

Comparative efficacy of calcium channel blocker and ACE inhibitor in the treatment of acute hypertension in acute post *streptococcal* glomerulonephritis

Abstract

Background: Acute Post *Streptococcal* Glomerulonephritis (APSGN) refers to the immunologic mechanism which triggers inflammation and proliferation of glomerular tissue, characterized by a relatively abrupt onset of variable degrees of gross haematuria, edema, hypertension and renal insufficiency. Patient may develop encephalopathy and/or heart failure due to hypertension or hypervolemia as a complication.

Objectives: The objective of the study was to find out the better drug for hypertension and/or its complications in terms of effectiveness, side effects and compliance.

Methods: This randomized clinical trial was conducted among 60 children aged 3-12 years, who were suffering from Acute *Streptococcal* Glomerulonephritis (APSGN) with hypertension and/or its complications. After enrolment, the patients were randomly divided into two groups as group A and group B. Both groups received the standard management of APSGN. In addition, children in group A received captopril (dose 0.5 up to 6mg/kg/day) and children in group-B received Nifedipine (0.25 up to 0.5 mg/kg/day). Their effectiveness in relation to timing of response, duration of therapy, duration of hospital stay, side effects and cost effectiveness of the drugs was assessed and compared statistically, and at p value of <0.05 the result was considered significant.

Results: Most patients had high systolic and high diastolic blood pressure. In captopril group mean systolic and mean diastolic blood pressure were 134.8±9.3 mm of Hg and 94.97±6.3 mm of Hg respectively. In Nifedipine group mean systolic and mean diastolic blood pressure 131.96±8.1 mm of Hg and 92.8±9.1mm of Hg respectively. The mean time needed to normalize both systolic and diastolic blood pressure (<95th percentile) in group A (Captopril) was 4.98±2.07 days and that of group B (Nifedipine) was 3.09±1.83 days. The difference between two group was statistically significant (p<0.05). Duration of antihypertensive therapy was longer in captopril group than in the Nifedipine group (<0.05). There were no significant side effects.

Conclusion: It is obvious from the study that Nifedipine controlled BP earlier and reduced the duration of hospital stay compared to captopril. For the control of hypertension in APSGN patients, Nifedipine is a better drug.

Recommendation: Nifedipine should be used in controlling hypertension in acute post *streptococcal* glomerulonephritis.

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Abbreviations: APSGN, acute post *streptococcal* glomerulonephritis; ANS, acute nephritic syndrome; RBC, red blood cells; BP, blood pressure

Introduction

Acute glomerulonephritis is one of the common glomerular diseases in children. Acute glomerulonephritis is characterized by a relatively abrupt onset of variable degrees of haematuria, edema, hypertension, oliguria along with diminished glomerular filtration rate, salt and fluid retention and circulatory congestion. Acute glomerulonephritis may follow infection with a variety of microorganisms, called acute post infectious glomerulonephritis occurring after B-hemolytic *streptococcal* infection, which is the commonest type in children, accounting for approximately 80% cases.¹ Acute Post *Streptococcal* Glomerulonephritis (APSGN)

follows infection by certain “nephritogenic” strains of hemolytic streptococcus infection of the throat (serotype 12) during cold-weather months or skin (serotype 49) during warm-weather months. This disease is most commonly sporadic.² The disease is prominent in boys aged 5-15 years. This disease is rare before the age of three.³ The predominance of incidence during pre-school and early school years probability can be attributed to the fact that at this age children are likely to have their first exposure to hemolytic *streptococcus*. It is more prevalent among the population particularly where poverty, overcrowding, poor hygiene living are prevailing and more in urban children.⁴ The typical patient develops an acute nephritic syndrome 1-2 wk after an antecedent *streptococcal* pharyngitis or 3-6 wk after a *streptococcal* pyoderma. The clinical features depend on severity of disease; asymptomatic disease is 4 to 10 times more frequent than clinical acute nephritic syndrome (ANS)⁵ ASO titer begin to increase 1-3 wks after infection, reach its maximum 3-5 wks and return to

normal level following two months.^{3,6} Serum complement level (C3) is depressed and return to normal by 6-8 weeks.^{6,8} Three to six months later the majority of patients no longer have proteinuria, but often urine still contains red blood cells (RBC) and casts (up to 2 years or more).^{7,9} Persistence of proteinuria is a marker of underlying chronic glomerular disease.⁹

