ARTICLE

Effect of Pre-operative Isometric Exercise (PIE) on vascular caliber of stage 2-5D chronic kidney disease pediatric patients: a randomized controlled study

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Objective: To determine the effect of pre-operative isometric exercise (PIE) on vascular caliber of pediatric chronic kidney disease (CKD) Stage 2-5D patients.

Material and Methods: This is a single-blind, randomized, single-center trial of 28 CKD patients. Fourteen participants allocated in the intervention group (PIE) were provided with a handgrip device and performed handgrip exercise consisting of two sets of 30 contractions daily while another 14 participants did not perform the exercise and were considered as controls (NE). For both groups, Duplex Ultrasonography was performed at baseline, four and eight weeks post-intervention.

Results: Twenty-four CKD patients were included and analyzed. The mean age was 15.8 (+/- 1.9) years. There were 16 (66.7%) females and eight (33%) Males, 10 (41.7%) underweight (<18 kg/m^2), 23 (95.8%) right-handed, 12 (50%) with Chronic Glomerulonephritis, and 10 (41.7%) with stage 2 CKD. Both the intervention and control group revealed a statistically significant increase in the caliber of the non-dominant cephalic (ante-cubital) vein at four- and eight-weeks post-intervention.

Conclusion: PIE might not significantly impact vessel diameter in pediatric CKD population as compared to adult CKD patients. Further studies on reliability of ultrasonography of blood vessels utilizing a larger sample size and more controlled milieu are recommended.

Keywords *Pre-operative Isometric Exercise, Vascular Caliber, Chronic Kidney Disease*

INTRODUCTION

Chronic Kidney Disease (CKD) pertains to abnormalities of the kidney structure or function present for more than three months[1] and can eventually lead to End Stage Renal Disease (ESRD).[2] It is an emerging global public health concern with a high economic burden.[3] The information on the epidemiology of CKD in the pediatric population is limited. The only data available is derived from patients undergoing renal replacement therapy (RRT) which is estimated to be nine per million of age-related population.[1,2] Locally, based on the Philippine Pediatric Society (PPS) Disease registry program, there are a total of 1,720 cases of Chronic Kidney Disease in children reported in the past 16 years (from January 2006 – November 2022). Among these cases, 96 or 5.6% were seen and managed at the Philippine Children's Medical Center (PCMC). At present, there are 80 active CKD patients with regular follow-up in the PCMC Nephrology face-to-face and telemedicine clinic.

Forty-three percent (34 out of 80) of these cases are classified as End Stage Renal Disease (ESRD) and are maintained on renal replacement therapy. Chronic Kidney Disease has five stages based on Estimated Glomerular filtration rate (eGFR) wherein Stage 1 is defined as GFR of more than or equal 90ml/min, Stage 2: 60-89ml/min; Stage 3 GFR 30-59 ml/min; Stage 4: GFR 15-29 ml/min and Stage 5: GFR <15ml/min. Stage 5 CKD is correspondingly referred to as End Stage Renal Disease (ESRD) whereas for patients who are on dialysis, the term CKD 5D is applied.

