What is the Critical age for the Improvement of Parenchymal Thickness after Pyeloplasty?

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ABSTRACT

Purpose

The most important point in cases of ureteropelvic junction obstruction (UPJO) is to decide on the need and timing of surgical treatment. Renal damage may become irreversible as the duration of the obstruction is prolonged. Worsening of hydronephrosis and decrease in renal parenchymal thickness after pyeloplasty may herald an irreversible renal damage. It is important to know at what age this damage begins. In this study, we aimed to determine the relationship between the age of the patients at the time of pyeloplasty performed for UPJO and parenchymal recovery.

Materials and Methods

In our study, 156 patients (mean age: 43.5 months) who underwent pyeloplasty with the diagnosis of UPJO between 2007 and 2019 were evaluated retrospectively. Demographic characteristics, ultrasonographic (USG) and nuclear renal scintigraphy findings, previous surgeries of the patients were recorded.

Results

Numerical variables were evaluated statistically, and the best cut-off point was determined. Parenchymal thickening was determined as the most important criterion in postoperative renal recovery which was more evident at early ages. Based on statistical assessments , the cut-off age for renal parenchymal recovery was determined as 38 months. While parenchymal recovery was inadequate after pyeloplasty performed in patients older than 38 months, the most significant improvement in renal functions was seen in children younger than 13 months of age.

Conclusions

Pyeloplasty should be performed in patients with UPJO before development of severe renal damage. Statistically, the best parameter to evaluate the recovery after pyeloplasty is the change in parenchymal thickness. With advancing age, it is impossible to reverse the obstructive nephropathy

Keywords: ages; child; renal parenchymal thickness; pyeloplasty; ureteropelvic junction obstruction,

INTRODUCTION

Antenatal hydronephrosis most frequently (10-30%) due to ureteropelvic junction obstruction (UPJO) is seen in approximately 1% of all pregnancies (10-30 %) (1,2). The prevalence of UPJO is estimated to be one in 1500 live births with a male to female ratio of 3-4 to1 (3). The diagnosis is usually made during prenatal ultrasonography screening (4,5).

As an easily accessible, inexpensive, noninvasive, and non-ionizing imaging technique, renal ultrasound (US) is the preferred modality for the diagnosis and monitoring of the patients with pediatric hydronephrosis. In previous patient cohorts, longitudinal evaluation of children with severe hydronephrosis has demonstrated improvement in renal functions in approximately 90% of children monitored non-operatively (6). Gradually worsening hydronephrosis detected on serial ultrasonograms is often considered a risk factor for loss of renal function (7,8). Unfortunately, renal ultrasound imaging is influenced by hydration status of the patients, presence of bladder pathologies, and personal skill of the ultrasonographer (9). In our study we tried to exclude these confounding factors with serial ultrasonographic examinations performed.

Diuretic renography is the standard test recommended to evaluate split differential renal function (DRF) among children with hydronephrosis (10). Use of this modality requires intravenous administration of radioactive agent and placement of a urethral catheter. Therefore, the desire for close patient monitoring must be balanced with the morbidity of ionizing radiation and catheterization. Diuretic renography is often used to assess ultrasonographic findings in detail before surgery.

Accepted indications for surgical intervention include worsening hydronephrosis detected on serial ultrasound imagings, renal function loss, or relevant symptoms such as pain, and signs of recurrent pyelonephritis (11). Additionally, the ideal imaging interval is unknown and inter-rater reliability of SFU (Society of Fetal Urology) grading system on renal ultrasound varies (12). Renal parenchymal echogenicity can also be used to predict relative renal function on diuretic renography, but increases in renal echogenicity are often late-stage changes associated with permanent renal damage (13).

It is important to distinguish patients who will recover spontaneously from those who require surgical treatment to preserve their renal functions.

Current protocols focus on close conservative monitoring. In cases with asymptomatic hydronephrosis, surgical intervention is decided if there is thinning of the renal parenchyma and renal drainage disorder observed in renal scintigraphy (14).

