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PARADOXICAL INCREASE IN CYSTATIN-C LEVELS IN CONVENTIONAL HEMODIALYSIS

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ABSTRACT

The conventional, low flux (LF) dialyser allows the removal of small molecular solutes like urea and creatinine. The removal of middle molecules (molecular weight between 500D and 60,000 D, which is nearly the size of albumin) is relatively low. Cystatin C has attractive characteristics as a representative middle molecule. ***Objective:*** *To determine per dialysis Cys C reduction ratio (RR) in low flux group and to compare it with urea, marker of dialysis adequacy.* ***Methods:*** *Thirty seven patients were subjected to conventional, low flux dialysis. Serum urea and Cystatin C were measured pre and post dialysis. Cystatin C was measured by latex enhanced Immuno turbidimetry.* ***Results:*** *The URR is72.273±14.686% in low flux group & the Cys CRR is -9.7 ± 6.7 %.* ***Discussion:*** *The paradoxical increase in Cystatin C in the low flux group shows the ineffective clearance of middle molecules by low flux dialysers which is associated with dialysis related morbidity & mortality. Hence, Cys CRR could be applied as a surrogate marker for the inadequacy of dialysis.*

KEY WORDS

Cystatin C, Middle molecules, low flux dialysis.

INTRODUCTION

The uremic syndrome is attributable to the progressive retention of a large number of compounds, which are called uremic retention solutes or uremic toxins. They interfere negatively with physiologic function. They include not only small plasma solutes, but also protein bound solutes and middle molecules [1] (molecular weight between 500D and 60,000D, which is nearly the size of albumin). Ineffective clearance of middle molecules results in dialysis related amyloidosis in long term dialysis patients. There is an increased incidence of carpal tunnel syndrome and osteoarticular lesions.

Development of erythropoietin resistance, dyslipidemia, especially decreased HDL cholesterol, increased triglyceride levels, and accumulation of advanced glycosylation end-products which have been implicated in the pathogenesis of atherosclerosis are the other morbidities associated with long term treatment with conventional dialysers [2].

Serum creatinine and urea are small molecules that are commonly measured to monitor renal function in patients with chronic kidney disease. The use of serum urea is recommended by the Kidney Disease Outcomes Quality Improvement (KDOQI) clinical practice guideline to assess dialysis clearance [3]. It has a molecular weight of 60 D [4]. The urea reduction ratio that is commonly used show only the removal of small solutes by conventional hemodialysis, the removal of middle molecules is not known.

Cystatin C is a single non-glycosylated polypeptide chain consisting of 120 amino acid residues with a

molecular mass of 13kDa, which is in the middle molecular range [5]. It is produced by all nucleated cells [6], freely filtered at the glomerulus and virtually all is reabsorbed and metabolised by proximal tubular cells [7-10]. Several studies have suggested that CyC is useful as a marker of hemodialysis toxin removal, since it has the attractive features as a representative middle molecule [11, 12].

This study was conducted to assess the efficacy of Cystatin C in assessing the middle molecular clearance by conventional hemodialysis.

MATERIALS AND METHODS

The study was approved by the human ethics committee of Sri Ramachandra medical college & research institute, Chennai, India and written consent was obtained from all the participants. A total set of 37 patients of both sexes were selected. All the patients were subjected to conventional, low flux hemodialysis. The dialyzers used were F6HPS for Low Flux group (Fresenius medical care).

All patients undergoing maintenance hemodialysis at SRMC, three times per week, with age group above 18years were included. Patients with thyroid dysfunction, malignancy, steroid therapy, HIV infection and Pregnancy were excluded from the study. All the blood samples were collected before and after the second HD session of the week, according to the guidelines for HD adequacy [13]. Blood samples were collected in tubes without additional anticoagulant and allowed to stand at room temperature for 30 minutes. Then, the samples were centrifuged to collect serum, which were stored at -70^{o}C until assayed. Urea nitrogen was measured using Urease–GLDH method on the Biolis premium 24i (Tokyo Boeki Medical System) analyzer according to the manufacturer's procedure. Serum Cystatin C was measured by latex enhanced Immuno turbidimetry on the same analyzer according to the manufacturer's procedure (14).

The efficacy of dialysis was then assessed by calculating the reduction ratio for serum creatinine as shown below: Urea reduction ratio (URR) = 100* (1-Ui / Uo) where Ui & Uo represent post dialysis and pre-dialysis serum urea levels. The same formula is used for the calculation of urea and Cystatin C reduction ratios.

SPSS 10 statistical software was used for the analysis of the results. Student's T test was used for the analysis of the pre and post dialysis samples of urea and Cystatin C.

RESULTS

There is a statistically significant decrease in urea levels from the pre dialysis value **(**97.865±42.508 mg/dl) to the post dialysis value (26.756±17.742 mg/dl) with P value of 0.000 (**Table.1, Fig.1**). There is a statistically significant increase in Cystatin-C levels from pre dialysis value (5.242±0.604 mg/L) to the post dialysis value (5.709±0.606 mg/L) with P value of 0.000(**Table.1, Fig.2**).