The gold standard in the management of ESRD is Kidney Transplantation (KT). Nevertheless, in instances where KT is unavailable or not yet feasible, renal replacement therapy is a life saving measure and a bridge in preparation for the definitive treatment. There are two modalities of renal replacement therapy which include Peritoneal Dialysis (PD) and Hemodialysis (HD). In patients requiring chronic hemodialysis, suitable vascular access is crucial in assuring adequate dialysis and more favorable long-term outcome.[5] There are three types of vascular access, namely the (1) Central venous catheters (CVC), (2) Arteriovenous grafts (AVG) and (3) Arteriovenous Fistula (AVF). In PCMC, CVCs are the most commonly used access due to their availability and less complicated surgical technique compared to permanent ones. A CVC is a temporary type of vascular access and is associated with high risk of catheter-related infection and thrombosis. The other two types are less common but act as long-term access with lesser impact on morbidity and mortality.[6,7] In PCMC, only three out of 16 HD patients or (19%) are currently utilizing AVF as access for hemodialysis. A functioning AVF is the preferred access due to less long-term vascular events including thrombosis, loss of primary patency and interventions.[8] Patients require suitable vessels for arteriovenous access creation.[5] A pre-requisite for optimal AVF is a vein diameter of more than or equal to 2.5mm.[9] This poses a challenge in the pediatric population who have smaller body weight and correspondingly with small vein diameter and weak arterial inflow.[11] Hence, any intervention that can increase the vein diameter remains of utmost importance. Previous evidence has demonstrated that Pre-operative Isometric exercise (PIE) can increase the vein diameter thereby enhancing the success rates of AVF creation and maturation. All these studies involved adult subjects who performed handgrip isometric contractions utilizing either a rubber ring, squeeze ball or a handgrip device.[12-16] To date, there is only one small case series of pediatric patients that has been done on this subject matter. Ramirez-Senent reported four cases of adolescents aged 13-19 years old requiring AVF but with unsuitable vessel sizes. All four patients underwent isometric exercise ranging from 9-30 months utilizing a handgrip device resulting in an increase in vessel diameter allowing AVF creation. They concluded that isometric exercise is a valuable option given its benefits including safety of the program and low cost.[17]

This study aims to determine the effect of Pre-operative Isometric exercise (PIE) on vascular caliber of pediatric chronic kidney disease (CKD) Stage 2-5D patients. Specifically, to describe the demographics and baseline characteristics of upper extremity vessels using duplex ultrasonography on pediatric CKD stage 2-5D patients; to evaluate the effect of PIE in the diameter of the radial, ulnar, brachial arteries as well as cephalic and basilic veins at four and eight weeks using Duplex Ultrasound and lastly to compare the mean change in diameter of the radial, ulnar, brachial arteries as well as cephalic and basilic veins between the control (no exercise) and the study groups (PIE) at zero and four weeks, and zero and eight weeks.

Methodology

A single-blind, randomized, controlled, single-centered trial with two treatment arms and a 1:1 allocation ratio was utilized in this study. Participants were recruited from the Nephrology outpatient clinic as well as the hemodialysis unit (HDU) and peritoneal dialysis unit (PDU) of the Philippine Children's Medical Center (PCMC). The primary investigator secured an informed consent/assent prior to the conduct of the study. The participants were CKD 2-5D patients aged 12 – 18 years old with signed informed consent/assent from a parent or legal guardian. Participants were excluded from the study if they had limitations in performing the exercise due to physical or mental disabilities or were unable to follow instructions.

Using OpenEpi version 3, the sample size was calculated using 95% confidence level, 80% power, ratio of 1:1 for the control and exercise group, and mean change in diameter of 0.39 (SD 0.06) for the control and 0.47 (SD 0.07) with the intervention group. [12] The computed sample size per group is 11 or total of 22 CKD pediatric patients. To account for 20% loss to follow-up, an additional three per group were recruited.

Participants were randomized into two groups, the intervention and control group using block randomization with sealed envelope method. The primary investigator who processed the data and the radiologist who measured the vessel diameter were blinded on the allocation of patients into the two groups. Only the patient, care giver and research assistant were informed of the group assignment whether in the intervention or control group. A thorough physical examination of all participants was done to ensure that the patient is physically and mentally fit to be in the study. A Duplex ultrasound at baseline was performed by one identified sonologist in both groups to measure the arteries including radial, ulnar and brachial as well as cephalic and basilic veins. Participants who were randomized in the PIE group underwent measurement of handgrip strength of the non-dominant hand using a hand grip dynamometer (Camry Digital

198lb/90kg Electronic Hand grip strength Dynamometer) (Figure 1). A physical therapist identified the level of resistance of the handgrip device based on the average handgrip strength for every patient which ranges from 10-100 kg. Additionally, a thorough instruction on pre-operative exercise protocol utilizing an instructional video was provided for the PIE group. The handgrip device (ATRONWA Hand Grip Exercise R-shape Adjustable 100kg) is a spring loader type, 200 grams in weight, equipped with a non-slip feature, an adjustable resistance knob with resistance level of 10kg-100kg and a digital counter (Figure 2).