Surgery was performed for those presenting with signs and symptoms of severe obstructive uropathy including renal parenchymal thinning, worsening hydronephrosis, flank pain, estimated glomerular function rate (eGFR) below 40% or 10% reduction in renal function during follow-up as revealed in renal scintigraphy. In those with high-grade obstruction, cortex thinning is more important than the anteroposterior diameter (APD) of renal pelvis and caliectasis. In this case, the possibility of

exposure to irreversible renal damage may be higher (15). After pyeloplasty, cases are evaluated by the presence of dilatation in the collecting system and by US monitoring of the renal parenchymal thickness. The characteristics of the renal parenchyma draws less attention in children with UPJO than evaluation of renal pelvis and calyceal dilatation. Evaluation of the renal parenchyma is very important for an estimation of renal functional reserve. Onen et al. proposed a grading system for hydronephrosis by combining the degree of pelvicalyceal dilatation with the percentage loss in renal parenchyma (16).

Reduction pyeloplasty is performed in many centers, but it is not indicated unless a significant and gradual increase in renal pelvis dilatation is noted . However, recovery of normal renal parenchymal thickness is accepted as an indicator of improvement in renal functions.

In addition, pre-, and post-operative renal scintigraphies may be comparatively evaluated at the risk of radiation exposure. Achievement of recovery or stabilization of renal functions after pyeloplasty in UPJO cases may be related to the timing of the intervention. Delayed pyeloplasty in the follow-up of patients may cause irreversible damage to renal functions. In our study, we aimed to determine whether there is a relationship between the increase in renal parenchyma thickness, which is an indicator of improvement in renal function after surgery, and the age at which pyeloplasty was performed.

MATERIALS AND METHODS

The records of all pediatric pyeloplasty cases in a single center covering the period from January 2007 to March 2019 were retrospectively reviewed. Children who had undergone all tests and examinations preoperatively including ultrasound (US) and nuclear renography scans were included in the study

Voiding cystourethrography was performed for those who had undergone pyeloplasty within the first 6 years of their lives, had urinary tract infection, and ureteral dilatation detected in ultrasonography in the following years. Children who had suspected voiding symptoms (including abnormal urine stream) , ureteral dilatation, duplex collecting system, fused kidneys, bilateral renal pelvis dilatation, or any bladder abnormality in the US were excluded from the present study. Nine vesicourethral reflux patients detected on voiding cystourethrography were also excluded from the study.

A total of 156 pyeloplasties (mean age 43.5 months; median age 17.9 months; 45 female, and 111 male patients) who were operated in a single center (Ankara City Hospital) were included in the study. Surgery was performed on those with severe obstruction. For the determination of surgical indications, ultrasonography and renal scintigraphy findings were evaluated as a whole.

Our pyeloplasty indications were as follows;

1- The presence of ultrasonographic findings indicating decrease in renal parenchymal thickness, increases in the degree of hydronephrosis (calyceal dilatation, gradual and continuous

expansion of collecting system,) and in the anteroposterior diameter (APD) of renal pelvis

2- Renal scintigraphy findings associated with a renal function percentage below 40% or 10% decrease in the percentage of the differential renal function estimated during follow-up, obstruction curve, and prolongation of half-life (t 1/2) of the agent used in diuretic renography

3-Especially in older children, those who presented with pain together with findings of hydronephrosis (35.9%) were considered symptomatic and underwent surgery.

All patients underwent dismembered pyeloplasty surgery using Anderson-Hynes technique through a mini flank incision using a retroperitoneal approach. A perinephric drain and a urethral catheter were inserted in all patients. Intraoperatively, crossing renal vessels (11.5%) and relatively narrow segments (88.5%) were detected. External intrarenal stents or double-J stents were used in all pyeloplasties. Double-J stents were removed four, and pyelostomy catheters 10 days after surgery. Antibiotic treatment was used for one week postoperatively, then prophylactic antibiotherapy was continued for one month to prevent development of indwelling catheter -related infection.

Demographic and clinical data related to gender, and age of the patients, laterality of hydronephrosis, indication of the first pyeloplasty, presence of a crossing vessel, history of prenatal hydronephrosis and/or urinary tract infection, US findings and percentage of renal function demonstrated on nuclear renogram and evidence of reflux (if any) were collected . Additionally, patients' pre-and postoperative 2nd-year APD, calyceal diameters, and renal parenchymal thickness were recorded.

