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A comparative study between Nifedipine and Captopril for controling hypertension in children with acute glomerulonephritis (AGN).

Dr. Md. Abu Sayeed[1], Dr. Md. Rafiqul Islam[2], Dr. Dilruba Ibrahim Dipti[3]
[1]*Assistant Professor, Department of Paediatric Cardiology, Dhaka Shishu Hospital. Bangladesh*
[2]*Assistant professor, Department of Paediatric Endocrinology and metabolic Disorder, Dhaka Shishu Hospital. Bangladesh.*
[3]*Registrar, Department of Paediatric Cardiology, Dhaka Shishu Hospital. Bangladesh.*
Corresponding Contributor: Dr. Md. Abu Sayeed,

Abstract
Background and Aim: *The aim of this study was done to see the efficacy of captopril and nifedipine to control hypertension in AGN in respect to their clinical response, duration and cost of treatment.* ***Methods:*** *This randomized clinical trial was done among 60 children ages ranging from 3-12 years who were suffering from AGN with hypertension and/or its complications in the department of Paediatrics, Dhaka Shishu(children) hospital, Dhaka, Bangladesh during from January 2018 to December 2018. After enrolment the patients were randomly divided into two groups as Group A and Group B. Both groups received the standard management of AGN. In addition children in group-A received captopril (dose 0.5 up to 6 mg/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, side effects and cost effectiveness of the drugs were assessed statistically and at p value of <0.05 the result was considered significant.* ***Results:*** *Mean systolic and diastolic blood pressure (BP) in group A were 134.8±9.31 and 94.97±6.33 mm Hg respectively and those in group B were 131.96±8.16 and 92.80±9.11 mm Hg respectively. After intervention both the drugs were found effective to normalize BP (BP <90th centile). The mean time/ duration taken to normalize BP by captopril was 4.86 ± 1.73 days and that by nifedipine was 2.17 ±1.73 days , duration of treatment was 6.75 ± 2.04 days and 3.67 ± 1.24 days and cost of captopril treatment was 11.95 ± 8.65 taka and 1.77 ± 1.15 taka respectively and all relationship were highly significant (p<0.001)..*
Conclusion and Recommendation: *Nifedipine is more effective to control BP in relation to its earlier clinical response, duration and cost of treatment than Captopril in children with AGN. Further large scale multi center study may be designed.*

Keywords: *Acute Glomerulonephritis, Blood Pressure, captopril, nifedepine*

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I. Introduction

Transient hypertension is observed in more than 80% patients with AGN and many of them are at risk of death because of hypertensive encephalopathy and/or heart failure[1]. The prognosis of AGN virtually depends on early and good control of hypertension[2]. Reports on randomized clinical trials among the children with anti hypertensive drugs are limited[1]. However, the recommended anti-hypertensive agents are ACE inhibitor (captopril), Ca channel blocker (nifedipine) and diuretics because they are generally effective and have minimum side effects. Some studies had shown the superiority of nifedipine in reducing BP in severe hypertension in children. Similarly captopril was also proved as effective in many studies. In clinical practice, sometimes there is dilemma about choosing the right anti-hypertensive agent. Therefore, the present study was designed to see the efficacy of these two (2) drugs to control hypertension in children with AGN.

II. Methods & Materials

It was a randomized clinical trial done in the department of Paediatrics, Dhaka Shishu(children) hospital, Dhaka, Bangladesh during from January 2018 to December 2018. A total of 60 children, age ranging from 4-12 years who suffered from AGN with hypertension (BP above 95th centile) and/or with heart failure or encephalopathy were enrolled in the study. Patients whose BP was ≤ 95th centile or who had acute renal failure were excluded from the study. After enrollment, the cases were fully assessed both clinically and with laboratory support. Blood pressure (BP) of the cases were measured following the standard procedure e.g. with appropriate sized cuff, in lying posture and in calm and quite status of the patients. Along with other treatment

