EFFECTIVENESS OF IMMUNOSUPPRESSANTS ALONG WITH ACEI/ARBS IN TREATING PROTEINURIA IN PATIENTS WITH SOLITARY KIDNEY POST NEPHRECTOMY

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ABSTRACT

Objective: To ascertain the effectiveness of immunosuppressants along with ACEI and /or ARBS in proteinuria in patients with solitary kidney post nephrectomy.
Study Design: Prospective quasi-experimental study.
Place and Duration of Study: Combined Military Hospital Peshawar and Multan, from 2010 to 2016.
Subjects and Methods: The sample population comprised of 07 cases of post nephrectomy solitary kidney developing proteinuria from 2010-2016 reporting to hospitals. Patients were given initially ACEI and/or ARBS to lower proteinuria for three months. They were followed up to see for complete or partial remission. Deltacortil 1mg/kg max 60mg/day along with ACEI and /or ARBS was added to patients who didn't go into remission.
Results: Out of 7 patients, 3 (42.9%) were males and 4 (57.1%) were female patients. Addition of deltacortil 1mg/kg max 60mg/day along with ACEI and /or ARBS reduced proteinuria to less than 1 gram in 3 patients (2 males and 1 female) and less than 300mg in 4 patients (1 male and 3 females).There was a reduction in the mean 24hrs urinary protein excretion as a whole from the baseline 2.33 ± 0.84 g/24 hrs to 0.48 ± 0.33 g/24 hrs. Remission was achieved on the average in three months and maintenance on tapering doses for 12 months. Cyclosporine was used in three cases who relapsed on tapering steroids and remission was achieved with 5-10mg steroids and 100-200mg of cyclosporine.
Conclusion: Non respondent patients with solitary kidney developing proteinuria being treated with ACEI and /or ARBS had good chance to lower their proteinuria with steroids. Relapses even with steroids responded to cyclosporine.

Keywords: Immunosuppressants, Post nephrectomy, Proteinuria, Solitary kidney.

INTRODUCTION

Pakistan is a developing country with a very high prevalence of CKD[1]. Hemodialysis being an expensive mode of treatment poses a great burden on our health care budget[2,3]. Among the wide variety causes of CKD. FSGS has emerged as the most common cause of GN-related ESRD[4] with 2.3% attribution compared with 0.4% for membranous GN and 0.3% for IgA nephropathy according to one study.

FSGS is not a single disease entity rather a histological diagnosis. Secondary forms of FSGS may result from reduced renal mass or hyperfilteration (hypoplastic kidney, reflux nephropathy), other underlying renal diseases, longstanding hypertension, or obesity. FSGS is associated with worse prognosis and spontaneous complete remission is rare, with progression to ESRD over 5-10 years in patients having nephrotic range proteinuria. Literature review revealed five-year renal survival rates of 60 to 90%, and 10-year renal survival rates of 30 to 55%[5,6]. Thus, attainment of remission is the ultimate goal, and concentrated efforts to implement cost-effective strategies to prevent and preserve renal function should be advocated especially in our setup.

Solitary kidney post nephrectomy, has been the most frequent and common causes of secondary FSGS, and adaptive response occurred in such cases because of reduced renal mass leading to compensatory intraglomerular hyper-

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tension and hypertrophy in the remaining glomeruli[7], ultimately leading to FSGS over a period of years and this effect is dose dependent with greater risk of developing proteinuria, glomerulosclerosis and progressive renal failure in those patients who lost greater than 75% of renal mass[8]. RAAS antagonism therapy addresses hemodynamic alterations in solitary kidney post nephrectomy by causing dilatation of efferent arterioles leading to reduction in intraglomerular pressure and inhibition of angiotension II including glomerular hypertrophy and fibrosis[9]. ACEi/ARBs both reduce proteinuria and blood pressure in solitary kidney post nephrectomy but very rarely induces remission without immunosuppression[10-12]. Glucocorticoids have direct effect on podocyte by increasing the number of myeloid suppressor cells which downregulate T cell function[13,14] and their use in patients with solitary kidney with persistent proteinuria despite being on supportive therapy have not been under taken so far to definitely establish their role and efficacy in preventing renal failure, but prior studies on the combination of an immunosuppressive agent (mycophenolate mofetil) to the ACE inhibitor (or an angiotensin II receptor antagonist) in decreasing hematopoietic cell infiltration and proteinuria have been documented[15,16].