After the obstruction is removed, it takes approximately 2 years for the renal pelvis to gain full flexibility (30). For these reasons, second-year US findings were taken into account instead of early or latest follow-up US findings. Postoperatively all children were followed up for at least 2 years, (mean 6.7 years).

Statistical Analysis

Data were analyzed retrospectively. IBM SPSS Statistics ver. 23.0 (IBM Corp., Armonk NY) was used for statistical analysis. The fitness of numerical variables to normal distribution was examined using Kolmogorov-Smirnov test. Qualitative variables were summarized by numbers and percentages, and numerical variables by mean ± standard deviation (SD) and median (IQR). The values of both groups were compared with the Mann-Whitney U test. ROC curve was used to evaluate the diagnostic performance of numerical variables and to determine the best cut-off point. The value with the highest Youden index (sensitivity+specificity-1) score was determined as the optimum cut-off point. The sensitivity, specificity, positive and negative predictive values of the test were calculated according to the determined cut-off point. A value of $p<0.05$ was considered statistically significant.

RESULTS

After reviewing the surgical database, 176 pyeloplasty cases were detected during the study

period. Twenty pyeloplasty cases including patients with ureterovesical obstruction (n=1), bilateral UPJO (n=4), horseshoe kidney (n=5), multicystic kidney (n=1), ectopic kidney (n=1), atrophic kidney (n=1), a duplex system (n=3) were excluded. Cases with bilateral hydronephrosis were not included in the study, considering that comparison of parenchymal thickness between both kidneys would not be accurate. Finally a total of 156 children were enrolled in the study (**Table 1)**.

First of all, statistical analysis was performed to see if there was any improvement in parenchymal thickness under and over 1- year- old infants. Pyeloplasty (41%) performed in 64 children under 1 year of age, significantly increased postoperative renal parenchymal thickness compared to those above 1 year of age (p = .029) (**Table 2a**).

In the postoperative follow-ups, we observed that the decrease in renal calyx diameter (p= .075) and the change in pelvis diameter were not significantly (p= .207) different in children aged less than 1 year compared to those above 1 year of age (**Table 2a**).

Postoperatively, renal MAG-3 scans were performed in 81 patients with absolute indications. The increase in differential renal function in postoperative renal MAG-3 scintigraphies was 2.31% on average (±1.83 SD) when compared with preoperative values. Insignificant improvement was observed in renal functions according to age as evidenced in renal MAG-3 scintigraphy (p= .338). A positive weak correlation was found when the relationship between the improvement in renal differential function and renal parenchymal recovery of 81 patients who underwent renal MAG-3 scintigraphy after pyeloplasty was examined statistically using Pearson correlation analysis (r 0.23, p= .037). Renal MAG-3 scintigraphy was not required in remaining 75 patients who had significant improvement as observed in postoperative US performed such as absence of parenchymal thickening without any increase in pelvic diameter.

In the follow-up of 156 patients, an indwelling ureteral catheter was left in situ in 10 (6.4%) patients due to temporary stenosis, while 3 (1.9%) patients underwent re-pyeloplasty within the first year.

We can correctly classify those with or without adequate improvement in operated cases with UPJO with 79% (AUC± Std. Error: 0.79±0.046) change in parenchymal thickness. The best cut-off point to identify those with and without improvement is determined by using Youden Index. The ROC curve was used to evaluate the diagnostic performance of numerical variables and to determine the best cut-off point (**Figure 1a, 1b**). Taking the 1.5 value as the best cut-off point for the change in parenchymal thickness, this test had 51% sensitivity and 99% selectivity. There was a significant difference between the age of the patients and the degree of recovery obtained in renal functions (p <0.01). Sufficient recovery in renal functions was achieved in younger children (median (IQR): 12 (38.9) months) compared to those older ones (median (IQR): 42.8 (92.7) months). The best cut-off age for sufficient recovery was 38 months. Using 38 months of age as a cut-off point, we can determine the sufficiency of recovery in renal functions with 61% sensitivity and 72% selectivity (**Table 3)**.

