CHAPTER 5

DISCUSSION

The efficacy of ACE inhibitor Enalapril in treating adults with congestive heart failure has been well approved. In conjunction with conventional therapy, Enalapril can provide beneficial hemodynaimic effects, increase cardiac output, decrease systemic vascular resistance, increase exercise capability and prolong survival. Recently, a small sample of uncontrolled study also show enalapril is helpful in managing children with congestive heart failure. The rationale for this study is to confirm the role of Enalapril in the treatment of children with congestive heart failure by a desirable randomized placebo controlled study.

5.1 Modified and unprocessed procedures during the implementation

According to the initial proposal, there were some procedures be modified or unprocessed due to some limitation and feasibility problems in our institute.

When we designed proposal, we considered that in pediatric population there is a strong age related drug response and disposition. Different group age child may have different causes of congestive heart failure, age should be at least divided or stratified. In our original proposal, we choose age from 3 to 12 years in our trial. But recently, the city of Shanghai is campaign for further bring down mortality below age 5, our institute is now focusing more at the younger age children according to the government's demand. Base on this situation, our sample age has been shifted to the

younger group which is below 3 years old. This age change will help our hospital to provide better treatment to a group of yonder children in the real clinical setting in the future.

Based on the primary question of the study, a minimum sample size (including 5% drop out) of 114 patients should be enroled in this trial. The actual number of patients in this study now is up to 84. The main reason is the delay of implementing of this trial because of the unexpected natural disaster. We actually started this trial from September instead of March. Since sample size was not completed, the conclusions of this trial should be applied cautiously.

According to the proposal designed last year, the end point of this study is one month. Based on the local policy change for average hospitalization and medical insurance coverage, the average hospitalization our city now is being set around 12-14 days, it is therefore impossible for us to keep most of our patients remain in the hospital around 30 days. 60% of our patients came from other cities every year, we so far are not able to control the out patients follow up in pediatric cardiology population in order to avoid some confounding factors. Thus the end point was set for 14 days. This we believe made the results more valid and reliable.

The New York functional classification measurement was not conducted in this study. Since the patients age had been shifted below age 3, NK functional classification is not valid for this group of patients.

5.2 Methodology considerations

5.2.1 Effectiveness of randomization procedures

Inspection of the data (Table 4.1-4.4) revealed no significant differences between two groups with regard to demographic characteristics, hemodynamic, clinical baseline and laboratory tests as well. The near equivalence of treatment groups at baseline by stratified patients with their etiology of CHF, allowed valid between groups comparisons. For the variables being monitored and documented the success of randomization method was adopted in this study.

5.2.2 Design features

This was a randomized, double-blind, controlled clinical trial which minimized the selection bias, measurement bias and other confounding factors as likely as possible. By using the stratify strategy, the different etiology of CHF was well balanced in both group.

5.2.3 Generalizability

The sample population in this study covered most common causes of congestive heart failure. Enalapril treatment is base on the conventional therapy and added an additional vasodilator. For clear definition of inclusion criteria and exclusion criteria, this study has limited age (below 3 years old) and all the patients were observed during the hospitalized period. So the results of this study should be applied for those hospitalized patients with congestive heart failure caused by congenital heart defects or impaired heart function including post cardiac surgery and dilated myocardiopathy.

5.3 Therapeutic effects

Present trial has confirmed that adding Enalapril in conjunction with conventional therapy can provide additional benefit both in hemodynamic and clinical aspects