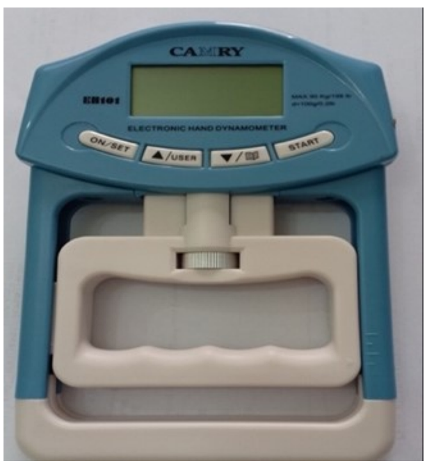


Figure 1: Handgrip Dynamometer

Figure 2: Handgrip Device

The participants in the PIE group performed daily handgrip exercise utilizing the non-dominant arm, to ensure that the outcome is less likely influenced by factors apart from the intervention. The exercise based on the study of Sauco et al consisted of two sets of 30 handgrip contractions per day using a handgrip device. Every handgrip contraction must be sustained for three to five seconds. Participants must do 10 contractions per cycle with a one-minute rest after each cycle. These handgrip exercises were done twice a day. Each patient was provided with their own handgrip device with strength adjusted to 30-40% of their maximum grip strength and as prescribed by the physical therapist. An instructional video was provided to all participants in the PIE group and served as their guide while performing the daily exercise. No other forms of exercise were performed during the entire study period. Clinical follow-up was done every four weeks to ensure that proper exercise protocol was performed.

Duplex Ultrasonography focusing on the identified arteries and veins were performed by the blinded sonologist on both groups at the initial visit, and at the fourth- and eighth-week visit. Veins and arteries of both upper extremities were measured twice with a tourniquet and recorded. The average of the two measurements was taken as the final measurement. To prevent inter-observer variability and bias, only one radiologist blinded to the group allocation performed the vascular mapping and only one ultrasound machine was used throughout the study period. On the day of the imaging study, CKD 2-4 patients were advised to consume adequate amounts of fluids based on their maintenance requirements to prevent dehydration while patients on dialysis consumed their usual fluid limitation and underwent ultrasound pre-mid-week dialysis session. The temperature in the examining room was maintained at the same preset settings of 22-24 degree Celsius in every measurement.

To ensure compliance, a handgrip device with counter was provided to the participants. The caregivers were instructed to make an exercise diary by recording the cumulative number of handgrip contractions performed daily as reflected in the handgrip counter. The research assistant was in constant communication with the participants in the PIE group. A social media group chat was created to include all of the participants in PIE group with the research assistant as the administrator. The instructional video was sent twice daily as a reminder to all the PIE group participants to perform the handgrip exercise. The social media group likewise served as a tool to monitor the progress of the exercise regimen and to report if there were untoward symptoms experienced by the patient while performing the exercise.

