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Efficacy of tolvaptan in reduction of kidney cyst volume and restoration of kidney function in ADPKD in tertiary care hospital

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ABSTRACT

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a frequent cause of end-stage renal disease. Despite improvements in blood pressure and conventional treatment, there seems not any significant impact on the need for renal replacement therapy in these cases. Inhibition of cyclic adenosine monophosphate pathway by tolvaptan was efficient in preclinical/animal studies and in clinical studies involving ADPKD patients; tolvaptan (vasopressin V2 receptor antagonist) has been recently released in the market to delay disease progression. **Aims and Objectives:** The aim of this study is to evaluate the role of tolvaptan in reduction of total kidney volume (TKV), total renal cyst volume, and decrease of progression of renal impairment and restoration of kidney function. **Materials and Methods:** We have screened 60 cases, of whom 54 were assigned to either tolvaptan group (36) or placebo (18). Overall 36 cases completed the trial (24 from tolvaptan group and 12 cases from placebo group). Estimated GFR (glomerular filtration rate) calculated and stages were noted. TKV and total cyst volume measured by ultrasonography at days 0, 30, 90, and 180 along with other vitals. The total number of patients enrolled was randomly divided into two broad groups by concealed envelop technique: Intervention group (with tolvaptan) and placebo or control group. The intervention group was given tolvaptan along with standard conventional management for ADPKD as per relevant stages. The placebo group was given placebo tablets with same size and color (multivitamin tablet) along with standard conventional management for ADPKD as per relevant stages. The periodic estimation of cyst volume, kidney volume, serum creatinine level, and estimated glomerular filtration rate recorded and analyzed with ANOVA method with confidence interval 95%. **Results:** Analysis of the data showed fewer ADPKD-related events per cases of follow-up with tolvaptan than with placebo. These results were confirmed by the analysis of the 1st time and after 6 months of study. Our data suggest that increase of TKV and total cyst volume was less in tolvaptan group as compared to placebo group. Overall, treatment effect on the growth of TKV was 0.219% per month with a $P<0.0001$. **Conclusions:** The administration of tolvaptan for 6 months was associated with slowed kidney growth and functional decline and with a reduced frequency of ADPKD-related complications among patients with a relatively preserved GFR.

Key words: Kidney cyst; Complication; Prognosis; Tolvaptan; Total cyst volume

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disease, characterized by the progressive deterioration of normal kidney tissue, development of chronic kidney disease (CKD), and the onset of end-stage renal disease (ESRD).[1] The disease is characterized by progressive cysts formation, especially in the kidneys, leading to massive kidney enlargement, pain, and hematuria and approximately 70% develop ESRD between their 4th and 7th decades of life. ADPKD occurs worldwide and in all races.[2,3]

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The disease is caused by mutations in the PKD1 or PKD2 genes that encode the integral membrane proteins, polycystin-1 and polycystin-2. Mutations in PKD1/PKD2 alter intracellular calcium homeostasis and, in turn, attenuate cyclic intracellular. Cyclic adenosine monophosphate (cAMP) levels are thought to act through calcium-mediated regulatory pathways, including protein kinase A and its downstream effectors, to induce cyst growth in ADPKD.[4,5] On the basis of these observations, therapeutic interventions that lower intracellular cAMP levels might be expected to have significant benefit in ADPKD.[6] The antidiuretic hormone arginine vasopressin is a major inducer of cAMP production in the distal nephron through its interaction with the vasopressin V2 receptor (V2R) and, hence, has been a major focus of recent studies. A recent study showed that tolvaptan, a vasopressin V2R antagonist, decreased total kidney volume (TKV) growth and estimated glomerular filtration rate (GFR) loss in ADPKD with creatinine clearance ≥60 mL/min.[7] In rodent models, V2R antagonism inhibited disease development and either halted or caused regression of established disease.[8] Finally, in the pivotal Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes 3:4 Trial (TEMPO 3:4; ClinicalTrials.gov identifier: NCT00428948), long-term treatment with tolvaptan significantly decreased kidney growth and kidney pain, while slowing the decline in kidney function.[9] In patients with ADPKD with decreased kidney function, response to tolvaptan is lower for TKV, urinary volume, and osmolality, but larger for fractional free water clearance. This latter finding suggests that patients with ADPKD with lower GFRs might benefit from long-term treatment with tolvaptan, as has been observed for patients with preserved GFRs.[7,10]

Aims and objectives

- To evaluate the percentage of total kidney volume volumetrically measured by CT (percentage per 6 month) is to be compared before and after administering tolvaptan to same patients.
- To study changes in total cystic volume, volumetrically and to be compared before and after administering tolvaptan to same patient
- To analyse the percentage change in EGFR will be compared with patients.
- The efficacy of response to tolvaptan will be evaluated.