and supports, anti-hypertensive drugs were selected randomly using a randomization table. Children received captopril was categorized as Group A (n=30) and those received nifedipine as Group B (n=30). The dose of captopril was ranging from 0.5 to 6 mg/kg/day in 2-3 divided doses as required3 and that of nifedipine was (0.25 to 0.5 mg/kg/day)3. Blood pressure as well as other symptoms and signs including any complications were recorded every 2 hourly on the first day and every 6 hourly from the 2nd day onward till the patients remain in the hospital. Investigations like Urine for R/M/E, Blood CBC, Hb%, Serum creatinine, electrolytes, x-ray chest, ASO titre, C3 level etc. were done and the results were recorded. The dose, efficacy, duration of therapy and adverse effects of the antihypertensive drugs, if any, in each group were noted. Antihypertensive drugs were discontinued when BP become normal (systolic and diastolic BP below 90th centile for age and sex). If hypertension remained above 95th centile after 48 hours of any antihypertensive drug then the other one was decided to give. The time needed to bring BP below 90th percentile, the duration of antihypertensive therapy (i.e. the time for BP become <90th percentile), duration of hospital stay and outcome of patients in each group were recorded. The costing of each group was calculated. At the end of data collection, it was checked carefully. A master sheet was prepared first for the purpose of tabulation. Simple statistical analytical methods were used where necessary to process and present in data in table form. The patients were divided into the following age groups: <4 years, 4-7 years 11 months, 8-10 years and >10 years. Data were presented in the form of table and graphs. Descriptive statistics was presented with frequency table. Association was illustrated with cross tables and test statistics was added in the foot note of the table. Bar and pie charts were generated to illustrate descriptive statistics.

Case definition of AGN:
Children aged 3-12 years suffering from gross hematuria, edema, hypertension and/or renal insufficiency[4,5] with or without history of sore throat or pyoderma were defined as AGN in this study**.**

Case definition of hypertension:
Hypertension was defined as an average systolic and/or average diastolic BP greater than or equal to the 95th percentile for age, sex and height, measured on admission[6,7,8].
Normal BP was defined as systolic and diastolic BP less than the 90th percentile for age, sex and height[9,10].
Prehypertension or borderline hypertension was again defined as average systolic or diastolic pressures between 90-95th percentile.

Data processing
Data Management

- Collected data was sorted and screened for any discrepancy. The edited data was entered on to the template of SPSS 11.

Data analysis

- For background variables and socio-demographic data descriptive statistics and relative frequency (percentage) was generated.
- Association between socioeconomic variables and related factors was assessed through chi square test. Level of significance was considered at $P < 0.05$.
- Multivariate analysis was done to determine individual risk factor adjusting for others Odds ratio and 95% CI was reported.

III. Results

The mean age of the children (n=60) was 6.43±2.33 years (age range 4-12 years).
Among them more (48.3%) were in the 4-7 years age group than the 8-10 years (30.0%). The ratio between boys and girls was 2.53:1.[Figure-1]