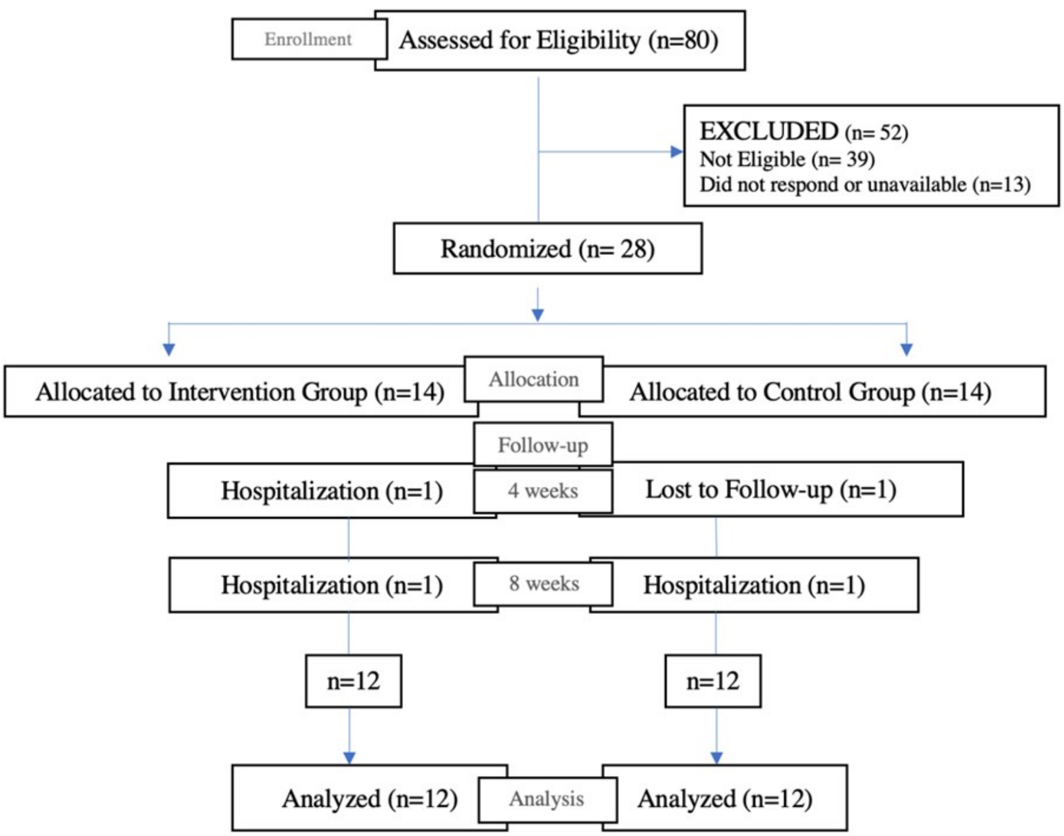
The primary outcome of this study was the mean change in the vascular diameter between the intervention and control group at zero and four weeks and zero and eight weeks. Ultrasound measurement of blood vessels was done on baseline, fourth week and eight weeks for both groups. Qualitative variables were described using frequency and proportion distribution while quantitative variables were described as mean and standard deviations. For the primary outcome, Fisher's exact test for categorical variables and independent *t*-test were used to compare the mean changes in the vein diameters from the baseline of the intervention and control groups at weeks four and eight. Paired t-test was used to compare the changes from baseline to four weeks and eight weeks in the two groups. A p-value of less than 0.05 is statistically significant. IBM SPSS Software Version 20 (IBM Corporation) was used in the analysis.

Implementation of this study was guided by the ethical principles stated in the Declaration of Helsinki, World Health Organization, International Conference on Harmonization – Good Clinical Practice and the National Ethics Guidelines for Research and the International Ethical Guidelines for Epidemiological Studies). The technical aspect of the study was presented for approval by the Clinical Trial and Research Division. The Institutional Research- Ethics Committee (IR-EC) approved the proposal last April 19, 2023. This trial was funded through a research grant from the Philippine Children's Medical Center (PCMC) and the Pediatric Nephrology Society of the Philippines (PNSP).

RESULTS

A total of 80 CKD patients were screened; 52 were excluded for non-eligibility or unavailability (Figure 3). The recruitment period started on May 23 until June 22, 2023, while follow-up ended last August 17, 2023. There were 28 CKD pediatric patients enrolled and randomized however, four dropped out of the study: one participant from the PIE group was admitted for bacterial peritonitis and one from the control group did not follow-up after four weeks of intervention because of schedule conflict. At the eighth week post intervention, an additional two participants were hospitalized: one from the PIE group had bacterial peritonitis while another from the control group had catheter related blood stream infection (CRBSI).

Figure 3: Enrollment Flowchart



A total of 24 CKD pediatric patients that were included and analyzed in the study. There were 12 CKD pediatric patients in the PIE and 12 CKD pediatric patients in control group. The mean age of CKD pediatric patients was 15.8 (+/- 1.9) years. The baseline characteristics are in Table 1.