Statistically, the best parameter to evaluate the recovery after the operation is the change in parenchymal thickness (p= .029). In our study we determined that the possibility of reversing the kidney damage caused by the obstruction statistically disappeared as the child gets older. The most striking postoperative improvement in parenchymal thickness compared to preoperative values was achieved in cases younger than 13 months (Table 2b). When pyeloplasty surgery is delayed for a long time, then the chance of parenchymal healing is reduced.. In our study, the cut-off age for parenchymal thickening was determined as 38 months. Pyeloplasty should be performed in UPJO patients before severe renal damage occurs. Especially in pyeloplasty performed in children over 42 months, parenchymal healing was found to be statistically almost nonexistent.

DISCUSSION

In order to prevent renal damage, appropriate follow-up and timely surgical treatment are important criteria in patients with asymptomatic UPJO with a history of antenatal hydronephrosis. If surgery is delayed, irreversible losses in kidney function occur (17-20). Preoperative renal dilatation and parenchymal thinning are expected to improve in the postoperative period in patients operated within appropriate time frame. We observed that postoperative renal parenchymal recovery is achieved in statistically significantly lesser number of patients older than 38 months of age who were operated in our clinic.

Since the rate of antenatal diagnosis has increased in UPJO cases today, it is possible to be operated on at an earlier age. In the literature, surgical indications have been usually reported as renal deterioration, urinary obstruction, and urinary tract infection. Indications for surgical intervention comprise impaired split renal function (< 40%), a decrease in split renal function of > 10% in subsequent studies, poor renal drainage after the administration of furosemide, increased anteroposterior pelvic diameter as detected on the US, and grade III and IV dilatation as defined by the Society for Fetal Urology (20-23).

UPJO has been reported in up to 54% of cases depending on the degree of prenatal hydronephrosis (24). In our study, antenatal hydronephrosis were at a rate close to that reported in the literature (51%). Since our patients had a history of antenatal hydronephrosis, close follow-up with ultrasound was available. Thus, our patients had the chance to undergo pyeloplasty in case of need at a young age. In our study, pyeloplasty was performed in patients younger than 2 (53.2%), and 3 years of age (60%).

Renal ultrasound is the cornerstone in the diagnostic pathway of children with hydronephrosis. The most reliable and reproducible measurement is the anteroposterior diameter of the renal pelvis The degree of dilatation of the calyces and parenchymal thinning are also very important parameters in the analysis of the degree of hydronephrosis (15). The success of pyeloplasty is determined based on the resolution of pelvicalyceal dilatation and recovery of normal parenchymal thickness as observed on serial ultrasonographic examinations. After pyeloplasty, a decrease in the degree of

hydronephrosis on US, absence of parenchymal loss and improvement in renal drainage as observed on renograms indicate the success of the surgery. A renal ultrasound is performed 6-8 weeks after pyeloplasty or stent removal to ensure that the pelvicaliectasis and parenchymal thickness have improved. An overall decrease in the degree of pelvicalectasis over time is a good indication that the obstruction is relieved. While the expected maximum improvement in renal function and drainage is seen in the first year after the operation, this period may extend up to 2 years (25). For this reason, in our cases parenchymal thickness, diameters of renal pelvis and calyces were evaluated by the US in the second postoperative year.

Approximately, 23% of congenital hydronephrotic kidneys followed with an observational approach eventually required surgical intervention (26). The observational protocol should consist of obtaining serial renal USGs. Due to its wide availability and noninvasive nature, renal ultrasonography has become the primary initial diagnostic tool for the identification and evaluation of prenatal and postnatal hydronephrosis. Parenchymal thinning may be an evidence of chronic renal obstruction (27).