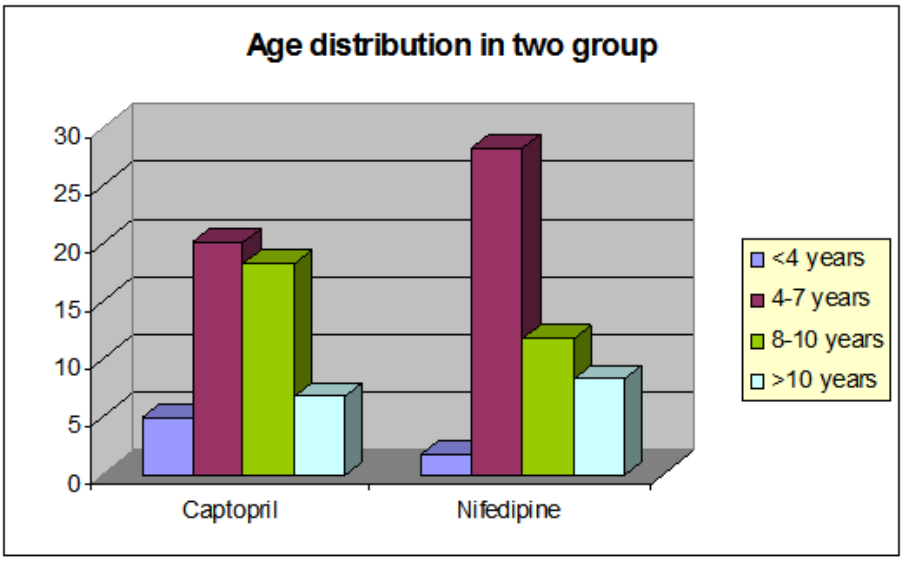

Figure 1: Age distribution in two groups (years)

The common clinical and laboratory presentations of the cases

Mild to moderate pallor was observed in 49 (81.7%) patients, but there was no severe pallor found. Edema was observed in 57 (95.0) patients, but ascites was present in only 17 (28.3) patients. Pulse rate was high in 19 (31.7%) patients and rhythm was irregular in 10 (16.7%) patients. Cardiomegaly and galloping were present in 19 (31.7%) and 11 (18.3%) patients respectively. Among the patients having cardiomegaly, 15 (78.9%) developed heart failure. On the other hand, all (100.0%) the patients with gallop rhythm had heart failure. There were tachypnea in 20 (33.3) patients, basal crepitations found in 15 (25.0%) and hepatomegaly in 34 (56.7%) patients. Hepatomegaly was tender in 13 (38.2%) and non-tender in 21(61.8%) patients. Proteinuria was observed in 52 (86.7%) patients. Mild to moderate proteinuria were in 44 (73.3%) and severe proteinuria in 8 (13.3) patients.

Serum creatinine was normal in only 2 (3.33%) patients. In 42 (70.0%) patients it was up to 1.3 mg/dL, but in 16 (26.67%) patients it was beyond 1.3 mg/dL. Mean serum creatinine was 1.05 mg/dL. Serum C_3 was done in all the patients. It was reduced in 54 (90.0%) cases and normal in 6 (10.0%) cases.

Among the sixty patients, 39 (65%) patients were having AGN without complications. But the rest 21 (35%) had various complications with AGN; 11 (18.33%) had heart failure, 6 (10.0%) had hypertensive encephalopathy and 4 (6.67%) had hypertensive encephalopathy and heart failure (Figure 2).

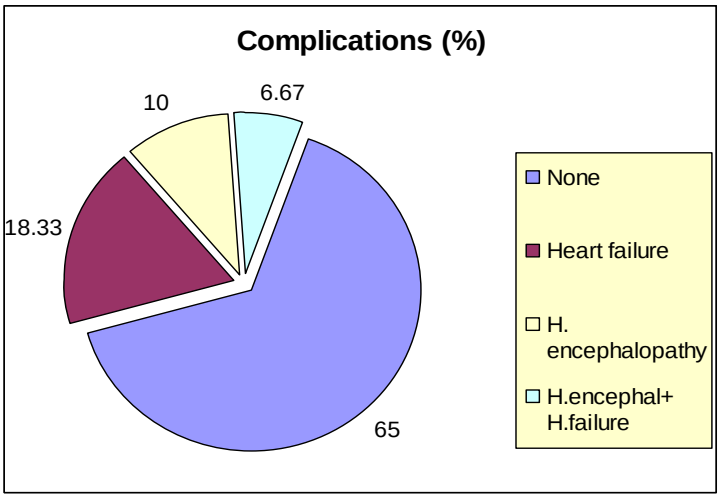

Figure 2: Different complications of AGN in the study (%)

The mean systolic and diastolic BP in group A on admission were 133.37±8.81 and 93.88±7.90 mm of Hg respectively and those in group B were 134.67±7.56 and 93.63±8.11 and there was no statistical difference ($p>0.05$).

