

Study of post operative outcome in pediatric Pelviureteric junction obstruction and role of interstitial cells of Cajal

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Abstract:

Introduction: The region of Pelviureteric junction has an innervations pattern with presence of interstitial cells of Cajal, the distribution of which has a bearing at the ultimate postoperative outcome. Aim is to study the post-operative outcome in congenital Pelviureteric junction obstruction by biochemical, radiological and radionuclide study and to correlate the presence and density of interstitial cells of Cajal as a predictive prognostic factor in congenital Pelviureteric junction obstruction.

Materials and Methods: Specimens obtained following Anderson-Hynes pyeloplasty from 20 patients with intrinsic Pelviureteric junction obstruction were evaluated histopathologically and presence of interstitial cells of cajal were compared in good and poor outcome groups of patients. Cajal cells between the muscle layers stained with CD117 were enumerated per HPF and evaluated as follows: n = 0-1 (-); n = 2-5 (+); n = 6-10 (++); n = ≥ 11 (+++).

Result- Sixteen patients were obstruction free and were classified as Group I. Four patients did not improve and they were placed in Group II. All the patients with a poor outcome had negative grading at the PUJ and p-value was 0.002 which is significant.

Conclusion- This study shows that altered density of CD117 positive cells in PUJ obstruction have a role in the transmission failure of peristaltic waves & postoperative outcomes.

Keywords: Pelviureteric junction obstruction, Interstitial cells of Cajal, Anderson-Hynes pyeloplasty, CD117

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I. Introduction

Congenital hydronephrosis or Pelviureteric junction obstruction is characterized by impaired urine flow from the renal pelvis to proximal ureter, followed by dilatation of collecting system and potential damage to renal parenchyma. This is the most common cause of antenatal hydronephrosis.^[1]

The region of Pelviureteric junction has an innervations pattern with presence of interstitial cells of Cajal, the distribution of which has a bearing at the ultimate postoperative outcome.

Aim and objective is to study the post-operative outcome in congenital Pelviureteric junction obstruction by biochemical, radiological and radionuclide study and to correlate the presence and density of interstitial cells of Cajal as a predictive prognostic factor in congenital Pelviureteric junction obstruction.

Pelviureteric junction obstruction (PUJO) is regarded as most common congenital anomaly of the ureter. It occurs in 1 per 1000-2000 newborns^[2,3,4], M/F: 2/1. There is a predilection for the left side in children (66%), whereas the reverse is true for of adults. Bilateral PUJO in 10% to 36% .

The underlying mechanism of Pelviureteric junction obstruction remains unclear. A decrease in smooth muscle cells at the Pelviureteric junction (PUJ), abnormal muscle orientation, and collagen deposition, as well as a reduction in Cajal cells^[4] and neural elements^[5] has been suggested to play a role in the pathogenesis of congenital Pelviureteric junction obstruction.

Interstitial cells of Cajal (ICCs) are named after Santiago Ramon Y. Cajal (Spanish Pathologist & Nobel Laureate).^[6]

A successful pyeloplasty^[7] is most specifically measured by preservation of or improvement of renal function. Several investigators have reported improvement in renal function in children with obstruction detected early and surgery performed before renal impairment occurs. Atraumatic tissue handling, careful

dissection, and preservation of ureteral blood supply all contribute to a successful anastomosis. The ureteropelvic anastomosis should be watertight and tension free.

Operative outcome after Pyeloplasty is to be assessed by biochemical, radiological and radionuclide study & to correlate the presence of ICC as a predictive prognostic factor in congenital PUJO.

II. Methods

Study design and statistics

This is a prospective study on 20 patients (having Pelviureteric junction obstruction) admitted from October 2015 to March 2017. The ethical approval was taken from ethical committee of the institution. Informed and written consent was taken from parents. The data were analyzed using SPSS 17.0 version for Windows to see the correlation between the histopathological grading of interstitial cells of Cajal and post-operative outcome.

Evaluation of immunohistochemical staining (CD117)

Cajal cells between the muscle layers stained with CD117 were enumerated per HPF and evaluated as follows: n = 0-1 (-); n = 2-5 (+); n = 6-10 (++); n = \geq 11 (+++).

