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Original Article

Assessment of Adequacy of Haemodialysis by Urea Kinetic Modeling (UKM)

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ABSTRACT

Dialysis adequacy is an important parameter with regards to morbidity and mortality in chronic haemodialysis (HD) patients. Measuring the adequacy of HD is not an easy task. There is no objective, reliable and universally accepted criteria for measuring the adequacy. Clinically, several parameters must be considered to provide adequate dialysis, such as control of fluid overload and electrolytes disturbance, correction of metabolic acidosis and dialysis dose. This cross-sectional study explores the assessment of the adequacy of haemodialysis by urea kinetic modeling (UKM), a vital method for determining the optimal dialysis dose. This study was conducted at the haemodialysis unit of the National Institute of Kidney Diseases and Urology (NIKDU), Dhaka, Bangladesh between the periods of 1st January 2012 and 30th June 2013. Purposive sampling of 120 end stage renal disease (ESRD) patients on maintenance haemodialysis (MHD) getting dialysis for at least one month through arterio-venous fistula (AVF) and at least 2 dialysis sessions per week. Out of 120 patients, 72 (60%) were male and the ratio was 1.5:1. The mean age of haemodialysis patients in this study was 51 years (range: 18-75 years). Approximately 62 (52%) patients were on an 8-hour per week haemodialysis session. Our study showed mean total clearance of urea normalized or corrected for distribution volume (Kt/V), urea reduction ratio (URR), time average concentration of urea (TACurea) and normalized protein catabolic rate (nPCR) of all study population was 1.21±0.40, 62±12, 83±26, and 1.29±0.46, respectively. In 12 hours per week haemodialysis group achieved target Kt/V >1.2 was only 26 (45%), on the other hand, in 8 hours per week haemodialysis group achieved target Kt/V >2 was only 3 (5%). Among the study population only 52 (43%) patients achieved URR >65%, 13 (11%) patients TACurea was less than 52 mg/dl and 107 (89%) patients achieved nPCR >1g/kg/day. The mean values of the URR was significantly higher for dialysis patients who achieved a Kt/V of >1.2 than for those who did not achieve a Kt/V > 1.2. To achieve haemodialysis adequacy of KDOQI 2006 recommendation needs to increase the frequency of HD that is 3 sessions per week (12 hours/week) and needs to give more attention to other factors that increase urea clearance. To improve patient management with end-stage kidney disease, needs of continuous research to enhance our understanding of haemodialysis adequacy and its dose calculation.

Keywords: *End stage renal disease(ESRD), Urea reduction ratio (URR), Haemodialysis (HD), Time average concentration of urea (TAC urea), Normalized protein catabolic rate (nPCR),*

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INTRODUCTION

Haemodialysis is the most common form of renal replacement therapy (RRT) for ESRD patients

worldwide. The burden of kidney disease patients requiring renal replacement therapy is increasing day by day. Haemodialysis is a therapy where diffusion and convection have been combined in an attempt to replace renal function. The goal of dialysis in patients with end stage renal disease (ESRD) is to restore body's extracellular and intracellular composition to the greatest extent possible to that of normal. The aims of dialysis treatment are to prolong patient survival, reduce morbidity and improve quality of life. Urea Kinetic Modeling (UKM) is an important tool in the measurement of dialysis for the assessment of dialysis adequacy. Urea Kinetic Modeling (UKM) is a dialysis method of assessing the appropriate dose of dialysis that determines a maximum clearance of waste products and a good quality of life. It is based on the rate of generation and removal of urea, as assessed by several indicators, percent reduction of urea during dialysis (URR), total clearance of urea normalized or corrected for distribution volume (Kt/V), normalized protein catabolic rate (nPCR) and time average concentration of urea (TACurea). Numerous outcome studies have demonstrated a correlation between the delivered dose of haemodialysis and patient mortality and morbidity[1].