MATERIALS AND METHODS

A prospective concurrent parallel double-blinded randomized controlled trial study was conducted at the Department of General Medicine of a tertiary care hospital, from January 2019 to February 2020, after clearance from the Institutional Ethics Committee (NO/NMC/10005). Sixty patients who are diagnosed as ADPKD (both normal and impaired kidney function) admitted to this hospital are included in this study and informed consent has been taken. A total of 54 diagnosed ADPKD patients enrolled in the study with inclusion criteria of age limit 18–50 years and having kidney volume of 750 ml and above. The greatest difficulty is to make the diagnosis in patients younger than 30 years and without a family history of the disease, since the formation of renal cysts depends on the age, and the disease may be caused by new mutations in up to 15% of cases. In patients suspected of ADPKD, the presence of renal cysts on ultrasonography allows the diagnosis,[5] depending on the age:

1. Patients aged 15–29 years, with three or more unilateral or bilateral cysts (sensitivity 0.695, specificity 1; positive predictive value of 1, and a negative predictive value of 0.780),
2. With a likelihood ratio of 3.27; patients aged between 40 and 59 years, with two or more unilateral or bilateral cysts (sensitivity 1, specificity of 0.978; positive predictive value of 0.972, and negative predictive value of 1)
3. Patients aged 60 years or older, with four or more cysts in each kidney (sensitivity of 1 and specificity of 1).

Patients with diabetic nephropathy, simple renal cyst, hydronephrosis, pyelonephritis, renal malignancy, hepatic diseases, and prior use of tolvaptan for any cause were excluded from enrolment. The demographic data and patient history, physical examination, family history, medicine, and treatment histories are noted down after taking informed consent. Relevant hematological and biochemical investigations were done. Estimated glomerular filtration rate (eGFR) calculated and stages are noted. TKV and total cyst volume measured by ultrasonography at days 0, 30, 90, and 180 along with other vitals. The total number of patients enrolled was randomly divided into two broad groups by concealed envelop technique, intervention group (tolvaptan group) and placebo group. Eighteen patients dropout during study. A total of 36 patients completed the study till 6 months (24 from tolvaptan group and 12 from placebo group). Among these 36 patients, 24 patients are male (16 from tolvaptan group and eight from placebo group) and 12 patients are female (eight from tolvaptan group and four from placebo group). The age of the male patients is between 22 and 50 years, whereas the age of the female patients is between 18 and 50 years. The intervention group was given tolvaptan along with standard conventional management for ADPKD as per relevant stages.

The placebo group was given placebo tablets with same size and color (multivitamin tablet) along with standard

conventional management for ADPKD as per relevant stages. Among these 36 patients, 12 patients in CKD Stage I (eight from tolvaptan group and four from placebo group), 18 patients in CKD Stage II (12 from tolvaptan group and six from placebo group), and six patients are in CKD Stage III (four from tolvaptan group and two from placebo group). Patients belongs to placebo groups later on offered tolvaptan after completion of their study period so that they were not been deprived of the drug.

The periodic estimation of cyst volume, kidney volume, serum creatinine level, and eGFR recorded and analyzed with ANOVA method with confidence interval 95%. Descriptive statistics were done with variables including TKV, total cyst volume and age, sex using the mean, SD, frequencies, and percentage. Pearson's correlation coefficient was calculated among TKV, total cyst volume for all the patients, and also dividing the data set into three groups according to their CKD stage.

Statistical analysis

Descriptive statistics: Continuous variables including TKV, total cyst volume, and age were described using the mean, SD, frequencies, and percentage were calculated for categories of sex to investigate the correlations among TKV and total cyst volume, Pearson's correlations coefficient were calculated by visits. Visits are designed as day 0, day 30, day 90, and day 180 during the period of the project for all the patients and also dividing the data set into three groups according to their CKD stage and corresponding plot to visualize the data is shown using bar charts, boxplots, and histogram, to show the effects of two treatment groups when stage of CKD is taken care of repeated measure analysis of cyst volume: This analysis uses a linear model to the growth of TKV and total cyst volume with respect to the baseline day with explanatory variables: CKD stages, months from baseline, treatment group, and corresponding interactions and the variables age and sex. The coefficients and p-values of corresponding explanatory variables and the analyses have been determined by rerun with these selected set of explanatory variables and repeated the estimated coefficient with SD, ANOVA tables. 95% Confidence intervals for the corresponding coefficients are accepted. Estimated equation for various settings has been shown, and the ROM placebo corresponding figures are attached to represent the whole analyses.