5.3.1 Hemodymanic effects

The present study approved that Enalapril added as an additional drug can provide more beneficial hemodynamic effects to compare with conventional therapy alone. Our study design is use a load independent left ventricular systolic function index to demonstrate the change of cardiac contractility before and after treatment within and between the group. By comparing individual LVWS-VCFc index before and after treatment in each group with the normal rage of LVWS-VCFc index, this study show 55% patients in Enalapril group had their cardiac contractility LVWS-VCFc index moved up into a normal range to compare with only 23% in the controlled group. Proportional difference is statistically significant. In order to maintain some important signals, we at the same time, compared absolute change of VCFc. Results show both group before and after treatment had significant increase. It indicated that by using either digoxin with diuretics alone or added enalapril additionally, can improve cardiac contractility within a short period. By comparing absolute mean change before and after study between two groups, this study show a strong signal that an additional increase of VCFc can be provided by Enalapril. By illustrating the variation of mean change of VCFc between two groups, Enalapril group also show a wide range of variation, this indicated each individual response to enalapril very differently. The normal range of LVWS-VCFc used in this study is based on 40

normal children, age below 3 years old in our institute. It has a strong correlation coefficient: r=-0.72, VCFc=-0.0072LVWS+1.6288. This index has also been tested and reported by several international institutes[20,23] which showed: intraobserver variability of VCFc and LVWS was 2.3 and 3.2%; interobserver variability of VCFc and LVWS was 3.6% and 5.5%. Linear regression demonstrated excellent correlation for separate observers determining VCFc (r=0.91) and LVWS (r=0.93). Correlations were also excellent for 1 observer repeating determinations of VCFc (r=0.96) and LVWS (r=0.95).

Unlike the results in adult patient[8,11], our results show the change of shortening fraction before and after treatment within and between group have no significant differences. Experiences in adults, patients who can achieve by enalapril were the significant change of shortening fraction and cardiac chamber dimension, whereas the underlying problem in adults with heart failure is usually pump failure. In pediatric patients particularly in those with congenital heart defects, preload and afterload situation varied quite differently, the change of preload and afterload will definitely influence the shortening fraction. So shortening fraction is not a sensitive parameter represent the real cardiac contractility status in pediatric patients, and is some time is difficult to interpret its clinical effectiveness[23].

In this study we have shown that 4 (27%) in control group and 6 (43%) in Enalapril group, with impaired cardiac function had their cardiac contractility back to the normal range. 12 (44%) in controlled group and 17 (61%) in Enalapril group with congenital heart defects had their cardiac contractility back to normal range. These proportions have no significant difference. While most of studies in adults resulted a significant different change of cardiac function within impaired cardiac function

cases, but in the majority such kind of studies, observation period is at least 3 months or years. That may the indication these effects may happen in long term treatment. In order to obtain whether Enalapril will achieve significant positive results in those impaired cardiac function patients, longer observation period is needed, which we expect the improvement with the time.

5.3.2 Clinical effects

With respect to the achievement of clinical improvement, we compared some clinical symptoms and signs before and after treatment within and between groups. This study show all positive results regarding in reducing heart rate, respiratory rate liver size and gaining body weight within the group. By comparing the mean changes between two groups, Enalapril group show a significant further improvement in change of heart rate and respiratory rate and liver size. We believe that in children with congenital heart disease volume overload is the results of large systemic to pulmonary shuts, valve regurgitation or outflow tract restriction. So, the causes of CHF in children may be more complex than adults, thus ACE inhibitor not only act as, like in adults, a combination of afterload reduction and inhibition of salt and water retention, it also may result in an increase of systemic blood flow and a decrease in the size of left to right shut or regurgitation in pediatric patients. ACE inhibitor decrease systemic vascular resistance and increase the capacitance of the systemic vascular bed will diminish pulmonary congestion[24]. That is part of the reason why ACE inhibitor can have tremendous impact in reducing the congestive symptoms in

children. In the aspects of gaining body weight and changing the cardiac size by measuring the cardiacthorecic ratio, this study can not find a significant difference between two groups. It is contradictory to the results of previous uncontrolled study [14.25]. But rather this result can be interpreted that Enalapril may not help too much to reduce the cardiac size or Enalapril may effectively change cardiac size in long term treatmet, further study is needed.

It was suggested that timing of cardiac surgery in those with intracardiac shunts can be altered by the use of ACE inhibition[15,26]. But this study showed no different between two groups which number of improved sufficiently for surgery to be deferred. Expert consent tell us, we may not be able to achieve such positive result base on 14 days treatment, time may still is a factor.