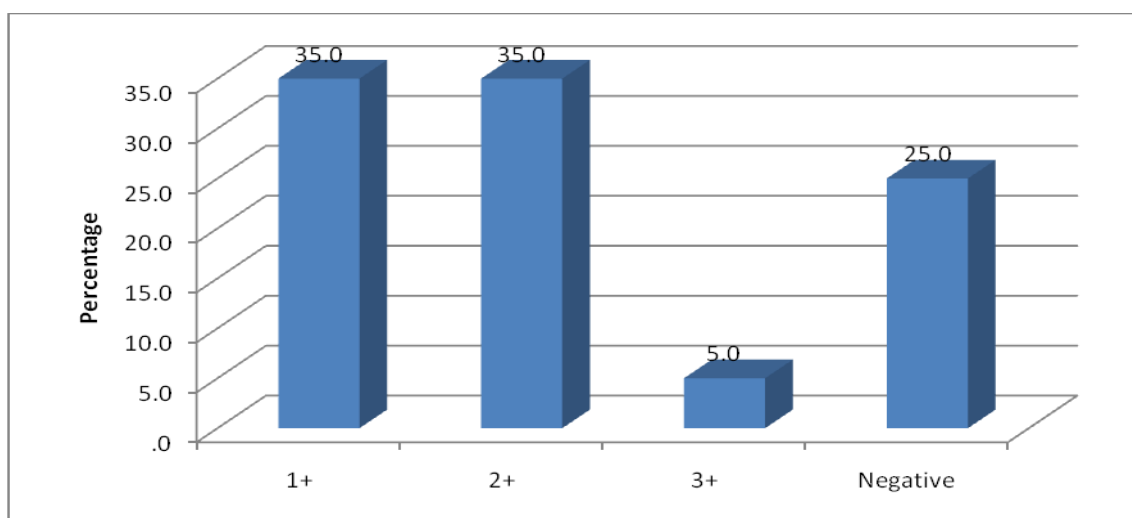


Figure 1: Percentage of Different Grading of ICCs

Post-operative outcome were assessed in congenital PUJO by biochemical, radiological & Radionuclide study. Follow up at 1 month by USG- KUB and at 3 months by KFT, USG and DTPA. Radionuclide study (DTPA) was done elsewhere or in any other government institution.

Descriptive statistics like mean, median and proportion were used. To describe the study result appropriate statistical test were applied. SPSS software (SPSS 17, Chicago, Illinois, USA) were used for statistical analysis Continuous variables were expressed as median values and ranges (minimum to maximum), as well as in percentages. Significance was set at a level of $p \leq 0.05$ (two-sided).

III. Results

Our study was a prospective observational study which was carried out on 20 consecutive patients of pelvi-ureteric junction obstruction who were presented to our department. Male and female ratio was 4:1. All patients were new cases under 12 years of age. Patients underwent preoperative workup for anaesthesia fitness and subsequent surgery.

Grading was done on the basis of number of ICC present at PUJ which was obtained after pyeloplasty. Pre-Operative and Post-Operative APD mean value was 15.05 and 12.60 respectively and **p-value was 0.000 which is significant**. Mean value of APD 1 Month vs. 3 Month was 12.60 and 10.50 in Pre and Post-operative finding whose **p-value was 0.000 which is significant**.

Table 1: Comparison of Antero-posterior Diameter (APD) of Pelvis in Ultrasonography

| | PRE-OPERATIVE | | POST-OPERATIVE | | T | p-value | 95% Confidence Interval of the Difference | |
|-----------------------|---------------|------|----------------|------|-------|---------|-------------------------------------------|-------|
| | Mean | SD | Mean | SD | | | Lower | Upper |
| APD | 15.05 | 1.85 | 12.60 | 2.06 | 6.691 | 0.000 | 1.684 | 3.216 |
| APD-1month vs. 3month | 12.60 | 2.06 | 10.50 | 1.28 | 6.185 | 0.000 | 1.389 | 2.811 |

Patients underwent DTPA scan in the postoperative period .Difference between preoperative and post-operative DTPA were compared and divided into two groups. Sixteen patients were free of obstruction and had improved renal function and were classified as Group I. Four patients did not improve and they were placed in Group II.

Table -2: Groups based on post-operative outcome

| | Group | | Total |
|-----------------|------------------------|-------------------------|---------|
| | Group I (Good Outcome) | Group II (Poor Outcome) | |
| No. of patients | 16 | 4 | 20 |
| Percentage | 80.00% | 20.00% | 100.00% |

Mean value of Difference (Post Op.-Pre Op.) in Kidney Differential Function (KDF) in Group I (Good Outcome) and Group II (Poor Outcome) is 8.69 and -0.93 respectively. **P-value of Difference in KDF is 0.000 which is significant.**