RESULTS

Fifty-four patients were assigned to either tolvaptan group (36) or placebo (18) overall 36 patients completed the trial

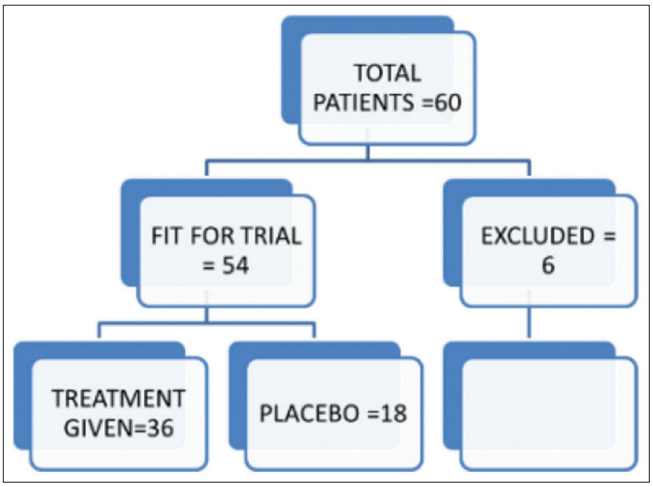

Figure 1: Demographic presentation of all screened cases

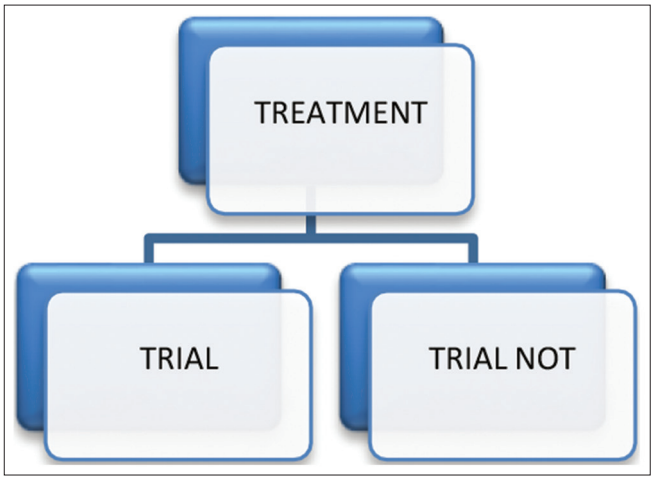

Figure 2: Demographic presentation of cases who were assigned in treatment with tolvaptan

(24 from tolvaptan group and 12 patients from placebo group) and nearly half of the patients (12 from tolvaptan group and six from placebo group) discontinued the study drugs because of early withdrawal and a lack of measurable follow-ups (Figures 1 and 2).

Primary end point

Over the period, the TKV increased by per year (95% CI) with tolvaptan versus per year with placebo. Tolvaptan changed the rate of growth by −1.3% points per year in CKD Stage I, −0.6% points per year in CKD Stage II, and −1.2% points per year in CKD Stage III, pre-specified subgroup analysis showed that tolvaptan had a beneficial effect on TKV (Figure 3) in all subgroups with patients stratified according to sex, age, and estimated eGFR level at baseline.

Secondary end points

The slope of kidney function (as assessed by means of the reciprocal of serum creatinine level) with a slope of treatment with Tolvaptan in following doses like−2.5 (mg

per ml) ^−1 per year as compared to −3.4 (mg per ml) ^−1 per year. This treatment effect was confirmed by comparing data from pre-treatment baseline to post-treatment visits (Figures 4-6). These effects are nominally greater among patients with hypertension and diabetes mellitus.

Clinical progression

Analysis of the data showed fewer ADPKD-related events per persons of follow-up with tolvaptan than with placebo. These results were confirmed by the analysis of time to first events. After 6 months of study, our data suggest that increase of TKV/total cyst volume was less in tolvaptan group as compared to placebo group (Figure 7).

