name *Streptococcus pyogenes* is a form of *β hemolytic streptococcus* bacteria in which is a common infection worldwide. The organism causes acute infection such as tonsillitis, scarlet fever, acute rheumatic fever, pneumonia, and meningitis. Post-infectiously it is well known to cause severe complications such as rheumatic heart disease and glomerulonephritis.

1.1 Epidemiology and global burden of the disease.

GAS infection is still common around the world although in some parts it has shown a declining trend. Global burden of GAS infection has put the incidence of 470,000 cases of PSAGN occurred annually worldwide with approximately 5000 deaths (1%) of which 97% occurred in the less developed countries (Carpentis et al, 2005).

The incidence of PSAGN is still 'endemic' in developing countries like Malaysia. The last study done in 1990 in the state of Kelantan showed an incidence of 121 cases of PSAGN in

a 1 year period of July 1987 to June 1988 (D'Cruz et al, 1990). No new epidemiological study was done after that.

Similar accounts of incidence of 'endemic type' of PSAGN has also been described in Iran (Derakhshan et al, 2008), Indonesia (Albar et al, 2005), Chile (Berrios X et al, 2003). In these studies which compared the incidence of PSAGN over 5 to 20 years period however showed a pattern of declining incidence of the disease in these countries.

Incidence of PSAGN in developed countries remained low now days (Carpentis et al 2005). There are certain instances of 'sporadic type' of PSAGN which occurred in outbreaks. It caused a surge of incidence of PSAGN in these countries, as reported in Australia (Blyth CC et al, 2007) and in Japan (Akio F et al, 2001).

The exact cause of declining incidence of PSAGN worldwide is still unknown. What is known is that GAS infection is most common in poverty settings. Improved sanitation, less overcrowding, advancement in access of medical care that includes early treatment of GAS infection with antibiotics, generally over the world in developing countries helps to reduce its incidence (Carpentis et al 2005).

1.2 History

The association of GAS infection with nephritis was first described scientifically by Wells CD in 1812. He observed the incidence of acute nephritis following a scarlet fever and development of edema with urine that contained red substances and a coagulable substance. He also described the latent period between the two problems and observed that the siblings of a child with nephritis were more likely to develop nephritis after a scarlet fever than the siblings of non-nephritis children (Wells CD. 1812).

Richard Bright in 1836 combined the observation of findings of coagulable substance in the urine with the clinical features of edema and autopsy evidence of kidney derangement (Bright R. 1836). The term 'Bright's Disease' was accepted as a medical term in describing acute and chronic glomerulonephritis later on. Only during the late 19th century and early 20th century did the description of post scarlet fever glomerulonephritis is much more refine and the term 'acute glomerulonephritis' becomes the accepted term (Rodriguez-Iturbe B et al. 2007).

Further studies and experimental work described *β hemolytic streptococci* was the pathogenic species in scarlet fever and later development of acute glomerulonephritis.

Therefore, the term 'post-streptococcal acute glomerulonephritis' was coined for the syndrome (Dick GF and Dick GH. 1924, Dochez AR et al. 1924). Later, a study by Longcope and his team in 1927 mentioned that there was no evidence to suggest that direct invasion of the organism in the kidney causes the acute glomerulonephritis (Longcope WT et al. 1927).

Other work by several research team from the 1938 to 1969 described the serological findings of anti-streptococcal antibodies (Lyttle JD et al. 1938), depression of complement (Kohler et al. 1969), and the concept of 'nephritogenic' strain of β hemolytic streptococci causing PSAGN (Futcher et al. 1940, Seegal D et al. 1941) in its pathophysiology. This firmly established the concept of PSAGN which was a non-suppurative, immunologicaly mediated complication of GAS infection.

Formation of immune complex resulting from PSAGN was observed and describes initially by Clements von Pirquet and Shick B in 1910 and 1912 respectively (von Pirquet C. 1911, Shick B. 1912). They initially associate the findings observed in PSAGN to the acute serum sickness due to its similar latent interval. All of these immune complex formations in the glomerulus trigger local changes that activate the complement cascade. However, only the alternative pathway is activated leading to the low C3 and normal C4 levels observed (Gewurz et al. 1969, Wyatt RJ et al. 1988). Subsequently cellular changes

and migration of lymphocyte to the glomerulus causes damage to the glomerulus and the glomerular basement membrane leading to reduced glomerular filtration rate (GFR), hematuria, and protenuria. Reduced GFR leads to water retention, leading to edema, hypertension and azotemia.