Since we performed excision and reduction of the renal pelvis in our series cited in the literature, renal pelvis diameter was not an accurate parameter in the postoperative follow-up of our cases. However, in the follow-up of the patients, the anteroposterior diameter of the renal pelvis and the thickness of the renal parenchyma were monitored closely. While reduction pyeloplasty is being performed in many centers, the follow-up of patients based on the decrease in the degree of renal dilatation is not instructive unless there is a significant increase, but improvement in parenchymal thickness is accepted as an indicator of improvement in renal function. It is more appropriate to monitor the degree of improvement in renal functions with changes in renal parenchymal thickness and width of calyces detected on serial US performed during postoperative follow-up instead of APD.

Renal scintigraphy is applied more limitedly during the follow-up of the patients due to radiation exposure. Renal scintigraphy was evaluated in 81 of our cases in the sixth month postoperatively. An average of 2.31% (±1.83 SD) improvement in renal functions was observed in the scintigraphy performed in the 6th month postoperatively. In our study, a positive weak relationship was found when the Pearson correlation analysis was performed between the improvement of renal differential function and renal parenchymal recovery of 81 patients who underwent renal scintigraphy after pyeloplasty, ($r= .23$, $p= .037$). In patients who underwent scintigraphy after pyeloplasty, improvement in renal function was correlated with the measurements of parenchymal thickening in ultrasonography.

Recovery of renal function occurs not only in patients allocated to surgical correction after delivery due to poor renal function but also in those on conservative treatment who required pyeloplasty due to deteriorating renal function during observation (28). Normally functioning kidneys may deteriorate during observational follow-up period, however renal functions of many patients will recover after pyeloplasty (29).

Pyeloplasty in children with UPJO should be done before serious renal damage develops. The most statistically significant parameter showing postoperative improvement in our study was the favourable change in renal parenchymal thickness (p= .029).

CONCLUSIONS

In our study, we found that the recovery of normal parenchymal thickness was less frequently achieved in children with UPJO who were operated on after 38 months of age. In cases of UPJO, we found that postoperative renal parenchymal healing or thickening was more important for the success of pyeloplasty in patients younger than 38 months relative to older children. The authors believe that the decision for pyeloplasty should be made carefully, especially in asymptomatic UPJO patients younger than 38 months. Because after this age, delayed pyeloplasty may not achieve recovery of renal functions.

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Author Contributions

The above-listed authors (Derya Yayla, Gokhan Demirtas, Bilge Karabulut, Huseyin Tugrul Tiryaki) were involved in the design of the submitted study, acquisition, analysis, and interpretation of the data, drafting of the manuscript and editing it for accuracy and content. Each author approved the final draft of the manuscript before submission. Additionally, all authors agreed to be responsible for all aspects of the submitted work.

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CONFLICT ON INTEREST

The authors declare that they have no conflict of interest.

The research protocol was approved by the Institutional Review Board of Ankara City Hospital (date:……; registration no:.)

Informed Consent was obtained from the parents of the children included in the study . All procedures performed were in accordance with the ethical standards of our institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Registry and Registration No. Of the study: Ministry of Health in Turkey, Ankara City Hospital No:1 Clinical Trials Ethics Committee Chairman, Ethics Committee- E1-20-592, 2020

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Table 1. ***Demographic characteristics of patients***

Variables		*Patients,n*	*%*
Gender	Female	45	28.8
	Male	111	71.2
Age (mean±SD, Median (IQR)) *		43.5±42.8	17.9 (64.0)
Age groups	≤ 13 months	67	42.9
	≤38 months	96	61.5
	> 42 months	52	33.3
Laterality	Right	52	33.3
	Left	104	66.7
Minimal pelvicaliectasis in the contralateral kidney		89	57.0
Neurological disorders		8	5.1
	Duchenne Muscular Dystrophy	1	
	Neurofibromatosis type 1	1	
	Down syndrome	1	
	Hydrocephalus	1	
	Macrocephalus	2	
	Hypotonia	1	
	Castello's syndrome	1	
Indications for the first pyeloplasty	History of prenatal hydronephrosis	80	51.3
	Abdominal pain	56	35.9
	History of urinary tract infection	20	12.8
Causative factors	Relatively narrow segments	138	88.5
	Crossing vessel	18	11.5
Differential renal function as detected in renal scintigraphy	≤20%	12	7.7
	21-40%	83	53.2
	41-55%	57	36.5
	> 55%	4	2.6
Postoperative differential renal function as detected in renal scintigraphy	2.31% (±1.83 SD) rate of increase	81	51.6
Vesicourethral reflux (VUR)		VUR (n) 9	VUR (%) 5.2