Mean systolic BP in Captopril group became 128.2 mm of Hg on day 2 from 133.2 mm of Hg on day 1; whereas in Nifedipine group, it became 116.8 mm of Hg from 134.4 mm of Hg (Fig. 3). Similar difference was observed in diastolic BP; where mean DBP became 84.9 mm of Hg on day 2 from 93.9 mm of Hg on day 1 in Captopril group. In Nifedipine group, it became 76.4 mm of Hg from 95.1.

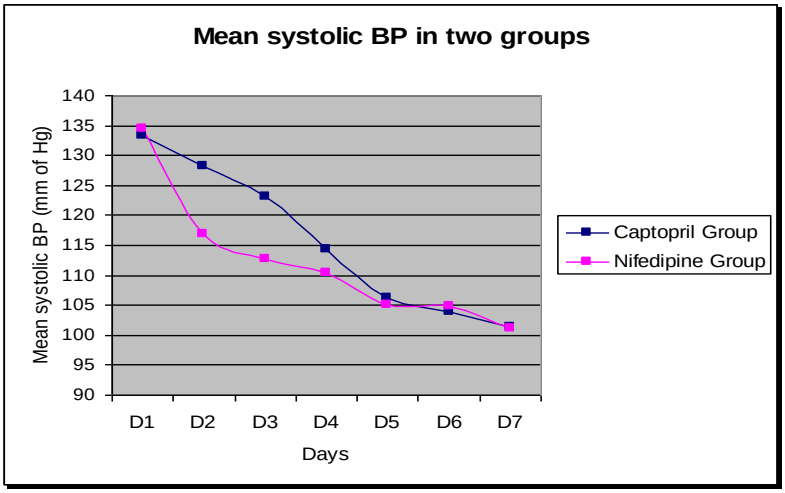

Figure 3(A): Response of Antihypertensive in reducing SBP

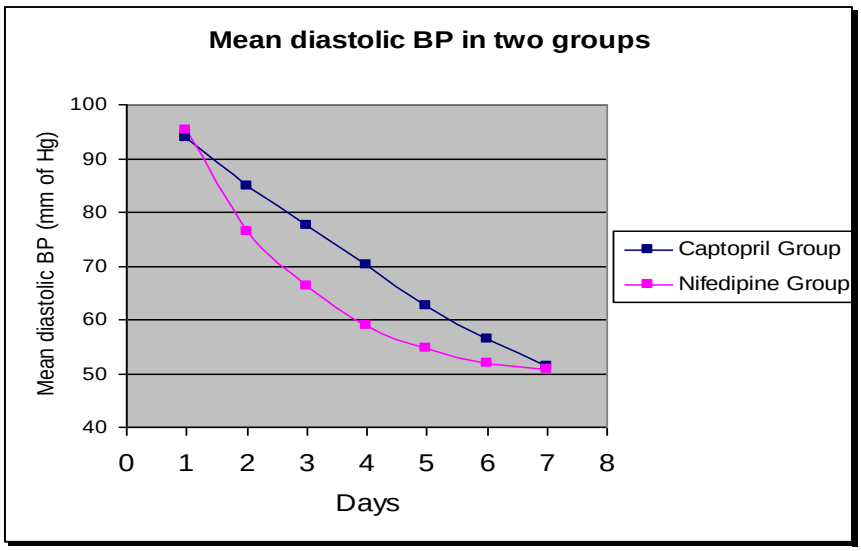

Figure 3(B): Response of Antihypertensive in reducing SBP

The days (mean ± SD) required to bring BP < 95th centile in the captopril group was 4.86 ± 1.73 days (range: 1.66 to 7.66 days) and that in nifedipine group was 2.17 (±1.73) days (range: 0.66 to 5.66 days). The difference between two groups was significant ($p<0.01$, CI was 1.92 to 3.46).