Table 3: Difference in Post Op.-Pre Op. KDF and GFR in correlation to surgical outcome

| POST PRE OP | Group I (Good Outcome) | | Group II (Poor Outcome) | | t | p-value | 95% Confidence Interval of the Difference | |
|-------------|------------------------|------|-------------------------|------|--------|---------|-------------------------------------------|--------|
| | Mean | SD | Mean | SD | | | Lower | Upper |
| DIFF_KDF | 8.69 | 2.95 | -0.93 | 1.89 | -6.149 | 0.000 | -12.902 | -6.331 |
| DIFF_GFR | 12.11 | 6.64 | 3.53 | 5.55 | -2.373 | 0.029 | -16.188 | -0.983 |

The status of the ICC at the PUJ specimen was correlated with the outcome. All the 4 patients with a poor outcome had negative grading at the PUJ. Chi-square value was 15 and **p-value was 0.002 which is significant.** Increase in ICC leads to better contractility and good outcome. Prognosis of future can be made at surgery with ICC report.

Table 4: Correlation of Interstitial Cells of Cajal at Pelvi-ureteric Junction with outcome

| Number of ICC | IHC Report | Group | | Total | Chi-square value | p-value |
|---------------|------------|----------------------------|-----------------------------|-------|------------------|---------|
| | | Group I (Good Outcome) (%) | Group II (Poor Outcome) (%) | | | |
| 0-1 | Negative | 1(6.3%) | 4(100%) | 5 | 15 | 0.002 |
| 2-5 | 1+ | 7(43.8%) | 0(0%) | 7 | | |
| 6-10 | 2+ | 7(43.8%) | 0(0%) | 7 | | |
| ≥11 | 3+ | 1(6.3%) | 0(0%) | 1 | | |
| Total | | 16 | 4 | 20 | | |

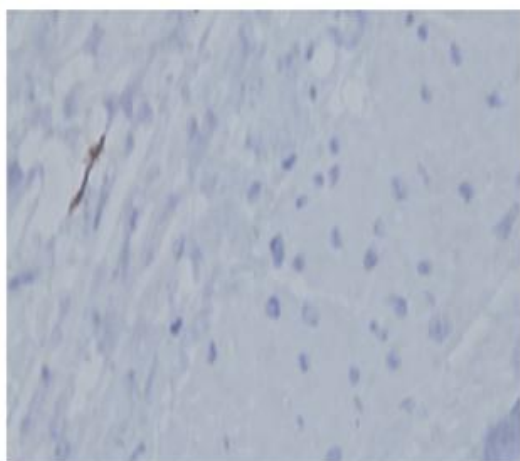


Figure 2: CD 117 (Negative) Interstitial Cells of Cajal (ICC)

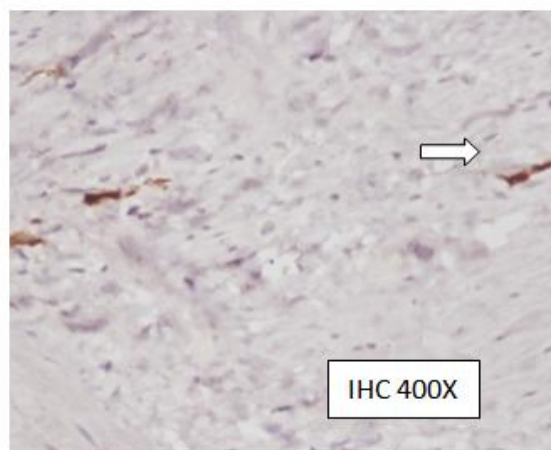


Figure 3: CD 117 Grade (1+) Interstitial Cells of Cajal (ICC)

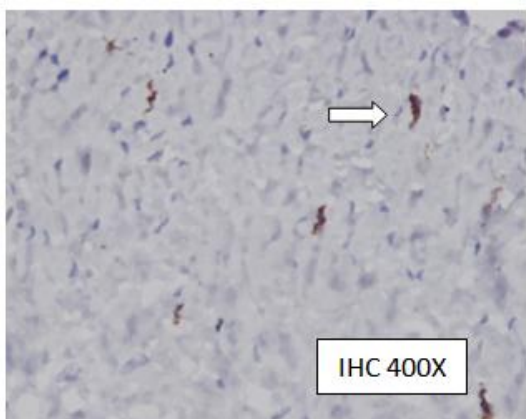


Figure 4: CD 117 Grade (2+) Interstitial Cells of Cajal (ICC)

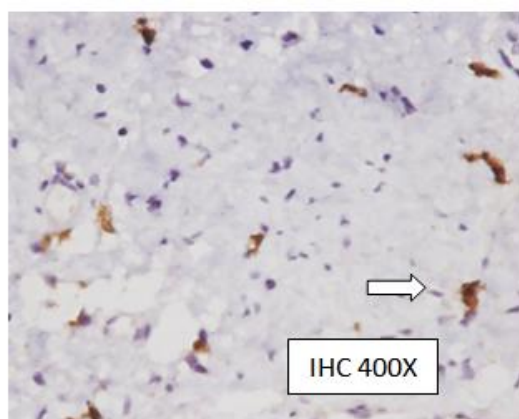


Figure 5: CD 117 Grade (3+) Interstitial Cells of Cajal (ICC)

Pre-Operative and Post-Operative APD mean value was 15.05 and 12.60 respectively and **p-value was 0.000 which was significant**. Mean value of APD 1 Month vs 3 Month was 12.60 and 10.50 in Pre and Post operative finding whose **p-value was 0.000 which was significant**.