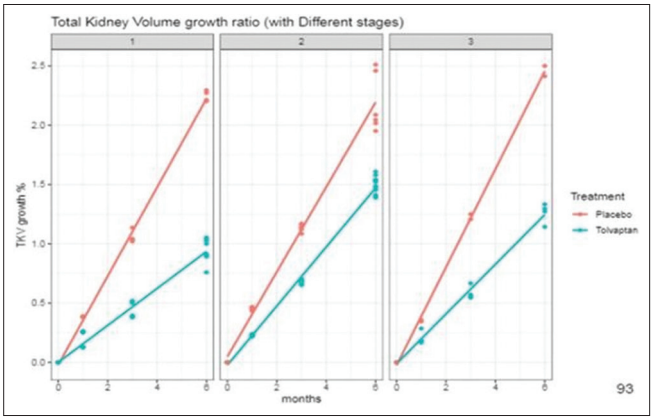

Figure 3: Total kidney volume growth ratio in intervention group & placebo group

Overall, treatment effect on the growth of TKV was −0.219% per month with a P<0.0001 (95% CI) whereas the same for total cyst volume was −0.5292% per month with a P<0.0001 (95% CI); the negative values signify that with the application of the study drug, the growth decreases in general. Also looking at the equations (or the coefficient), we can calculate the group-wise treatment effect per month also (e.g., the treatment effect by tolvaptan on growth rate of TKV for Stage I CKD would be 0.155–0.374). For Stage II CKD, it would be 0.284–0.357, for Stage III, it would be 0.208–0.413. The treatment effect for growth rate of total cyst volume for Stage I CKD would be 0.155–0.688, for Stage II CKD 0.222–0.570, and for Stage III CKD 0.187–0.459. (All values are written in percentage increase of corresponding quantity per month).

Correlation analysis

The total increase in kidney volume TKV and cyst volume (TCV) is very much correlated, which is very likely at a first glance. TKV and total cyst volume look extremely right skewed but after dividing the data according to the CKD staging of the patients; the TKV and total cyst volume seem much less skewed (Figure 8).

In this study, the correlation between TKV and total cyst volume was very strong and positive in the range of 0.886–0.985. This study also shows the correlation values according to different visits and CKD staging.