The mean duration of anti-hypertensive therapy required in the captopril group 6.75 ±2.04 days (range: 3-10.33 days) and that in nifedipine group was 3.67 ±1.24 days (range: 2.00 to 7.33 days). This difference was significant ($p<0.001$, CI 2.20 to 3.95).

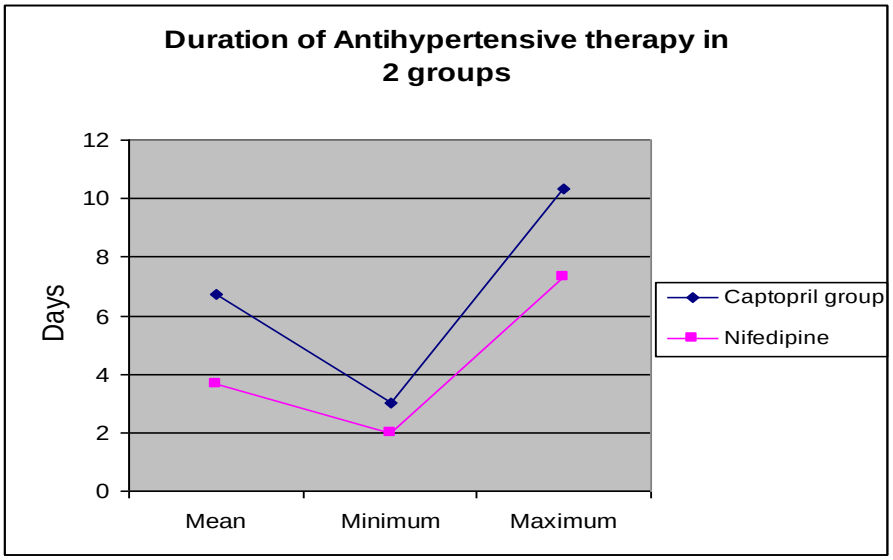

Figure 4: Duration of anti-hypertensive (days)

The mean cost of antihypertensive therapy was 11.95 ±8.65 taka in captopril group (range: 1.50 t0 33.50 taka) and 1.77 ±1.15 taka (range: 0.40 to 5.00 taka). The confidence interval (CI) was 6.99 to 13.37. The statistical difference between two groups was highly significant (p<0.001).

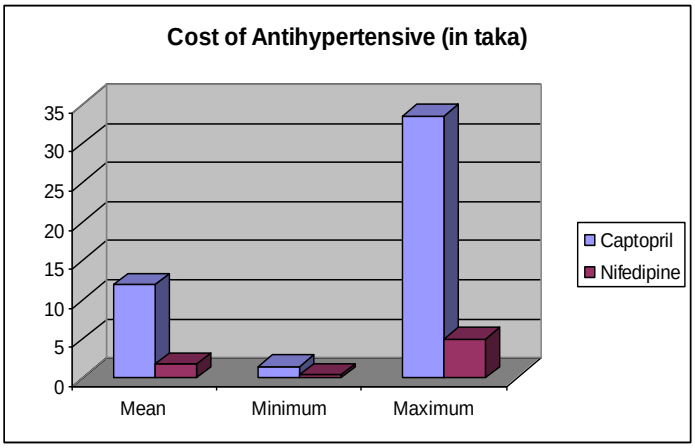

Figure 5: Cost of Antihypertensive (in taka)

There were no significant side effects of the antihypertensive given in both groups observed after therapy. Only one patient in Captopril group complained of cough, two in the same group developed hyperkalemia after treatment had started. One from Nifedipine group had constipation and 1 complained of dizziness. Table 10 shows the number of days the patients of two groups stayed in the hospital: mean 8.59 (±2.64) versus 5.53 (±1.49) days, minimum 3.00 versus 3.33 days and maximum 13.66 versus 9.0 days respectively in group A (Captopril) and group B (Nifedipine). The confidence interval (CI) was 1.95 to 4.17. The statistical difference between two groups was very significant (p<0.005).