1.3 Pathogenesis and pathophysiology of PSAGN

Although the disease of PSAGN has been well described since 1800's, the exact pathogenesis is not completely understood. Generally, the pathogenesis of PSAGN involves two factors, the infective agent and the host susceptibility factors. What has been known about the infective agent is that only certain GAS strain causes PSAGN. This type of GAS is called 'nephritogenic strain' and is noted when rheumatic fever and PSAGN, both complication of GAS infection did not coexist in the same patient (Seegal D et al. 1941).

Subsequent works isolated the nephritogenic strain of GAS from PSAGN patients. These strains are Lancefield M type 1, 2, 4, 12, 18, and 25, which was recovered from the upper respiratory tract. The Lancefield M type 49, 55, 57, and 60 were associated with impetigo-associated nephritis (Cunningham MW, 2000).

Several proposed mechanism for the pathogenesis of PSAGN has been described. The two main theories are the circulating immune complex formation with streptococcal antigenic components and subsequent glomerular deposition along with complement activation and the elicitation of an autoimmune response between streptococcal components and renal components, also known as 'molecular mimicry'.

In the first theory, glomerular immune complex can result from deposition of circulating immune complexes (Dixon FJ. 1963) or formation of immune complex *in-situ* (Lange K et al. 1983). The deposition of immune complexes causes recruitment of inflammatory cells and activation of the complement system, inducing glomerulonephritis. In this occurrence, the classical complement pathway is inhibited by the production of C4b- binding protein. This cause only the alternative pathway to be activated, leading to the clinical picture of normal C4 level but low C3 levels observed (Perez- Cabarellero D et al. 2004).

The pathogenic mechanism of 'molecular mimicry' occurring after infection of GAS causing PSAGN has been described in several studies. These studies have shown common antigenic determinants in the soluble fraction of the nephritogenic strain GAS and the glomerulus components (Markowitz AS et al. 1964, Kraus W et al. 1990). Antibodies to basement membrane collagen, laminin, and glomerular heparin sulphate have also been reported in the sera of patients with PSAGN (Kefalides NA et al. 1986).

Association between certain HLA antigens with the incidence of PSAGN leads to the disease susceptibility among siblings and certain ethnic and geographical groups. Some of the HLA type reported to cause increased susceptibility of PSAGN are HLA-DRW4 (Layrisse Z et al. 1983) and HLA-DRB*03011 (Bakr A et al. 2007).

The combination of infection with nephritogenic strain of GAS plus host susceptibility factor leads to the development of PSAGN. With inflammation and complement activation, the GFR of the kidney will be reduced. This produces the clinical picture of acute gross hematuria, reduced urine output and elevated serum blood urea and creatinine levels. Eventually this later leads to sodium and water retention, leading to facial puffiness, edema and hypertension (Berhmann et al. 2010).

As mentioned earlier, development of hypertension observed in patients with PSAGN is due to water and sodium retention. Changes that occurred in the glomerulus secondary to either immune complex deposition or by 'molecular mimicry' due to cross reaction of the streptococcal antigens with the glomerulus structure causes reduction on glomerular filtration rate. This later leads to reduction of urine output, causing water to be retained. In addition, the reduced filtration rate causes sodium not to be excreted in the distal tubules, causing more retention of water.

It is known that the renin-aldosterone system is inhibited and hypertension observed in PSAGN is mainly due to sodium and water retention mentioned earlier. Persistently, the renin and aldosterone level remained low despite severe hypertension observed (Powell HR et al. 1974, Rodriguez-Iturbe et al. 1981).

It is also been proven that some patients with PSAGN had 'inappropriate' levels of angiotensin II (Parra G et al. 1998, Rodriguez-Iturbe et al.1981). Angiotensin II a potent vasoconstrictor is converted from angiotensin I by the angiotensin converting enzyme. The 'inappropriate' levels of angiotensin II could contribute to severe hypertension observed in patients with PSAGN.

But recent studies have also shown that direct effect of certain streptococcal protein, mainly the erythrogenic toxin type B (ETB) and its precursor (ETBP) produced by nephritogenic strain of GAS to the level of Angiotensin II, a potent vasoconstrictor. These proteins causes increased level of Angiotensin II which can contribute directly to the hypertension observed in PSAGN (Viera N et al, 2009).