Haematuria is defined as the presence of at least 5 RBC per microliter of urine. Significant haematuria is suggested by >50 RBC/microliter of urine. In case of APSGN microscopic haematuria can persist for 1-2 yr after the initial presentation.¹⁰ Gross haematuria is present in 30 to 70% of children with APSGN. Urine is typically reddish brown smoky or cola-colored, gross haematuria may only last for few hours and does not persist beyond 1 to 2 weeks.¹¹ Edema is noted in 90% children with APSGN, if the fluid intake has been unrestricted, edema may extend to involve the hands and legs; edema is turgid and not flaccid as in nephrotic syndrome.¹² Hypertension in children is defined as average Systolic Blood Pressure (BP) and or Diastolic BP values >95th percentile for the corresponding age, sex and height on >3 occasions. Pre-hypertension is average systolic or diastolic BP 90th-95th percentile. Stage I hypertension is systolic or diastolic BP between 95th percentile and 99th percentile plus 5 mmHg. Stage II hypertension is systolic or diastolic BP >99th percentile plus 5 mmHg.¹³ Hypertensive emergency is defined as BP >30% of normal for age and sex or any elevation with evidence of encephalopathy, heart failure or pulmonary edema.¹⁴ Hypertensive urgencies are situations where the immediate risk of complications demand prompt institution of drug therapy, and reduction of blood pressure over 24 hour is appropriate. This is true for patients with AGN.¹⁵ Hypertensive encephalopathy during the course of APSGN may be secondary to hypertension. Hypertensive encephalopathy must be considered in patients with blurred vision, severe headaches, altered mental status or new onset of seizures. Hypertension, noted in 60-80% of patients hospitalized with APSGN, is the third important finding. Hypertension resolve following diuresis and loss of edema, persistence of elevated blood pressure beyond 4 weeks of illness suggests chronic glomerulonephritis or rapidly progressive course.¹² Acute renal failure is present in less than one percent (1%) of children but renal function is impaired in the majority of cases.¹⁶ Oliguria and azotemia are the main features and gross haematuria and edema may be absent.¹⁷ APSGN may be treated in outpatient setting. Hospitalization is indicated if the child has significant hypertension or a combination of oliguria, generalized edema and elevation of serum Creatinine or potassium.¹⁸ Severe hypertension or that associated with signs of cerebral dysfunction, demands immediate attention. The goal of treatment is the reduction of blood pressure to a level below the 95th percentile.^{19,20} There may be severe or mild to moderate hypertension in APSGN. Whatever is the type, reducing of BP by not more than one-third of the total planned reduction in the first 6-12 hours followed by another one-third over the next 24 hours, and a final third over the next 2-4 days is recommended.^{21,22} Mild to moderate hypertension does not warrant emergency management. Mild to moderate hypertension is treated most effectively with bed rest, fluid restriction, and less-frequent doses of the preceding medications. Loop diuretics may be required in patients who are edematous and hypertensive in order to remove excess of fluid and to correct hypertension. For patients resistant to treatment, Nifedipine is indicated.¹⁸ Captopril is effective, although it has the potential to cause hyperkalemia and usually is not first line drug in APSGN by many authorities.²³ Hypertensive encephalopathy requires antihypertensive therapy as well as anticonvulsants in case of convulsions. Common anticonvulsants used are IV or PR diazepam, IV or oral phenobarbitone, phenytoin etc.