Table 1. Demographics and clinical characteristics of pediatric CKD stage 2-5D patients

Characteristics	PIE n=12	NE n=12	p value	
Age (years +/- SD)	16.58 (1.31)	14.92 (2.15)		**0.032***
12-14yo	0 (0%)	5 (41.7%)	**.019***	
15-18yo	12 (100%)	7 (58.3%)		
Sex (%)			0.097	
Male	6 (50%)	2 (16.7%)		
Female	6 (50%)	10 (83.3%)		
BMI (kg/m2)	20.58 (3.370)	20.08 (5.518)		0.791
<18	4 (33.3%)	6 (50%)	0.301	
18-25	6 (50%)	2 (16.7%)		
>25	2 (16.7%)	4 (33.3%)		
Handedness (%)			0.5	
Left	1 (8.3%)	0 (0%)		
Right	11 (91.7%)	12 (100%)		
Etiology of CKD (%)			1	
CGN	6 (50%)	6 (50%)		
Lupus Nephritis	2 (16.7%)	3 (25%)		
Reflux Nephropathy	2 (16.7%)	1 (8.3%)		
Hypokalemic Nephropathy	2 (16.7%)	2 (16.7%)		
CKD Stage (%)				0.525
2	5 (41.7%)	5 (41.7%)		
3	4 (33.3%)	1 (8.3%)		
4	1 (8.3%)	2 (16.7%)		
5D	2 (16.7%)	4 (33.3%)		

Note. *p-value <0.05 is significant

The baseline characteristics of upper extremity vessels using the duplex ultrasound on pediatric CKD stage 2-5D patients showed that the diameter of the ulnar artery and cephalic (wrist) vein were significantly higher in PIE as compared to the control group with p-values < 0.05. The mean baseline measurements of radial artery and brachial artery as well as cephalic (antecubital) and basilic veins were comparable between the two groups. (Table 2).

Table 2. Baseline diameters of upper extremity vessels using the duplex ultrasonography on pediatric CKD stage 2-5D patients

Baseline	Non Dominant		p-value
	PIE n=12	NE n=12	
Artery	mm+/- SD		
Radial	2.08 (.289)	2.00 (.426)	0.581
Ulnar	1.92 (.289)	1.50 (.522)	**.024***
Brachial	3.33 (.492)	3.00 (.603)	0.152
Vein			
Cephalic (wrist)	2.33 (.651)	1.67 (.778)	**.033***
Cephalic (Antecubital)	3.08 (.996)	3.00 (.853)	0.828
Basilic	3.67 (1.073)	3.67 (.985)	1.00

Note. * p-value < 0.05 is significant

Based on the exercise diary, 10 out of 12 participants completed and performed the daily exercise. On the other hand, 2 (16.7%) patients had irregular compliance, and completed only 75-87.5% sessions of the prescribed exercise.

In the PIE group, the mean diameter from baseline to four weeks post-intervention was significant at cephalic (antecubital) vein with p-values < 0.05. The diameter of other arteries and veins were not significant with p-values > 0.05. In the control group, on the other hand, the mean diameter from baseline to four weeks post-intervention was significant at cephalic (antecubital) and cephalic (wrist) veins with p-values < 0.05. Other arteries and vein's diameter were not significant with p-values > 0.05. (Table 3)

Table 3. Pre and post intervention mean diameter of upper extremity vessels at four weeks in PIE intervention and control group