1.4 Profile, clinical features and complications

Clinically, patients with PSAGN presents with typical history of edema commonly described by facial puffiness and hematuria, with a preceding history suggestive of GAS infection such as sore throat and impetigo. Hypertension is one of the major signs clinically encountered and one of its most serious complications. If untreated, the hypertension can lead to the development of hypertensive encephalopathy that can further complicated by status-epilepticus, hypoxia and even death.

Several studies worldwide have described the typical profile of 'endemic type' of PSAGN in their respective countries. These studies which was conducted in India (1973), USA (1988), Iraq (1997), and Armenia (1996) and Indonesia (2005) all consistently showed hypertension is one of the major complication. Although the highest complication reported in patients with PSAGN was edema (82.1 – 100%), hypertension was reported in 61.8 to 87 % of patients with PSAGN as compared to gross hematuria in 31.4 to 93% of patients and oligouria in 23.9 to 100% of patients (Albar et al, 2005).

Locally, the profile of PSAGN in Kelantan has been described as well. In this study, of the 220 children admitted for PSAGN, 81% of them had hypertension, 98% had edema, and 88% had gross hematuria. Out of this, 43.6 % had severe hypertension and 11.4 % had hypertensive encephalopathy. The complication directly associated with uncontrolled

hypertension in PSAGN patients is worrying according to the findings (D'Cruz et al. 1990).

1.5 Definition of hypertension in children and measurements of blood pressure (BP)

Hypertension is commonly observed in patients with PSAGN as mentioned earlier. It resulted in the one of the serious complications associated with PSAGN like hypertensive encephalopathy and seizures. According to the 'Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents' from the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (*Pediatrics,* 2004), hypertension is defined as the systolic and diastolic blood pressure (BP) above the 95th Percentile for the gender, age and height, on repeated measurements. The working group also published a table defining blood pressure (BP) according to the 50th, 90th, 95th and 99th percentiles by gender, age and height.

The measurement of BP in children requires use of a cuff that is appropriate to the size of the child's upper right arm. Different sizes of BP cuffs are needed to measure correctly BP in children. An appropriate BP cuff for children should have the inflatable bladder width that is at least 40% of the arm circumference at a point midway between the olecranon and the acromion. An optimal cuff for an arm should have the bladder length covering 80 – 100 % of the circumference of the arm. Such requirement demands that the bladder width-to-length ratio be at least 1:2. Since not all the commercially available BP cuffs are manufactured in this ratio, the working group recommends that standard cuff dimensions

should be adopted. BP measurements are over estimated if the cuff is too small and are under estimated if it is too large. If the cuff is too small, the next largest cuff should be used, even if it appears to be large.

Systolic blood pressure (SBP) is determined by the onset of the 'tapping' Korotkoff sounds (K1). The disappearance of the Korotkoff sound (K5) is taken as the diastolic blood pressure (DBP). Standard device for BP measurements is mercury manometer, and auscultation of the Korotkoff sound is recommended.

Currently oscillometric devices are used more frequently in the measurements of BP in children due to their relatively ease of use and to reduce the observer's bias. It measures the mean arterial BP and calculates the systolic and diastolic values electronically. The algorithms used by the manufacturer are proprietary and differs from company to company. It must be validated on a regular basis.

1.6 Treatment of hypertension secondary to PSAGN

In Malaysia, the current guideline by the Ministry of Health recommends the use of nifedipine as the first line treatment for asymptomatic significant hypertension in PSAGN patients (Muhammad Ismail HI et al. 2008). BP should be reduced within 4 hours of starting treatment to prevent complication especially hypertensive encephalopathy. Of not other antihypertensive such as captopril can be added. In severe cases or cases with hypertensive encephalopathy, intravenous antihypertensive can be used. Because water retention is also associated with the hypertension, frusemide is recommended as an additional medication to reduce the blood pressure especially if the patient is fluid overloaded. Captopril is reserved as an adjunctive if nifedipine alone cannot control the blood pressure.

Although other centers overseas did not have proper guidelines in treating hypertension secondary to PSAGN, the use of calcium channel blockers with addition of loop diuretics was advocated to treat the high BP. The use of captopril should be used with caution due to possible worsening of renal failure and hyperkalemia (Ahn SY et al. 2008).