As there has always been a surge of interest to develop new treatment strategies for reducing proteinuria so this study tests the hypothesis that combination therapy of steroids and ACE inhibitors and ARBs is effective in reducing proteinuria in patients with solitary kidney postnephrectomy. There have been encouraging results from a prospective uncontrolled study of the treatment of primary FSGS with ACE/ ARB combination therapy with steroids in adults 12 however no such study available on this combination in secondary FSGS to date.

SUBJECTS AND METHODS

This was a prospective quasi-experimental study carried out in two tertiary care hospitals from 2010 to 2016, in which we enrolled 07 cases by non-probability purposive sampling, age between 18-50 years, with secondary FSGS post nephrectomy having proteinuria greater than 1 gm but with normal serum creatinine between 2010-2016. Exclusion criteria were the patients less than 18 years of age or having other causes of secondary FSGS like genetic causes, obesity, those who did not consent to or those with a past or current history of any psychiatric illness or delirium or who were pregnant or were undergoing dialysis, or previously been treated with calcineurin inhibitoror steroids. The mean age of this patient group was 35.4 ± 9.10 years (table-I). There were three males and four females. Baseline renal profile and 24 h urinary protein excretion was employed before the start of immunosuppressive treatment and ACEi/ ARBs. Mean 24 h urinary protein excretion of 2.33 ± 0.84 g (table-II). Consent for treatment with steroids and ACE inhibitors/ARBs was obtained from patients after a full explanation of the treatment options and potential side effects. Patients were given initially ACEI and /or ARBS to lower proteinuria for three months. They were followed up at the end of three months to see reduction in proteinuria. Complete remission was defined as proteinuria less than 200-300 mg/day and partial remission as 50% reduction in proteinuria and relapse as return of proteinuria who has undergone complete or partial remission. Deltacortil 1mg/kg max 60mg/day along with ACEI and /or ARBS was added to the patients who did not respond. Remission was achieved in three months on average but cyclosporine was added in 3 cases for relapse. Hepatitis B and C, and HIV were excluded by serological tests in all patients before treatment with immuno-suppression.

Statistical Analysis

Characteristics of participants were described by using the descriptive statistics. Chi-square was used to determine between-group variances in categorical correlates significance. All statistical analysis was performed using Statistics Package for Social Sciences (SPSS) version 20.0. Paired t-test was used and

differences between groups were considered significant if *p*-values were less than 0.05.

RESULTS

A total of 07 patients of solitary kidney postnephrectomy having proteinuria >1gm were approached to participate in the study. Out of 7 patients, 3 (42.9%) were males and 4 (57.1%) were female patients. Initial treatment with ACEI and /or ARBS for three months without significant reduction in proteinuria taken as less than 50% or less than 300mg had been given an addition of deltacortil 1mg/kg max 60mg/day. This regimen reduced proteinuria to less than 1 gram in 3 patients (2 males and 1 female) and less than 300mg in 4 patients (1 male and 3 females).There was a reduction in the mean 24 hrs urinary protein excretion as a whole from the baseline 2.33 ± 0.84 g/24 hrs to 0.48 ± 0.33 g/24 hrs. The mean time of remission was achieved on the average in 03 months and maintenance on tapering doses for 12 months. Cyclosporine was used in three cases who relapsed on tapering steroids and remission was achieved with 5-10mg steroids and 100-200mg of cyclosporine.

Table-I: Demographics of patients with proteinuria in solitary kidney post nephrectomy.

Variables	Values
Number (Male: Female)	7 (3:4)
Age (years)	35.4 ± 9.10 years

Table-II: Results of treatment with steroids for proteinuria in solitary kidney post nephrectomy.