The evidence demonstrates that mortality among ESRD patients is lower when sufficient haemodialysis treatments are provided. Clinical signs and symptoms alone are not reliable indicators of haemodialysis adequacy[2]. To ensure that ESRD patients treated with maintenance haemodialysis receive a sufficient amount of dialysis, the delivered dose should be measured and monitored routinely. The two (Kt/V and URR) are commonly used to evaluate the efficacy and adequacy of dialysis[3,4]. Kt/V, the ratio between the product of urea clearance (K, in ml/min) and dialysis session duration (t, in minutes) divided by the volume of distribution of urea in the body (V, in ml) and URR derived solely from the percentage fall in serum urea (URR) during a dialysis treatment. The key measures for urea clearance are Kt/V and URR, with recommended target values being Kt/V >1.2 (12 hours/week), Kt/V >2 (8 hours/week) and URR >65%. The delivered dose of haemodialysis depends on dialysis prescription (duration and frequency of dialysis, dialyzer size, dialysate and blood flow rate) and patient factors (size, weight, haematocrit level and vascular access)[5]. HD for 12 hours/week (4 hours/day for 3 days/week) is the standard and widely accepted regime to achieve adequate HD. But there is a tendency to shorten dialysis time to reduce cost and to increase patient's convenience[6]. So the study was conducted to observe optimum solute clearance per session of haemodialysis by measuring pre and postdialysis blood urea and applying Kt/V and URR formula and to measure the Time Average Concentration of urea (TAC urea) and to assess normalized Protein Catabolic Rate (nPCR).

MATERIALS AND METHODS

This cross-sectional study was conducted at the haemodialysis unit of National Institute of Kidney Diseases and Urology (NIKDU), Dhaka, Bangladesh, between the periods of 1st January 2012 and 30th June 2013. Total 120 ESRD patients on maintenance haemodialysis treatment for at least one month through arterio-venous fistula (AVF) and patient's age 18 to 75 years were included in the study. The study population was End Stage Renal Disease (ESRD) patients on maintenance haemodialysis (MHD), sampling was purposive. Patients who were on infrequent haemodialysis (<2 sessions/week) were excluded from the study. Relevant history, physical examinations, and laboratory reports were recorded in the data collection sheet. Height, weight (predialysis and postdialysis) and blood pressure were measured. BMI was calculated from the formula [postdialysis weight (kg)/height (m^2)]. Following laboratory investigations (complete blood count, serum creatinine, serum electrolytes, serum calcium, serum phosphate, serum albumin, total protein and haemodialysis adequacy parameters) were done among the study population only once at the entry into this study. All biochemical investigation was done from predialysis blood sampling except postdialysis blood urea, which was done from postdialysis blood sample. For this study, three blood samples for blood urea were taken (predialysis, postdialysis and next predialysis) to calculate Kt/V, URR, TACurea and nPCR. Dialysate flow was 500 ml/min, dialysis session time 4 hours and bicarbonate dialysate fluid was used.

Blood samples were taken from the arterial needle prior to connecting the blood tubing or flushing the needle before dialysis. Post dialysis blood sampling was drawn from the arterial needle after turning off the dialysis machine ultrafiltration and dialysate flow. Blood pump speed was reduced to 50 ml/min and allowed 15-20 seconds to pass. The means of clinical, biochemical and adequacy parameters were calculated and compared with target value of dialysis doses. Also compared various clinical, biochemical and adequacy variables between groups who achieved cut off values of URR, Kt/V, with those who did not achieve it. The aims and objectives of the study, along with its procedure, risks and benefits were explained to the respondent in easily understandable local language, and then verbal and written consent was obtained from each participant. The data was analysed with the statistical software SPSS 16.0 for Microsoft Windows (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as mean (±SD) standard deviation. Qualitative variables

were expressed as the frequency of distribution of each category and percentage. A Student-t test was used to compare patients who received adequate dialysis and were not adequately dialyzed. Statistical significance was set at p<0.05 and confidence interval set at 95% level.

RESULTS

This was a cross-sectional study for haemodialysis adequacy observed by UKM. A total of 120 patients were included. They were on maintenance haemodialysis (MHD) treatment for at least one month through AVF. This study showed 72 (60%) were male and 48 (40%) were female. The mean age of dialysis patients was 51 years (range: 18-75 years). The highest number of patients (32.5%) were in the age group of more than 60 years, 14 (11.7%) were in the age group of less than 30 years, 13 (10.8%) were in the age group of 31 to 40 years, and 20 (16.7%) were in the age group of 41 to 50 years (table-I). Approximately 52% of patients were on 8 hours per week haemodialysis session (figure-1).