	PIE			CONTROL (NE)		
	Pre-intervention diameter (mm) mean (SD)	Post - intervention diameter at 4 weeks (mm) mean (SD)	p-value	Pre-intervention diameter (mm) mean (SD)	Post - intervention diameter at 4 weeks (mm) mean (SD)	p-value
Artery						
Radial	2.08 (.289)	2.08 (.289)	1.00	2.0 (.426)	2.17 (.389)	0.339
Ulnar	1.92 (.289)	1.83 (.389)	0.586	1.5 (.522)	1.83 (.389)	0.1034
Brachial	3.33 (.492)	3.58 (.515)	0.082	3.0 (.603)	3.25 (.754)	0.191
Vein						
Cephalic (wrist)	2.33 (.651)	2.50 (.674)	0.339	1.67 (.778)	2.25 (.866)	**0.027***
Cephalic (Antecubital)	3.08 (.996)	4.0 (1.128)	**0.009***	3.0 (.853)	3.67 (1.155)	**0.026***
Basilic	3.67 (1.073)	4.33 (1.155)	0.207	3.67 (.985)	4.42 (1.564)	0.120

Note. *p-value < 0.05 is significant

The mean change in blood vessel diameter for both the intervention and control group was not statistically significant with p values >0.05. Comparing both groups, the mean change in the diameter of the upper extremity vessels at four weeks in the control group was higher and more consistent as compared to the PIE group. (Table 4).

Table 4. Comparison of the mean change in diameter of upper extremity vessels between PIE and control group at four weeks

	PIE	CONTROL	
	diameter mean change (mm) mean (SD)	diameter mean change (mm) mean (SD)	p-value
Artery			
Radial	0.00 (.426)	+.167 (.577)	0.428
Ulnar	-.083 (.515)	+.333 (.651)	0.096
Brachial	+.250 (.452)	+.250 (.622)	>0.999
Vein			
Cephalic (wrist)	+.167 (.577)	+.583 (.793)	0.156
Cephalic (Antecubital)	+.917 (.996)	+.667 (.888)	0.523
Basilic	+.667 (1.723)	+.750 (1.545)	0.902

Note. *p-value < 0.05 is significant

The mean diameter from baseline to eight weeks post-intervention in PIE group was significant at cephalic (antecubital) vein with p-values < 0.05. The mean effect of PIE intervention at eight weeks in the diameter of other upper extremity arteries and veins was not significant. Meanwhile, in the control group, the mean diameter from baseline to eight weeks post-intervention was significant at brachial artery and cephalic (antecubital), cephalic (wrist) with p-values < 0.05 (Table 5). The increase in both arterial and venous diameters at eight weeks post intervention was comparable with four-weeks post intervention wherein there was variable and smaller increase in the PIE group as compared to the control group (Figure 4 and 5).

Table 5. Pre and post intervention mean diameter of upper extremity vessels at eight weeks in PIE intervention and control group

	PIE			**CONTROL**		
	Pre-intervention diameter (mm) mean (SD)	Post -intervention diameter at 8 weeks (mm) mean (SD)	p-value	Pre-intervention diameter (mm) mean (SD)	Post -intervention diameter at 8 weeks (mm) mean (SD)	p-value
Artery						
Radial	2.08 (.289)	2.17 (.389)	.586	2.0 (.426)	2.17 (.389)	.166
Ulnar	1.92 (.289)	1.92 (.289)	1.00	1.5 (.522)	1.83 (.389)	.104
Brachial	3.33 (.492)	3.58 (.515)	.082	3.0 (.603)	3.58 (.669)	**.027***
Vein						
Cephalic (wrist)	2.33 (.651)	2.33 (.778)	1.00	1.67 (.778)	2.17 (.835)	**.007***
Cephalic (Antecubital)	3.08 (.996)	4.0 (1.044)	**.005***	3.0 (.853)	4.00 (1.279)	**.032***
Basilic	3.67 (1.073)	4.17 (1.467)	.352	3.67 (.985)	4.50 (1.087)	.064

Note. *p-value < 0.05 is significant

Similar to the findings at four weeks, the mean change in the diameter of the upper extremity vessels at eight weeks post intervention in the control group was greater and more constant as compared to the PIE group. Only the mean change in diameter at cephalic (wrist) in control group was statistically significant with p-value <0.05. (Table 6).