IV. Discussion

AGN causes significant hospital load also in Bangladesh. On average, it is responsible for 2%-5% of Pediatric admission in Bangladesh[11,12]. A total of 60 (sixty) patients were enrolled in this study. None was withdrawn from the study as there was no clinical deterioration or new complications arose. Acute PSGN is common in children aged 5-12 years and uncommon in <3 years[3]. The male-to-female ratio range is 2:1[13]. The most patients in this study were between 4-10 years (78.3%) which was similar to many other studies. The ratio between boys and girls (2.53:1) was also correlated with most studies. Most patients had very high systolic (mean 133.93±8.26 mm of Hg) and diastolic (mean 93.57±8.11mm of Hg) blood pressure. These were said to be very high as these values were much higher than 95th percentile of any age.

Patient may develop encephalopathy and/or heart failure due to hypertension or hypervolumia as a complication in AGN. Regarding complications, 5.0 to 10.0% patients may suffer from encephalopathy and 8.0 to 20.0% from heart failure[14,15,16]. In this study, 11 (18.33%) had heart failure, 6 (10.0%) had hypertensive encephalopathy and 4 (6.67%) had hypertensive encephalopathy with heart failure. The rate of heart failure only matched with one study, but most other studies shown much lower rate of complications than this study. Complications were most marked in >10 years age group (66.67%), next is <4 years (50.0%), 8-10 years (33.33%) and 4-7 years (24.13%) respectively in descending order. There was an obvious difference between the effects of the two antihypertensive. Nifedipine reduced both SBP and DBP much earlier than Captopril, thus reducing the morbidity of the patient as well as duration and cost of therapy. There were no significant side effects of the antihypertensive given in both groups (10.0% in captopril and 6.0% in nifedipine group) observed after therapy. As in other studies, our patients tolerated nifedipine well despite a sometimes large and unpredictable fall in BP. The even lower incidence of adverse events observed in our patient group compared with other studies of children, may be related to the presumed rapid rise in BP in APSGN. Regarding the hospital stay between two groups, Captopril group had a longer hospital stay than that of nifedipine group ($p<0.005$). There was no significant difference between two groups statistically in outcome ($p>0.05$).

As we have already mentioned that we found very high rate of complications (35.0%) of AGN than many other studies which might be due to the fact that all our cases were hypertensive (i.e. BP>95th percentile). Another important reason for high rate of complications is that we could start treatment much later than expected due to the late arrival of the patients to the hospital. Poverty, ignorance, negligence, lack of health seeking behaviour are the additional factors for this apart from poor health education. As a result we also got very high systolic and diastolic BP in most cases ((86.67% and 73.33% respectively). Though we were very fortunate that there were no fatalities in our study, but to reduce morbidity and mortality from AGN, early effective control of BP is always essential. Most important factors responsible for the failure to control HTN are selection of inappropriate antihypertensive drug, improper dose, unavailability of drugs, higher cost, poor response and non-compliance. In this particular study, nifedipine clearly stands ahead captopril in terms of early control of HTN, shorter duration of therapy, much cheaper and shorter hospital stay. Nifedipine is very useful to control the worst of the hypertension until an effective diuresis is established. It is also the only oral drug recommended for use in hypertensive crises. Ease of administration (no intravenous access or infusion pumps) and wide availability make it appealing in secondary and primary hospitals in our setting.

V. Conclusion

It was obvious from the study that Nifedipine controlled BP earlier; so that was given for a shorter period of time, much less costly and reduced the duration of hospital stay than did Captopril. By its less cost, early control of BP, shorter dosing and shorter hospital stay, it can reduce the morbidity of the patients; reduce the expenses of the family as well as the nation. So for the control of hypertension in AGN patients, Nifedipine is better drug at least in terms of activity, cost and morbidity.

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