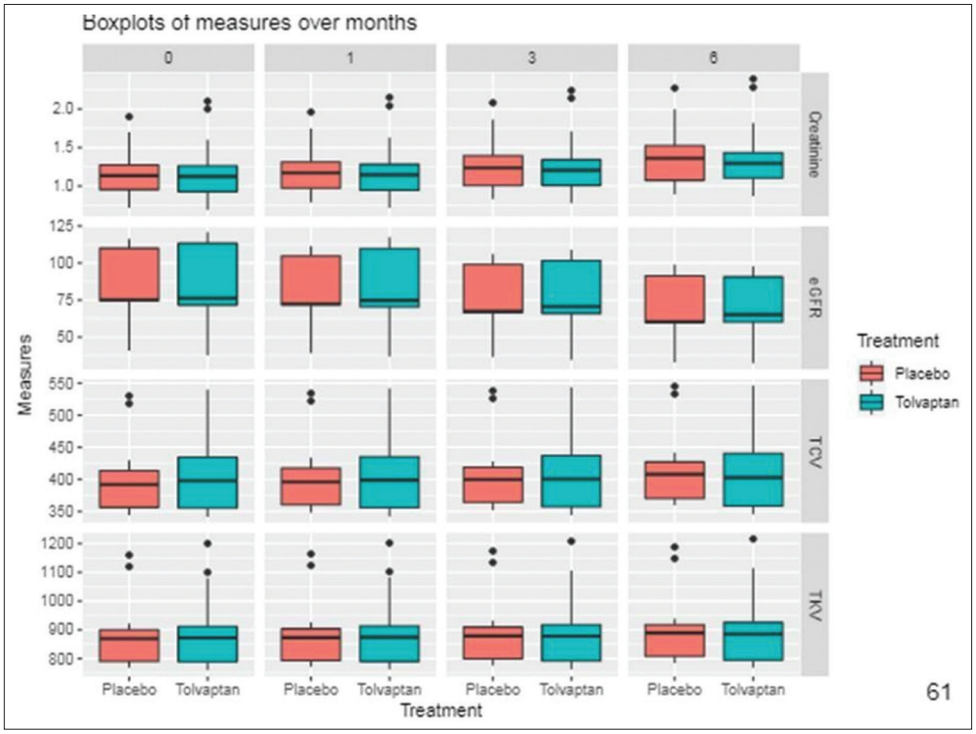

Figure 4: Boxplots of measures effect of tolvaptan

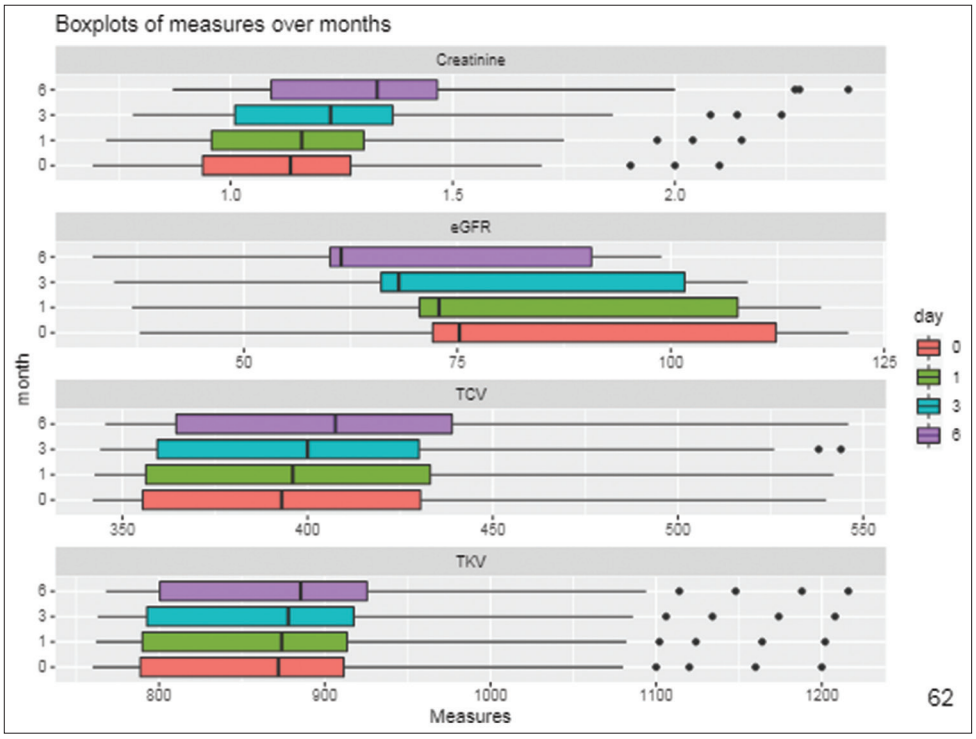

Figure 5: Boxplots of measures tolvaptan treatment effect over months

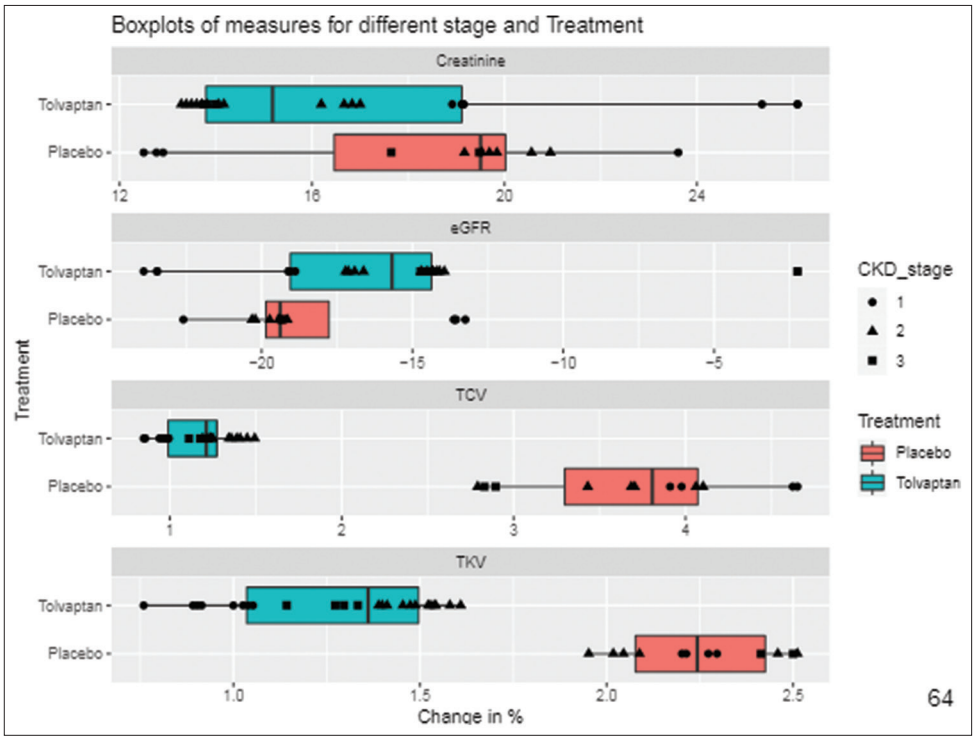

Figure 6: Boxplots of measures effect on different stage over months

Relative treatment effect

Rate of change of TKV by CKD stage: The TKV growth with respect to the treatment group separately for each group of CKD is studied (Figure 9). Then, the means for each group and treatment effects for each group with 95% CI are reported. There could be still some modifications which could have further analyzed data in a more intuitive and possible way.