Table 6. Comparison of the mean change in diameter of upper extremity vessels between PIE and control group at eight weeks

	PIE	**CONTROL**	
	diameter mean change (mm) mean (SD)	diameter mean change (mm) mean (SD)	p-value
Artery			
Radial	+.083 (.515)	+.167(.389)	0.656
Ulnar	0.00 (.426)	+.333(.651)	0.152
Brachial	+.250 (.452)	+.583(.793)	0.219
Vein			
Cephalic (wrist)	0.00 (.603)	+.500(.522)	**0.041***
Cephalic (Antecubital)	+.917 (.90)	+1.000(1.414)	0.865
Basilic	+.500 (1.784)	+.833(1.403)	0.616

Note. *p-value < 0.05 is significant

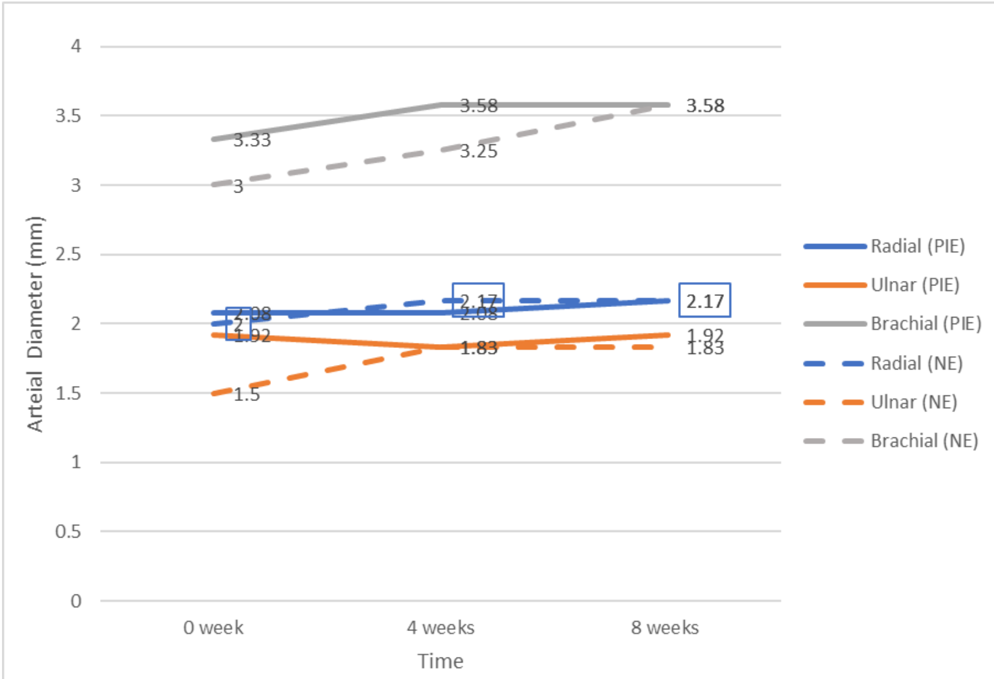


Figure 4. Line graph showing the mean arterial diameter of upper extremity of PIE and control Group (NE) at baseline, four- and eight-weeks post intervention

Figure 4 shows that from 0-4 as well as 0-8 weeks post intervention, most diameters did not show consistent improvement or increase. Only the brachial artery from the NE group had a consistent rise in the arterial diameter.