Table 1: Represents the urea and Cystatin C levels in patients undergoing low flux hemodialysis

	Pre dialysis	Post dialysis	%
No. of patients	37	37	
Urea (mg/dl)	97.865±42.508	26.756±17.742	
Cystatin C (mg/l)	5.242±0.604	5.709±0.606	
URR			72.273±14.686
CysCRR			-9.78±6.705

Fig 1: Shows the bar diagram of pre dialysis and post dialysis values of urea in low flux hemodialysis

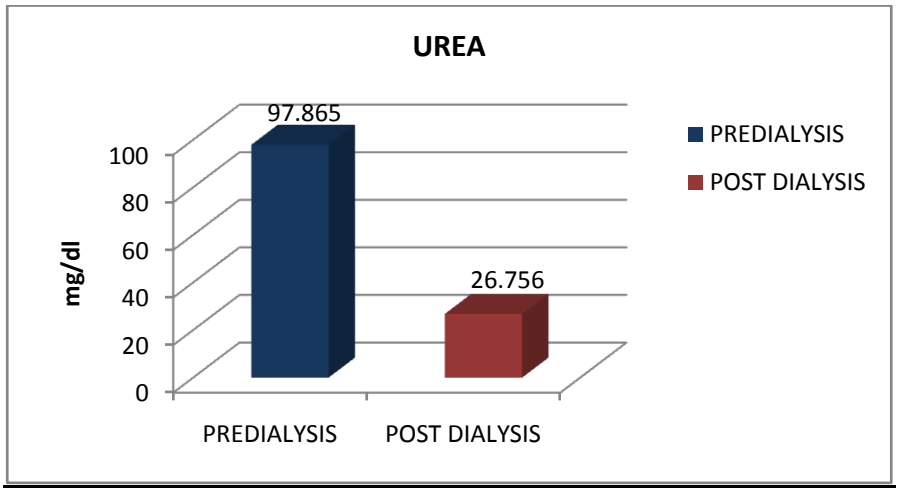
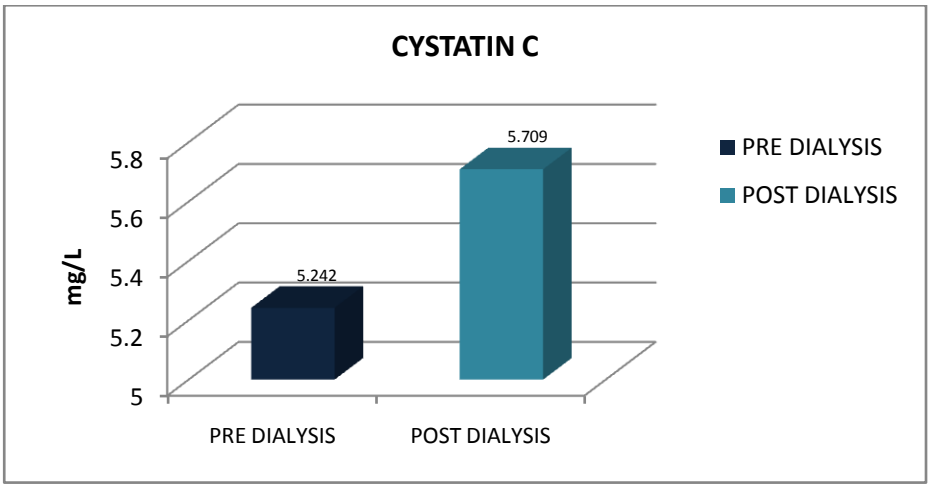


Fig 2: Shows the pre dialysis and post dialysis values of cystatin C in low flux hemodialysis



DISCUSSION

Krishnamurthy N et al., has shown a high statistically significant increase in the mean values of cystatin C with a CysCRR of -38% in the low flux group. Thysell et al., also showed a paradoxical increase in the Cys C level after dialysis (26.8± 14.4%) in low efficiency hemodialysis [12]. Montini et al., have found in their study, an increase in serum cystatin C in anuric patients during peritoneal dialysis.

The pore size of the low flux membrane is 1.5nm which does not allow the removal of middle molecules like cystatin C. The electrostatic interaction between the microproteins and other plasma proteins adsorbed onto the dialyser membrane hinders the filtration of these molecules. Cystatin C is strongly cationic and the charged nature of the molecule hinders its filtration. [15].

Small amounts of serum Cystatin C are adsorbed or sieved through the cuprophane membranes, rendering their kinetics still more complex [12]. The rise in cystatin C is attributable to the nature of the dialysing membrane and the composition of the dialysate. The rise in Cystatin C could be attributed to the effect of hemo concentration which occurs during dialysis. Hence, Cystatin C could be used as a surrogate marker for the inadequacy of conventional LF dialysis.

Further large scale studies are required for assessing the middle molecular clearance by high flux dialysers to reduce dialysis related morbidity & mortality.

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