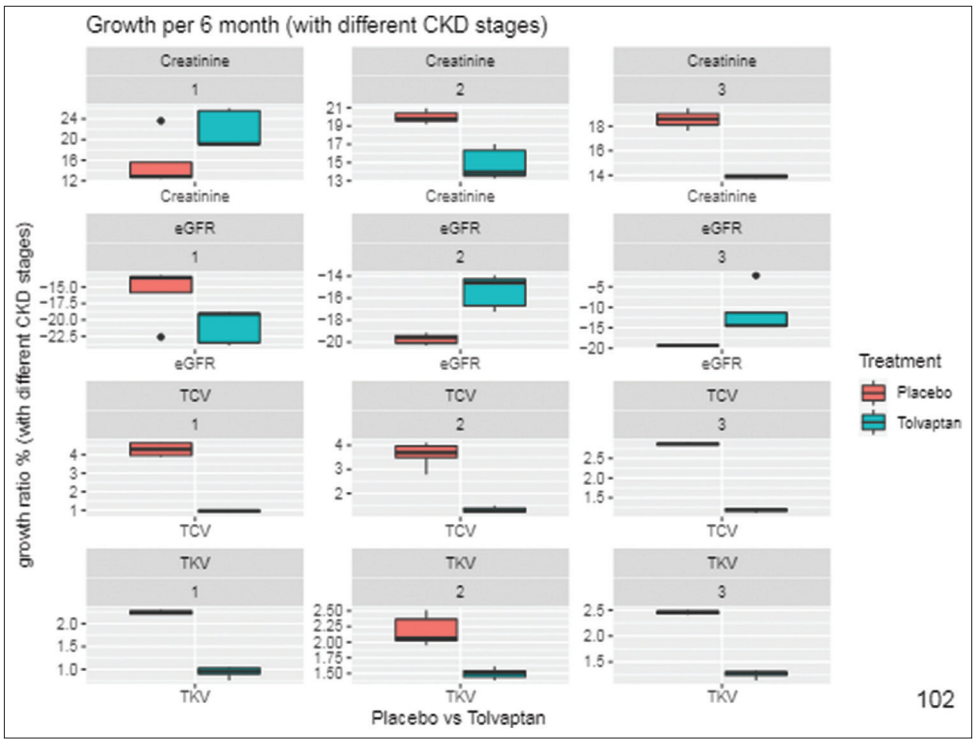

Figure 7: Data after 6 months of study

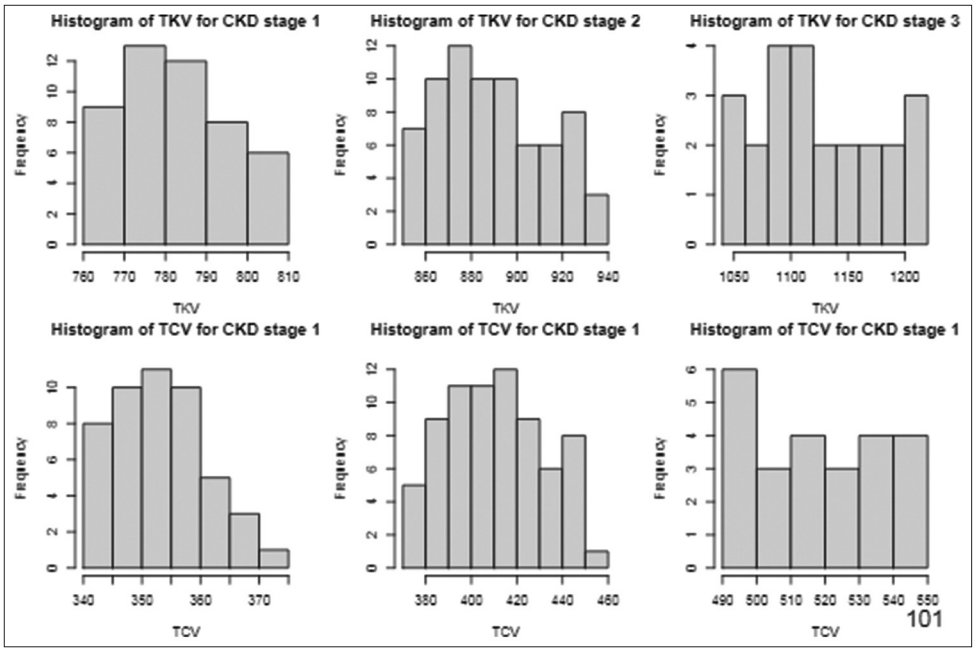

Figure 8: TKV & TCV in different stage of CKD

Effect of tolvaptan on rate of eGFR decline by CKD staging

After 6 months of the study, data suggest that eGFR always decreased, but there was less decrease in tolvaptan group. Figure 10 shows that in Stage II and Stage III CKD, tolvaptan works better to keep eGFR stable, but the data show that this is not same for the patients in CKD Stage I group. However, as the sample size is not very big, it is hard to tell conclusively about significant effect of