5.3.3 Laboratory tests and side effects observation

We found serum potassium slightly increase in both group, change has no significant difference. In both group the percentage of receiving sodium potassium supplements has no difference. And percentage of receiving additional diuretic regimens . In Enalapril group, Serum sodium increased significant, but overall change between two groups show no difference. The response of increase sodium concentration in this study is of some interesting. Similarly like previous uncontrolled study[27], the increase of serum concentration may not necessary mean total body concentration increased, because hyponatrataemia is a mark of severe heart failure and is associated with high concentration of both renin and antidiuretic hormone. It also is a consequence of water overload. The total body sodium concentration may be

normal or even higher. When Enalapril increasing the renal blood flow the immediate and short term response may lead to a increase of serum sodium concentration by its anti-renin hormone effect.

There were no major side effects observed. Although 3 patients in Enalapril group, 1 patient in control group remained at low dosage because of the low blood pressure, the rests seem to be no more systolic blood pressure falling at day 4 and day 14 after trial started even during the dose escalate time period. Study show children may are well tolerated to this vasodilator in comparison of blood pressure decreasing in adult.

A trend of decrease of serum creatinine and urea was observed in this study. This indicate that actual renal function may be improved by enalapril by its anti diuretics hormone mechanism. The high incidence of renal failure was reported in previous uncontrolled study[13], 8 in 68 patients developed renal failure during enalapril treatment. This incidence is still remain unexplained, all of these patients age were under 2 months with severe left to right shunt. Infant with large left to right shunt has been recognized as a dominant risk factor for renal failure in infant.

5.3.4 Dosage toleration

In this study, we adopted enalapril dosage at 0.25mg/kg/day by escalating form 0.1mg/kg/day, 0.15mg/kg/day till 0.25mg/kg/day. A dosage finding study by Lioyd[16] concluded that Enalaril dose less than 0.1mg/kg/day may not be sufficient from the pharmacokinetic and clinical espects to children. By reviewing all the limited published literatures, the initiated dose of these study all started from 0.1mg/kg/day,

maxim dose reach to 0.45-0.5mg/kg/day[13,15,29,30]. For those who received more than 0.3mg/kg/day were age above 3 years. Due to the limited clinical data, avoid severe side effects, after discussed with the experts in our institute, we decided our dose at 0.25mg/kg/day. All the patients seemed well tolerated to this dose arrangement. We should indicated that the maximum dose of Enalapril for children very much depend on the age and is still a debatable issue. This study is not a dose finding study, the dose in this study should be rationale and reliable on the evidence presented by previous investigation. Whether dose higher than o.25mg/kg/day will produce even better results, we believe so, but is not the issue in this study.

5.4 Consideration of the limitations in this study

5.4.1 Short term study

The most concern of the limitation in this study is the observation time period. This study was conducted just 2 weeks and outcome of interest were short term outcomes. The results show a positive effect of Enalapril in increasing cardiac contractility, improving congestive symptoms, and having fairly low side effects in pediatric patients. Some questions are remained which this study will not be able to resolve. In adults, Enalapril not only approve hemodynamic and clinic situation, it can reduce the mortality and hospitalized period based on long term treatment. Whether in pediatric patients these goals can also be achieved? Immediate and short term effects of enalapril showed a strong positive signal, whether long term effects to compare with conventional therapy can produce same positive results? For those with

congenital heart disease, enalapril will make any difference in the timing for cardiac surgery when patients are altered? Thus, a well designed long term trial will be necessary to carry out. It is our difficulty now to manage a out patient follow up system in pediatric cardiology field, which is crucial for this long term study. We hope such kind of study would be able to carry out in the future.

5.4.2 Economic consideration

In respect to short term effects of Enalapril in providing additional benefit to the children with congestive heart failure, we believe it is the evidence that enalapril should be added in to conventional therapy. To economically evaluate these additional cost, the information of long term effects especially the change of mortality rate, reducing hospitalized duration, and reducing the burden of parents is necessary.