Nifedipine commonly is given to children only in hypertensive crises.²¹ Thus Nifedipine reduces blood pressure by dilating peripheral arterioles in a dose-dependent fashion.^{21,24,25} They cause modest increase in heart rate and cardiac output shortly after starting of treatment.²⁶ In addition, glomerular filtration rate and renal plasma flow increase, and renal vascular resistance decreases with therapy.²⁶ The standard dose of Nifedipine is 0.25mg/kg/day to 0.5mg/kg/day.²⁷ The initial response to this dose occurs within 20 minutes, with duration of 4-8 hours. Peak concentration is reached within 20-45 minutes. Approximately 90% of the oral dose of Nifedipine is rapidly absorbed from the GI tract following oral administration.²⁸ The most common side effects are due to excessive vasodilatation. These effects may be expressed as dizziness, hypotension, headache, flushing, digital dysaesthesia and nausea. Patients may also experience constipation, peripheral edema, cough, wheezing and pulmonary edema,²⁸ the main concern with Nifedipine is that there is sometimes a large and unpredictable fall in BP, which may lead to decreased organ perfusion.^{29,30} Other postulated toxic effects of Nifedipine include pro-arrhythmic and pro-hemorrhagic effects,^{31,32} none of which have been proven.

Captopril is the most widely studied ACE inhibitor in children.^{21,33,34} It is usually given to treat chronic pediatric hypertension due to its ease of administration and relative lack of severe adverse effects.^{21,33,34} The hypotensive activity of captopril and other ACE inhibitors results from both an inhibitory action on the rennin-angiotensin system and a stimulatory action on the kallikrein-kinin system.²³ Thus it reduces both systemic vascular resistance and left ventricular pressure, and causes negative inotropic and chronotropic effects.²¹ They do not have a dose-response effect. Blood pressure tends to fall gradually until the converting enzyme is inhibited by 90%, as inhibitor increases, a precipitous drop in blood pressure may occur.^{34,35,36} Initial dose of captopril is 0.3 to 0.5 mg/kg/day, titrated up to 6mg/kg/day in 2-3 divided doses.²⁷ Blood pressure reduction occurs 1-1.5 hours after dose. Duration of action is dose related. Absorption is 60% to 75%; reduced 30% to 40% by food.²⁸ In general, ACE inhibitors are well tolerated. Serious untoward reactions are rare. Hypotension in first dose, cough, hyperkalemia, skin rash, angioedema may be found as side effects.

Patients and methods

The aim of this clinical trial was to see the comparative efficacy of Ca-channel blocker and ACE inhibitor in the treatment of hypertension in APSGN and was carried out in the Department of Pediatric Nephrology, Comilla Medical College, Bangladesh, since January 2015 till June 2015. Study population constituted of children admitted to pediatric nephrology ward with acute glomerulonephritis with some inclusion and exclusion criteria, and cases were enrolled by simple random sampling.

Inclusion criteria

- i. Children aged between 3-12 years.
- ii. APSGN with hypertensive heart failure.
- iii. APSGN with hypertensive encephalopathy.
- iv. Hospitalization duration and treatment at least 7 days and willing to participate in the study.

Exclusion criteria: (1) Children with other cause of hypertension. (2) Not willing to participate.

Evaluation

Children aged 3-12 years suffering from gross haematuria, edema, and symptoms of hypertension or features of complications like dyspnea, convulsions, and unconsciousness with or without history of sore throat or pyoderma were enrolled in the study. Then BP was recorded by the standard method and evidence of streptococcal infection was confirmed by raised ASO titre. Standard treatment of APSGN such as bed rest, fluid and protein restriction, antibiotics for streptococcus infection were given. They were randomly divided into two groups using a randomization table. Group A children received captopril and group B children received nifedipine irrespective of age and sex. The recommended initial dose of captopril was .3 to .5 mg/kg, upto 6mg/kg/day in 2-3 divided doses. On the other hand the standard initial dose of nifedipine was .25mg/kg/day up to .5mg/kg/day. Blood pressure as well as other symptoms and signs were recorded every 2 hours on the first day and every 6 hours for next 6 days. Any new complications were monitored. The dose, the duration and frequency of antihypertensive drugs were recorded. Antihypertensive drug was discontinued after BP reached the level below the prehypertension or borderline hypertension which was again defined as systolic or diastolic BP between 90-95th percentile. If hypertension was not controlled by one of the mentioned two antihypertensive's, the other one was decided to choose. Any adverse effects of the antihypertensive medications were recorded. The time needed for BP to become below 95th percentile, the duration of antihypertensive therapy, duration of hospital stay, patients outcomes in each group were recorded. The treatment cost for each group was calculated. Collected data were sorted and screened for any discrepancy and were edited if required. *Unpair t* test was performed to evaluate the differences significance.