tolvaptan for some of the groups. Effect of tolvaptan on rate of creatinine level decline by CKD staging: Similar to the eGFR study, our data suggest that creatinine always increased from baseline to 6-month period. However, there was less increase in tolvaptan group for most of

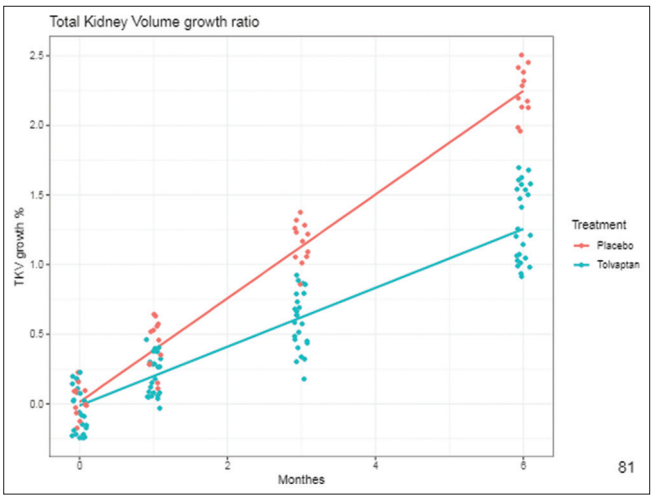

Figure 9: Rate of change of TKV by CKD stages

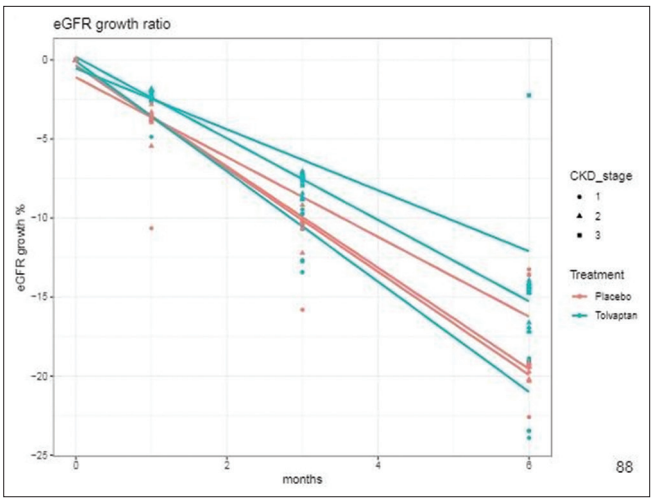

Figure 10: After 6 months study of eGFR

the cases. The table shows that in CKD Stages II and III, tolvaptan works better to keep creatinine stable but again the data also suggest that this is not the case for CKD Stage I.