Table 5: Comparison of Antero-posterior Diameter (APD) of Pelvis in Ultrasonography.

| | PRE-OPERATIVE | | POST-OPERATIVE | | T | p-value | 95% Confidence Interval of the Difference | |
|----------------------|---------------|------|----------------|------|-------|---------|-------------------------------------------|-------|
| | Mean | SD | Mean | SD | | | Lower | Upper |
| APD | 15.05 | 1.85 | 12.60 | 2.06 | 6.691 | 0.000 | 1.684 | 3.216 |
| APD-1month vs 3month | 12.60 | 2.06 | 10.50 | 1.28 | 6.185 | 0.000 | 1.389 | 2.811 |

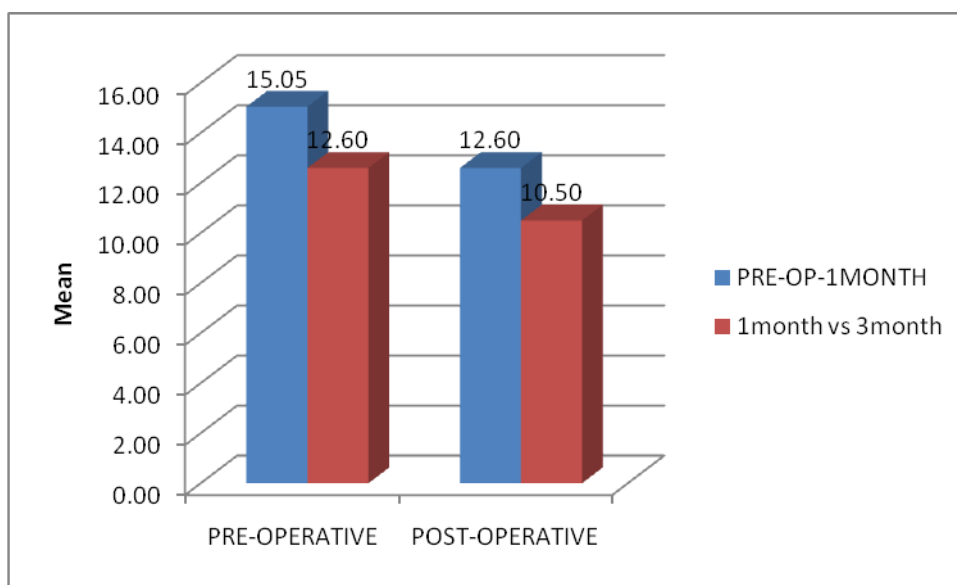


Fig-6 Comparison of Antero-posterior Diameter (APD) of Pelvis in Ultrasonography

IV. Discussion

Our study group consists of PUJO patients of different age and different time of pathology duration as well. The time of pyeloplasty and obtaining a PUJ sample was determined by the decreased renal function on renal scintigraphy. We cannot exclude the influence of PUJO duration on ICC expression. Possibly a chronic course of disease with exacerbations or even acute PUJ obstructions may induce ICC expression changes.

Several open and minimally invasive surgical techniques are used for the treatment of PUJO. Although open surgery remains the gold standard, with a success rate as high as 97%, the overall success rate in the present study was 75%. The role of surgical technique and histopathological pattern of the PUJ in surgical success remains unclear. Many studies have compared the histopathological pattern of normal and obstructed PUJ segments, but none have examined the role of the histopathological pattern of PUJO segments in surgical success. Ours is one of them to investigate the role of the histopathological pattern of PUJO segments in surgical success. Occasionally, some patients have a poor postoperative outcome with poor drainage or deteriorating

renal function necessitating redo surgery. One of the postulates of this study is that adequate ICC is required for a functioning Pelviureteric junction.