Variables	At presentation	At follow up	*p*-value
Urinary protein excretion (g/24hrs)	2.33 ± 0.84	0.48 ± 0.33	*p*-0.003

DISCUSSION

We present the unique and the first study so far published investigating the safety and efficacy of prednisolone and ACEi/ARBs in treating proteinuria in solitary kidney post nephrectomy with complete remission in 04 patients and partial in 03 patients with a mean reduction in proteinuria 0.48 ± 0.33g/24 hrs. In comparison to the previous studies, role of ACEi/ARBs in reducing proteinuria and ultimately slowing the progression of kidney disease have been well documented[17], however data on combination therapy including steroids and ACEi/ARBs for primary FSGS available but for secondary FSGS, data is scarce and No randomized placebo controlled trial has been conducted in humans to definitively establish the value of glucocorticoids in preventing or delaying the progression to ESKD in patients with secondary FSGS, though studies and trials available in animal model.

FSGS represents a histological finding rather than a pathophysiological process in clinical practice, the distinction between primary and secondary FSGS is not always straight forward. Hypertension and proteinuria are also consistently demonstrated to be independent risk factors for the progression of renal damage in a patient with solitary kidney[18,19]. Attainment of a complete remission heralds a favourable prognosis with less than 15% of such patients developing ESRD. ACE inhibitors/ARBs contribute to efferent arteriolar dilatation and reduction in intraglomerular pressure by causing an increase in kinins and also glomerular hypertrophy and fibrosis[9]. However, prednisolone treatment especially reduced the numbers of CD4 ± vc cells. And T cells immune mechanism in the interstitium have important role in the progression of this disease to end-stage renal failure[20].

We hypothesize that the combination therapy of steroids and ACEi/ARBs will lead to a more sustained remission compared with ACEi/ARBs in patients of solitary kidney post nephrectomy similar to the patients with primary FSGS[21]. Patients attaining partial or complete remission have a much better chance of renal survival (approximately 80 versus <50% at 10 years in nonresponders and untreated patients. In one

analysis of 136, remission was associated with a 5-year survival off dialysis of 94%, compared with 53% if remission was not achieved[22]. Likewise, the slope of renal decline was significantly flatter in patients who achieved complete remission. In our study 04 patients went into complete remission.

Tapering of steroids after 03 months treatment course was associated with relapse in 03 cases and remission achieved with 100-200 mg of ciclosporin in consolidation with 5-10 mg of deltacortil. The optimal treatment regimen for such patients is also unknown and no randomized control trials have been conducted in the past on this topic. But it is hoped that extensive durations of treatment with steroids will result in a reduced rate of relapse but further studiesand more data and longer follow up are required to confirm this.

There may be concern that the use of immunosuppressive medications (steroid) will lead to an increased risk of incumbent complications and other adverse events. In our study, no such adverse event observed and steroid was also tapered after 03 months. While this regimen was well tolerated during the observation period, we cannot avoid those plausibility from claiming treatment-related side effects developing later on.

'Our study has several important limitations. It is single center study without external validation including fairly small number of patients, of short duration and lacking comparison. As a result, they were not able to assess the impact of immunosuppressive therapy on renal or patient survival. Hard endpoints such as CKD and mortality are infrequent, and require many years of follow-up. Furthermore, lack of clinical variables of interest, such as serum albumin (± increase following treatment response) and nonuniform reporting of outcomes (i.e. only proteinuria response and patients with normal creatinine) limit the conclusions drawn from this study. Thus, we would encourage researchers in the field to add all these variables in future trials in secondary FSGS post nephrectomy patients. Clearly, our study highlights the need that more effort in general is necessary to improve patient care (outcome) in such patients.

CONCLUSION

Non respondent patients with solitary kidney developing proteinuria being treated with ACEI and /or ARBS had good chance to lower their proteinuria with steroids. Relapses even with steroids responded to cyclosporine.

Further research is needed to assess effectiveness of steroids as first-line therapy in secondary FSGS patients post nephrectomy. A large randomized trial would be challenging with potential issues in recruitment and retention because ACEi/ARBs have been used as main treatment for decades for secondary FSGS. Good quality observational studies would be particularly suitable to measure the effect of steroids on renal survival in post nephrectomy FSGS population.

CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

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