Results

A total of 60 patients were enrolled in this study. None of them was withdrawn from the study as there was no clinical deterioration or new complications arose. Standard treatment of APSGN was given. ACE inhibitor and Ca-channel blocker were given alternatively according to randomization results, irrespective of age, and sex clinical condition. Blood pressure was recorded every 2 hours on the first day and every 6 hours for next 6 days. Most patients were between 4-7 years 37 (61.6%), then 8-10 years 13 (21.6%). In the <4 years and >10 years groups there were 4(6.6%) and 6 (10%) respectively. Among the sixty patients in two groups, 40(66.6%) were boys and 20(33.3%) were girls. The ratio between boys and girls was 2:1. Among them, 21(70.0%) patients were boys and 9(30%) patients were girls in group A (Captopril), whereas 19(63.3%) were boys and 11(36.6%) were girls in group B (Nifedipine).

Oliguria, puffiness of face, dark color of urine and haematuria were found in all (100%) the patients. Proteinuria was found in 90% of patients. Evidence of pyoderma and H/O sore throat were found in 60% and 40% of the patients respectively. ASO titer was raised in 100% patients. Mean systolic BP in the Group A and Group B was 134.8±9.3 mm of Hg and 131.9±8.1 mm of Hg respectively and there was no significant difference between them (p>0.05). Mean diastolic BP in the Group A and Group B was 94.9± 6.3 mm of Hg and 92.8±9.1 mm of Hg respectively and there was no significant difference between them (p >0.05). Time required for systolic BP to become <95th percentile in Group A and Group B was 4.9±2.0 days and 3.0±1.8 days and there was significant difference between them (p <0.05). Time required for diastolic BP to become < 95th percentile in Group A and Group B was 4.9±2.0 days and 3.0±1.8 days and

there was significant difference between them (p <0.05). Duration of antihypertensive therapy in Group A and Group B was 8.5±2.6 days and 5.5±1.4 days and there was significant difference between them (p <0.05). There were no significant side effects of antihypertensive drugs neither in the Group A nor in the Group B. Two drugs were significantly (p>.05) effective in reducing blood pressure in APSGN.

Discussion

Acute post streptococcal glomerulonephritis is a common medical condition in Bangladesh. There is significant number of APSGN patients among the hospitalized children in our country. Hypertension is observed in more than 80% of patients and in about 80-97% of hospitalized children with APSGN. Fortunately, none of the sixty children was withdrawn from this study as there were no clinical deterioration or new complications arose. APSGN is common in children aged 5-12 years and uncommon in those less than 3 years. The male to female ratio is 2:1. The majority of patients in this study were in the older age group which was similar to other study conducted by Islam and Wadud.³⁷ The number of boys was over two times higher than the number of girls which also correlated with the study conducted by Rashid et al.³⁸ The most common presenting symptoms of AGN are edema, proteinuria and hypertension. The complete clinical picture of acute nephritic syndrome, edema, hypertension and oliguria are present only in 40% cases and about 96% have at least two of these symptoms. All (100%) children in this study were hypertensive as hypertension was one of the inclusion criteria. Gross haematuria and edema were observed in near all cases which was similar to many studies.^{37,38} The predominant trend in pediatric antihypertensive management is towards increasing reliance on angiotensin converting enzyme inhibitors and calcium channel blockers because of their general effectiveness, low incidence of adverse reactions and potential specific benefit in patients with renal disease.

There was an obvious difference between the effects of two investigated antihypertensives. Nifedipine reduced both systolic BP and diastolic BP much earlier than captopril (p <0.05). The time required for BP to become below 95th percentile in this study was much higher in Captopril group than in Nifedipine group. There was also a significant difference regarding the duration of antihypertensive therapy (p<0.05). Captopril had to be given for almost double time than that of Nifedipine (p<0.005). All these are supported by study conducted by Zapata et al.³⁹ There were no significant side effects of the antihypertensive given in both groups observed after therapy. One patient complained of cough, two developed hyperkalemia on investigation in captopril group. On the other hand, in Nifedipine group only one had constipation and another complained of dizziness (Tables 1-10).