*: mean ± standard deviation (SD) and median (IQR) values are presented

Table 2. ***Ultrasonographic and scintigraphic variables by age groups (2a, 2b)***

Variables	≤ 1 year		> 1 year		P value
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
Differantial renal function of scintigraphy	3.3±9.3	3 (7)	1.8±6.9	3 (6)	.338
Calyceal diameter	-7.8±7.6	-7.5 (8)	-11.6±11.8	-9 (8)	.075
Pelvic diameter	-17.3±13.3	-17.5 (14)	-20.7±14.4	-18 (13)	.207
Parenchymal thickness	3.3±2.2	4 (2)	2.5±2.5	2 (3)	.029*

2a) Mean variables by under 1 year old and above groups
SD: standard deviation, IQR: Interquartile range (Mean±SD)
*: $p < 0.05$

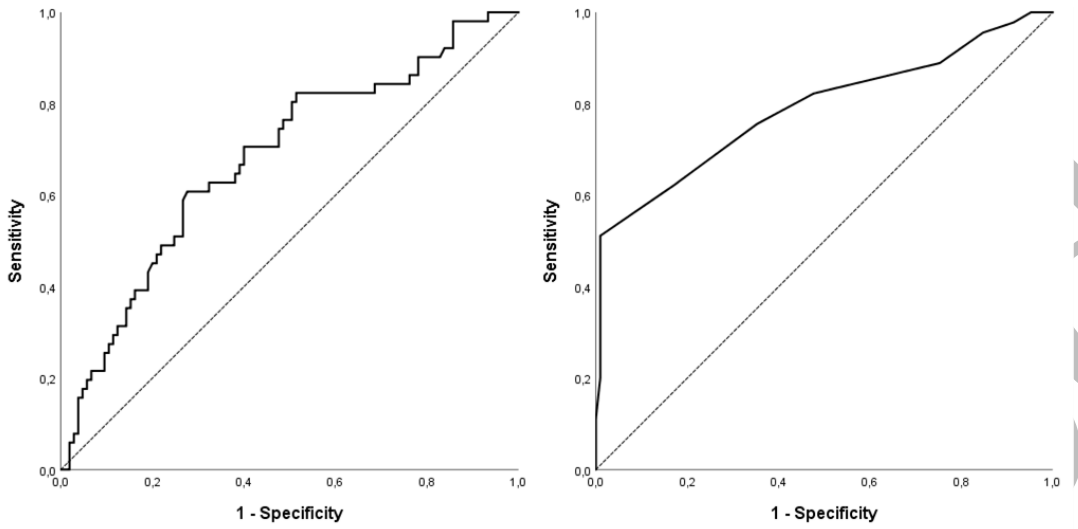
Variables	*≤ 13 month* *Mean±SD*	*13-38 month* *Mean±SD*	*> 42 month* *Mean±SD*
Differential renal function of scintigraphy	3.3±9.3	1.8±6.8	1.2±6.2
Calyceal diameter	-7.8±7.6	-11.5±11.8	-9.2±10.3
Pelvic diameter	-17.3±13.3	-20.2±14.4	-19.7±13.4
Parenchymal thickness	3.3±2.2	2.6±2.5	1.9±2.1

2b) Mean variables by cut-off age groups
SD: standard deviation (Mean±SD)

Table 3. Test performance by age and parenchymal thickening

Variables	*Cut-off*	*AUC*	*Sensitivity*	*Specificity*	*PPV*	*NPV*
Age	≥ 38.0	.68	.61	.72	.52	.79
Improvement in UPJO	≥ 0.50	.79	.51	.99	.96	.83

Fig 1. ***ROC curve for (1a) age, (1b) improvement in UPJO:***



a) Ages of the patients with diagnosis of UPJO **b)** Improvement in UPJO