Nifedipine, is a dihydropyridine calcium channel blocker which was first developed by Bayer, a German pharmaceutical company in 1970s. Calcium channel blockers blocks the voltage-gated calcium channel (VGCC) in the cellular wall. This leads to lack of calcium

intracellularly, which resulted in the relaxation of the vascular smooth muscle, causing vasodilation. In children, nifedipine and other calcium channel blockers (CCB) are both effective and well tolerated for treatment of hypertension in many clinical settings (Flynn et al. 2000). Concerns regarding safety of short acting nifedipine emerged in 1995 with reports of increased risk of developing myocardial infarction in adult population using it (Psaty BM et al. 1995).

Several other studies (Grossman E et al. 1996, Schwarts M et al. 1990, Leavitt AD et al. 1988) have shown its association with increased risk of cerebrovascular ischaemia, stroke, severe hypotension, syncope, conduction disorders and sudden death in adults. However, reports on its adverse effect in children are rare and it is concluded that short acting nifedipine is safe on most children with very few adverse effects despite it being associated with profound and unpredictable changes in blood pressure (Egger DW et al. 2002).

Angiotensin I converting enzyme inhibitors (ACE Inhibitors) has been used to treat hypertension in children for over 20 years. ACE inhibitors control the blood pressure by inhibiting the conversion of Angiotensin I to Angiotensin II, a potent vasoconstrictor. The conversion occurs in the lungs by mainly the activation of the 'Renin- Angiotensin-Aldosteron System' (RAAS) in response to a low sodium concentration at the proximal convoluted tubule in the kidney.

One of the earlier ACE inhibitors is captopril, developed originally in 1975 by Bristol-Myers Squibb by Miguel Ondetti, Bernard Rubin and David Cushman. The use of oral captopril has been described as effective in controlling childhood malignant hypertension since it is developed (Oberfield SE et al 1979). Its effectiveness again in controlling blood pressure in severe childhood hypertension has been described later (Freidman A. et al, 1980).

Since then a large multi-centre randomized study had been carried out to determine the safety of Angiotensin Conventing Enzyme drugs. In this randomized double blind study, it has been shown that enalapril, an Angiotensin Converting Enzyme drug, much similar to captopril had a good safety profile in children as young as 6 years old (Wells T et al. 2002).

1.7 Rationale of this study

ACE inhibitors, specifically captopril have seldom been used in the treatment of hypertension in PSAGN as a first line medication. This is because in PSAGN, despite the decreased GFR caused by the disease, renin levels have been shown persistently to be low (Powell HR et al. 1974, Rodriguez IB et al. 1981) as mentioned earlier. Therefore it was concluded that ACE inhibitors would not have any effect in controlling the hypertension since the 'renin-angiotensin-aldosterone' system is depressed.

However, the recent study (Viera N et al. 2009) showed 'inappropiate' level of angiotensin II level which was caused by ETB and ETBP produced by the nephritogenic strain GAS, independent of the 'renin-angiotensin-aldosterone' system also can contribute to the severe hypertension caused by PSAGN. With this, it can be postulated that inhibition of angiotensin II can help in controlling the blood pressure in patients with PSAGN with hypertension.

Several earlier studies have supported this and have also proven the beneficial effect of captoril in controlling hypertension in PSAGN patients (Parra G et al 1988, Morsi MR et al. 1992). Besides lowering the 'inappropriate' level of angiotensin II, captoril causes increased kinin reactivity from the blocking effect exerted on the inactivation of the kinins. In addition, it also increases PGE synthesis by stimulation of the phospholipase-induced

release of arachidonic acid from storage pools (Morsi MR et al.1992, Parra G et al. 1988). From these earlier studies, ACE inhibitors appear to be promising as a first line treatment controlling hypertension in PSAGN patients.

Currently there were no randomized control trials in proving captopril is at par or even better in controlling hypertension in patients with PSAGN. This study was designed to evaluate nifedipine and captopril for the treatment of hypertension in children with PSAGN. In addition, Kelantan is the best place to do this study since the disease is still prevalent in this part of Malaysia, based on a study in 1990.

2. OBJECTIVES

2.1 General Objectives

To compare the effectiveness of captopril versus nifedipine in controlling blood pressure in children with PSAGN with hypertension

2.2 Specific Objectives

1. To compare the changes in blood pressure over time in patients with PSAGN with hypertension in each treatment group.
2. To compare the duration needed for blood pressure control and the total duration of hospital stay in each treatment group.
3. To determine the need of additional anti-hypertensive (i.e: frusemide) in conjunction with the tested anti-hypertensive in controlling the blood pressure.
4. To assess the changes in the renal functions occurring in both of the tested group.