Table 1 Age distribution in the group A and group B

Age (Years)	Captopril Group-A		Nifedipine Group-B		Total N=60	
	N=30		N=30			
	n	%	n	%	n	%
<4	2	6.6	2	6.6	4	6.6
7-Apr	18	60	19	63.3	37	61.6
10-Aug	6	20	7	23.3	13	21.6
>10	4	13.3	2	6.6	6	10

Table 2 Sex distribution in the group A and group B

Sex	Captopril Group-A N=30			Nifedipine Group-B N=30			Total N=60		
	n	%	M:F	n	%	M:F	n	%	M:F
Boys	21	70	2.3:1	19	63.3	1.7:1	40	66.6	2.:1
Girls	9	30		11	36.6		20	33.3	

Table 3 Distribution of symptoms and signs in the study population and groups A and B

Symptoms	Captopril Group-A n=30	% Total of	Nifedipine Group-B n=30	% of Total	Total N=60	Percentage of Total
Oliguria	30	100	30	100	60	100
Anuria	2	6.6	1	3.3	3	5
Dark Color of Urine	30	100	30	100	60	100
Puffy Face	30	100	30	100	60	100
Swelling of Legs	27	90	29	96.6	56	93.3
Resp Distress	14	46.6	9	30	23	38.3
Palpitations	2	6.6	4	13.3	6	10
Convulsions	0	0	1	3.3	1	1.66
Headache	15	50	12	40	27	45
Visual Disturbance	1	3.3	0	0	1	1.6
Vomiting	3	10	2	6.6	5	8.3
Evidence of Pyoderma	20	66.6	16	53.3	36	60
H/O Sore Throat	10	33.3	14	46.6	24	40
Hematuria	30	100	30	100	60	100
Protienuria	28	93.3	26	86.6	54	90
Raised ASO	30	100	30	100	60	100
Titer						

Table 4 Systolic BP at admission in two groups

Study group	N	Mean (mm of Hg)	SD(±)	p-value
Captopril (Group A)	30	134.8	9.3	>0.05
Nifedipine (Group B)	30	131.9	8.1	

Table 5 Diastolic BP at admission in two groups

Study group	N	Mean(mm of Hg)	SD(±)	p-value
Captopril (Group A)	30	94.9	6.3	>0.05
Nifedipine (Group B)	30	92.8	9.1	

Table 6 Time required for systolic BP to become < 95th percentile (days) in two groups

Study group	N	Mean(days)	SD(±)	p-value
Captopril (Group A)	30	4.9	2	<0.05
Nifedipine (Group B)	30	3	1.8	

Table 7 Time required for diastolic BP to become < 95th percentile (days) in two groups

Study group	N	Mean(days)	SD(±)	p-value
Captopril (Group A)	30	4.9	2	<0.05
Nifedipine (Group B)	30	3	1.8	

Table 8 Duration of antihypertensive therapy in two groups

Study group	N	Mean(days)	SD(±)	p-value
Captopril (Group A)	30	8.5	2.6	<0.05
Nifedipine (Group B)	30	5.5	1.4	

Table 9 Side effects of antihypertensive drugs

	Study Group				Total
	A	%	B	%	
No side effect of antihypertensive	27	90	28	93	55
Constipation	0	0	1	3.3	1
Cough	1	3.3	0	0	1
Dizziness	0	0	1	3.3	1
Hyperkalemia	2	6.6	0	0	2
Total	30		30		60

Table 10 Patient's outcomes

Patient's outcomes	Study group	
	Group A	Group B
Improved	29	28
DORB	1	2
P value	<.05	<.05

Conclusion

It is obvious from the study that Nifedipine controlled BP earlier, much less costly and reduced the duration of hospital stay than captopril. For the control of hypertension in AGN patients, Nifedipine is a better drug.

Recommendation

Nifedipine should be used for controlling hypertension in acute post streptococcal glomerulonephritis.

Limitation of the study

This was a randomized clinical trial. It would be even better if it could be a blind study. So that bias could be avoided. There would have been a placebo group for making the study more reliable. Although the sample size was a good one, a larger sample size could bring more even better results.

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None.

Conflicts of interest

The author declares there is no conflict of interest.

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