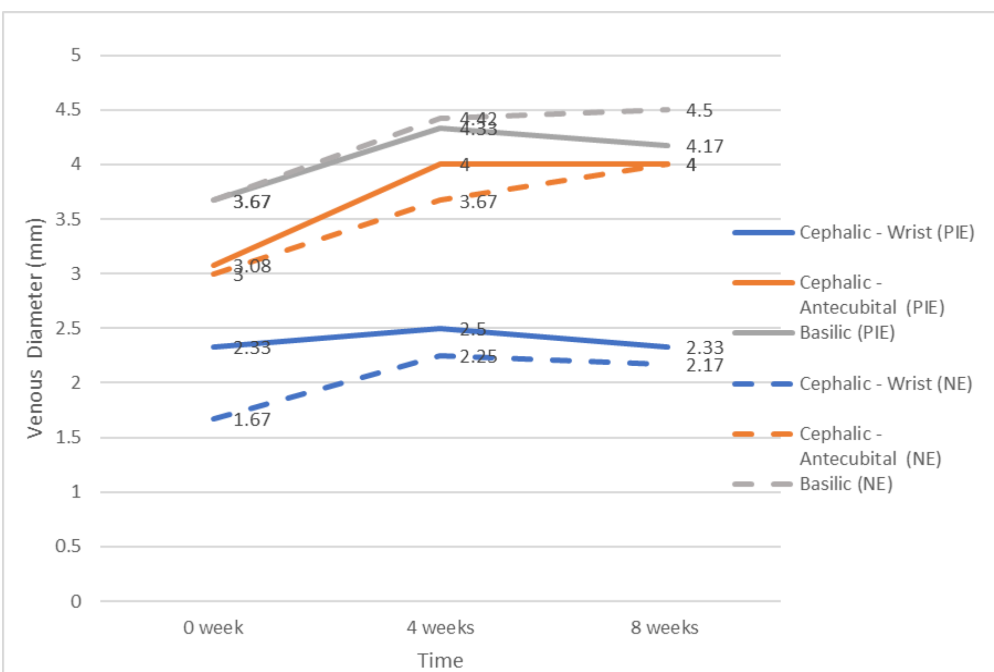


Figure 5. Line graph showing the mean venous diameter of upper extremity of PIE and control Group (NE) at baseline, four and eight-weeks post intervention

Figure 5 shows that from 0-4 and 0-8 weeks, the consistent increase in venous diameter was only appreciated in the cephalic (antecubital) and basilic vein of both PIE and NE group.

More than half (7 out of 12) of the participants did not report any symptoms experienced during handgrip exercise while a third (4 out of 12) reported tolerable pain on the fingers which was noted generally in the first few days of the exercise. A quarter (3 out of 12) of patients had numbness and or tightness noted in the fingers which resolved spontaneously.

Discussion

This study showed that PIE might not significantly impact vessel diameter in pediatric CKD population in contrast to adult CKD patients. There was a significant increase in the caliber of the non- dominant cephalic (ante-cubital) vein in the intervention group at four and eight weeks post intervention (4.0mm +/- 1.128 p 0.009; 4.0 mm +/- 1.04; p 0.005) though a substantial increase in diameter was also found in the cephalic vein of the control group at four and eight weeks (3.67 +- 1.15 p 0.024; 4.0+/- 1.3 p 0.032). Similar results were observed comparing the mean changes of cephalic vein diameter from baseline to four and eight weeks of both intervention and control groups. The participants in the control group were not provided with handgrip device nor instructed to perform any form of exercise. The increase in size of the cephalic vein in the exercise group may not exclusively be attributed to the PIE as an intervention but from other factors yet to be determined. Perhaps the most plausible explanation is that intra-observer variability contributed to the considerable change in the diameter of cephalic veins in both the intervention and control group. In this study, inter-observer variability during ultrasonography was mitigated by assigning only one radiologist to perform the measurement of the blood vessels.

Another possibility is natural occurrence of blood vessel enlargement corresponding to the physical growth and maturation experienced by a developing child. Vessels can dilate on a short term but can similarly undergo remodeling resulting to permanent vessel diameter changes.[18] According to Gifre-Renom et al, vessel enlargement postnatally is distinct compared to the embryo. The former occurs only when the vasculature is exposed to chronic change in flow resulting in vascular adaptation through either enlargement or inward remodeling to accommodate the altered blood flow. Blood vessels grow and regress in healthy tissues according to functional demands. Thus, spontaneous increase in vessel size in children might be a less likely consideration as a cause of the significant results observed in the control group of this study.

Two previous non-RCT studies in adults with CKD demonstrated an increase in vein diameter on the non-exercised or control arm[14-15]. The study of Leaf, 2003 and Uy, 2012 however utilized the contralateral arm as control and observed a concurrent statistically significant increase in the size of the cephalic vein.

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