DISCUSSION

The administration of tolvaptan for 6 months was associated with slowed kidney growth and functional decline and with a reduced frequency of ADPKD-related complications among patients with a relatively preserved GFR. The finding is consistent with the previous studies of Gansevoort et al.[11] The results of the analysis show that treatment effects are more pronounced in during CKD Stage II and Stage III patients compared to CKD Stage I probably because CKD Stage I group included more patients with milder slowly progressive disease and these findings were very similar to Bhatt et al.,[12] which study also shows better effect of tolvaptan on Stage II and III patients.

The reduction in the rate of kidney growth in the tolvaptan group compared to the placebo group accompanied by a slower rate in the decline of EGFR reflected by lower on treatment EGFR slopes in patients with CKD Stage II and Stage III. Tolvaptan enhanced hydration is known to exert an acute reversible renal hemodynamic effect likely through inhibition of tubule glomerular feedback, Boertien et al.,[8] and Gabow et al.,[13] also report about inhibition of tubule glomerular feedback. Because this could have affected the EGFR slope on treatment, a sensitivity analysis comparing the change in EGFR values from pre-treatment baseline to post-treatment visits has been carried out in the study group. The results of the analysis show that treatment effects are more pronounced in during CKD Stage II and Stage III patients. This analysis showed a statistically significant, slower decline of eGFR not only in patients with CKD Stage II and Stage III but also those in CKD Stage I treated with tolvaptan.[14] Katsumata et al., also showed slow decline of eGFR in all stages of CKD. The large treatment effect of tolvaptan on TKV, total cyst volume, and eGFR in the patients with CKD Stage III is reassuring, at least, as it relates to progression throughout CKD Stage III, given concern that tolvaptan could become less effective as the disease progresses consistent with its effect on kidney enlargement (including both kidney volume and cyst volume) and eGFR decline, tolvaptan delayed the progression of the disease of patients with CKD Stage II and Stage III at baseline to more advanced CKD stages at the last follow-up visits compared to the patients in CKD Stage I. Our findings provide a glimpse into the wide variation in the rates of renal volume evolution in patients with ADPKD. It is clear that in patients with mature polycystic kidneys, the increase in renal volume is highly correlated to the cyst volume.

Our findings also establish that renal cyst and kidney enlargement is a continuous process in most of the patients with ADPKD, like study of Reed et al.[16] Unexpectedly, we found that the kidneys behaved as though the cysts within them enlarged at a steady rate specific to the patients. Thus, it would appear that the most of the pairs of polycystic kidneys behave as if the cysts within them were programmed to grow at a uniform rate although exceptions exists in which regional factors may stimulate some cysts to grow at a faster rates than others. Cross-sectional studies have demonstrated considerable heterogeneity in the size of the cysts within and between kidneys.[16] Despite this heterogeneity, overall renal growth (including TKV and total cyst volume) appeared to be coordinated within and between kidneys of individual patients.

The absolute and fractional rates of renal enlargement are directly associated with absolute renal volume. The previous studies[17,18] that used USG/CT to determine TKV

have suggested that the cysts are major factor contributing to renal insufficiency in ADPKD.

The study was designed to include patients with normal function who were at high risk for renal insufficiency to demonstrate a clear-cut reduction in the GFR at some point during the study. Longer follow-up/larger number of patients would have been required to detect similar effects in patients with CKD who had less advanced/possibly less severe disease.

Limitations of the study

The main strength of this study was the tertiary care hospital set-up, having infrastructure supportive enough to enable us to study kidney cyst volume and restoration of kidney function in ADPKD with diverse mode of presentation. We were able to do the necessary investigations in every case. However, we were severely constrained by limited study duration that leads us to have small sample size.

CONCLUSIONS

The results of the analysis show that treatment effects are more pronounced in during CKD Stage II and Stage III patients compared to CKD Stage I. This study showed a statistically significant, slower decline of eGFR in patients with CKD Stage II and Stage III, and also those in CKD Stage I treated with tolvaptan. The large treatment effect of tolvaptan on TKV, total cyst volume, and eGFR in the patients with CKD Stage III is reassuring in patients with mature polycystic kidneys, the increase in renal volume is highly correlated to the cyst volume. The absolute and fractional rates of renal enlargement are directly associated with absolute renal volume.

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Author's Contribution:
AN- Concept and design of study, acquisition of data, and prepared first draft of manuscript; **SjS-** Acquisition of data and revising it critically, interpreted the results; **SM-** Reviewed the literature and revision of the manuscript; and **SmS-** Coordination, statistical analysis, and interpretation.

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