2.3 Null Hypothesis

There is no difference in blood pressure changes for children with hypertension caused by PSAGN receiving nifedipine or captopril.

3. METHODS

3.1 Study Design

This study was a randomized controlled trial, approved by The Research Ethical Committee of School of Medical Sciences (PPSP), Universiti Sains Malaysia on 23 November 2010. (Ref: USMKK/PPP/JEPeM [230.3(02)]. It was registered with Australian and New Zealand Clinical Trials Registry (ANZCTR), with registration number ACTRN12611000778987.

3.2 Setting

The study was done in Wad 6 Selatan, Hospital Universiti Sains Malaysia. The study was carried out from March 2011 until March 2012

3.3 Subjects

The study population was recruited from patients admitted to Ward 6 Selatan, Hospital USM with clinical sign and symptoms of PSAGN.

3.4 Inclusion criteria

All patients with clinical signs and symptoms PSAGN with hypertension (Blood Pressure of > 95 percentile of their respective height, age and gender) with the age between 1 year old to 12 years old, weight of 10 kg to 50 kg were eligible for the study.

Clinical sign and symptoms of PSAGN includes history and clinical findings of facial puffiness and hematuria (urine RBC detected), decreased urine output or symptomatic hypertension. It should be preceded with history of impetigo or pharyngitis. This is supported by investigations such as complement levels, throat swab, urine FEME, a positive ASOT or anti-DNAase.

3.5 Exclusion Criteria

1. Patients with non post-streptococcal AGN e.g.: SLE with Lupus Nephritis, Nephrotic syndrome, etc.
2. Patients with PSAGN without hypertension (defined as BP > 95 percentile according to height, age and gender).
3. Encephalopathic patients defined as having seizures, severe headache and having fundoscopy changes that needs urgent antihypertensive or intravenous antihypertensive.

4. Second episode of PSAGN with hypertension.
5. Other causes of elevated BP e.g. essential hypertension, pheochromocytoma
6. Patients with known renal problems.

3.6 Interventions

A written consent was taken for all eligible subjects that fulfill the inclusion criteria before they were enrolled in this study. The consent was mainly given by parents or respective caretakers who were above 18 years old. After written consent is taken, the subjects were randomized into two groups. These two groups are either was receiving captopril or nifedipine as their anti-hypertensive medication.

The nifedipine that was used in this study were generic medication, since the original manufacturer of nifedipine, Bayer® no longer produce short acting nifedipine (Adalat®). The drug was bought from an Indian generic drug manufacturer Sai Mirra Innopharm Pvt. Ltd. from India. We chose to use the 10 milligram (mg) tablet form.

The nifedipine, a 3, 5-dimethyl 2, 6-dimethyl-4-(2-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate compound, is rapidly absorbed after oral administration. It is detectable in the serum after 10 – 15 minutes and the peak blood levels occur in approximately 30 minutes. Its half life is approximately 2 hours. It is metabolized mainly in the liver.

As for captopril, a generic medication manufactured by STADApharm GmbH of Germany was used in this study. The reason to use this brand of captopril is that it is one of the few pharmaceutical companies that still produce captopril tablets in 12.5 mg dosing.

The captopril (Captopril STADA® 12.5MG), is a (*2S*)-1-[(*2S*)-2-methyl-3-sulfanylpropanoyl] pyrrolidine-2-carboxylic acid compound. Following oral administration of captopril, rapid absorption occurs and detectable within 15 minutes with peak blood levels at about one hour. After oral administration, the apparent elimination half-life for total radioactivity in blood is about 12 hours for the 12 to 48 hours time interval. It is primarily eliminated in the urine.

The two medications were then repacked by the pharmacist and dispensers at Sattelite Pharmacy, HUSM into half tablets. The half tablets contain nifedipine 5 mg and captopril 6.25 mg each. Each of this was then wrapped in a small aluminum foil as a blinding strategy, to prevent bias by the doctors and nurses. The aluminum foil was only opened right before the medication is being taken by the subjects. We also assumed that the subjects also were unaware of the type of medication given, since they have not taken anti-hypertensive medications before. As for this, only the respective pharmacist of the respective dispensers knew what type of medication was served.