It is well known that ICC is required to generate smooth muscle electrical slow waves. ICCs are located between nerve endings and smooth muscle cells, so they can transmit signals from neurotransmitters and take part in neurotransmission^[8]. ICCs may act as pacemakers or they can take part in the neurotransmission between nerves and smooth muscle cells. Similar observations have been made in other tubular organ with peristalsis.^[9-15]

Some researchers maintain that the changes in the expression of c-kit-positive ICCs are the primary causes of PUJO, which is suggested by the decreased density of ICCs observed in a number of studies.^{[6][16]}

Yang,^[6] in his publication from 2009, similar to Solari et al^[16] demonstrated changes in the number of ICCs regarding the expression of ICCs in intrinsic PUJO and controls with Wilms' tumor. Yang was, however, much more careful in suggesting that these disorders are the original cause of PUJO. In his discussion, they reported that a reduction of the number of ICC may play an important role in the etiology and pathogenesis of PUJO.

The study by Alper Eken^[17] used a similar grading system as Senol *et al.*^[18]. They reported 74.3% patients with few cells in ten HPFs. They concluded that in PUJO, a decrease in the number of ICC, as well as the changes in the morphologic structure of the ICC, indicates that these cells have a role in the pacemaker system and are associated with ureteral peristalsis.

In the study done by C. Senol *et al.*^[18], ICC in the PUJ were graded as rare (0–3 cells/10 HPF), few (4–6 cells/10 HPF), and many (≥ 7 cells/HPFs). Nearly 68.4% of cases in their study were graded as rare which was similar to this study where 60% of cases were graded as negative(0-2) and 1+(3-5).

Male to female ratio in our study was 4:1, which is comparable to 2.55:1, as reported by Palmer et al.^[19] and 6.5:1, as reported by Jain et al.^[20] In 12 (60%) children the left kidney was affected and in 8 (40%) the PUJO was on the right side, which is comparable to study of Palmer et al.^[19] in which UPJO occurred more frequently on the left side (59.3%) and in Jain et al.^[20] who reported that left kidney was affected in 63.3% of children. However, as we have only twenty patients in our study, inference of ratios based upon our study is not justified.

Pre-operative and post-operative blood pressure was monitored. Pre-Operative mean BP was 74.20 and 52.60 for Systolic and Diastolic respectively. Post-Operative mean BP was 17.52 and 9.78 for Systolic and Diastolic respectively. P-value for systolic and diastolic blood pressure was 0.000 and 0.002 respectively. **P-value for BP is significant.**

de Waard D et al^[21] concluded and confirms that hypertension should be looked for in patients with dilated or obstructed upper urinary tracts, and considered an indication for surgery. In the vast majority of cases relief of obstruction cures hypertension.

Preoperative and postoperative kidney differential function and GFR was assessed. Pre-Operative mean KDF and GFR was 28.38 and 22.26 respectively. Post-Operative mean KDF and GFR was 35.48 and 32.65 respectively. **P-value for KDF and GFR was 0.000 and 0.000 respectively which is significant.** Mean value of Difference in KDF was 1.06, 10.29, 4.43 and 6.00 in Grade Negative, 1+, 2+ and 3+ respectively. **P-value was 0.003 which is significant.**

The present study is the study which was done to find a correlation between ICC in the PUJ and surgical outcome in pediatric age group. Patients underwent DTPA scan in pre and the postoperative period. Difference between preoperative and post-operative DTPA were compared and were divided into two groups. Sixteen patients were free of obstruction and had improved renal function and were classified as Group I. Four patients did not improve and they were placed in Group II. Four patients had a poor outcome after pyeloplasty; they had no ICC at the resected specimen. All the 4 patients with a poor outcome had negative grading at the PUJ. Chi-square value was 15 and **p-value was 0.002 which is significant.** P-value of Difference in KDF and GFR was 0.000 and 0.029 respectively which is statistically significant. This proves our hypothesis that ICCs has strong correlation with postoperative outcome.

V. Conclusions

Our study is one of the first of its kind in children, on 20 consecutive cases of pediatric PUJO which recorded various features such as demographic, morphological, clinical, operative and outcome in the study population. Our study correlates the status of ICC in PUJ with the outcome of pyeloplasty in pediatric patients. Tissue was taken from one place (Pelvi-ureteric junction) and ICC was measured once in one patient which is more cost effective. During surgery excessive dissection should be avoided and vascularization should be preserved: the resected amount should be in proper amount and the anastomosis should be tension free with dependent drainage. Further larger studies are required to confirm the role of ICC in the pathogenesis of PUJO and prognosis after pyeloplasty on long term basis. Once established as a marker for postoperative success it can be used to counsel, prognosticate the family members regarding the outcome of the surgery at the first

postoperative day. Further investigations will provide knowledge about ureteral motility and PUJ pathophysiology, and it will open up new horizons in the management of these common urological diseases in children

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