The mean URR of the study population was significantly lower than the target value (p-value 0.003). Kt/V of the 8-hour per week haemodialysis group significantly lower than the target value (p-value 0.001) but there was no significant difference in the 12-hour per week haemodialysis group (p-value 0.35) at 95% confidence interval. Mean TACurea significantly higher (p-value 0.001) than target value (<52 mg/dl). Mean nPCR significantly higher (p-value 0.001) than target value (table-III).

Among the 62 patients in the group of 8 hours per week haemodialysis only 3 (5%) had Kt/V more than 2 and 59 (95%) had Kt/V less than 2. Among the 58 patients in the group of 12 hours per week haemodialysis 26 (45%) had Kt/V more than 1.2 and 32 (55%) had Kt/V less than 1.2. Among 120 patients only 52 (43%) achieved URR >65%, 13 (11%) patients achieved TACurea was less than 52 mg/dl and 86

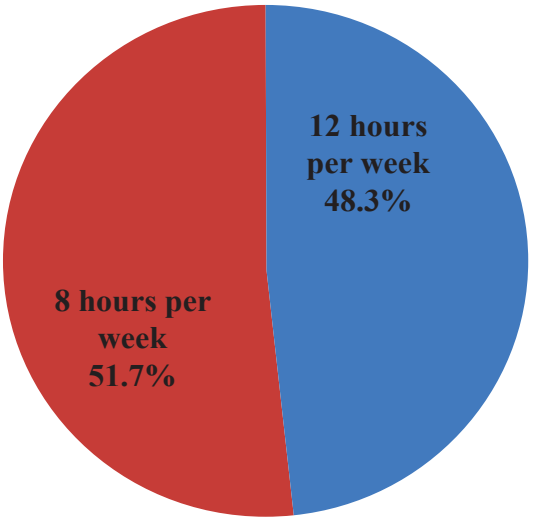

Figure-I: *Haemodialysis time per week.*

Table-I: *Distribution of participants according to age and gender (n=120).*

Variables	Frequency	Percentage
Gender		
Male	72	60
Female	48	40
Age group		
<30	14	11.7
31-40	13	10.8
41-50	20	16.7
51-60	34	28.3
>60	39	32.5

(72%) patients achieved nPCR >1 g/kg/day (table-IV).

URR% was significantly higher in patients with Kt/V >2 (p=0.001), but serum calcium was better maintained in patients with Kt/V <2 (p=0.016) (table-V).

Only URR% was significantly higher in patients with Kt/V >1.2 (p=0.001) but BMI significantly higher in patients with Kt/V <1.2 (p=0.043) (table-VI).

Haemoglobin, Kt/V and nPCR significantly better in URR more than 65% groups but BMI significantly higher in URR less than 65% groups (p=<0.05) (table-VII).

DISCUSSION

Dialysis adequacy is an important parameter with regards to morbidity and mortality in chronic haemodialysis patients[7]. The main aims of dialysis treatment are to

Table-II: *Clinical, biochemical and dialysis adequacy parameters of haemodialysis patients (n=120).*

Variables	Mean±SD
Age (years)	51±14
Body Mass index (kg/m^2)	23±4
Haemodialysis duration (month)	23±19
Haemoglobin (gm/dl)	9.4±2.0
Creatinine (mg/dl)	9.6±2.9
Albumin (gm/dl)	3.5±0.5
Calcium (mg/dl)	9.2±1.0
Phosphorus (mg/dl)	5.4±2.0
Urea Reduction Ratio (URR) %	62±12
Single session Kt/V	1.21±0.40
Weekly Kt/V (calculated)	3±1.13
TACurea (mg/dl)	83±26
nPCR (gm/kg/day)	1.29±0.46

Table-II shows the clinical parameters of HD patients, including age, BMI, haemodialysis duration and biochemical variables like haemoglobin, creatinine, potassium, calcium, phosphorus, serum albumin, URR, single session Kt/V, weekly Kt/V, TACurea and nPCR .

Table-III: *Comparison of sample mean value with target value (n=120).*

Adequacy parameters		Sample mean values ±SD	Target values	p-value (95% Confidence Interval)
URR (%)		62±12	≥65	0.003 (59.70-64.03)
Kt/V	8 hrs/wk (n=62)	1.24±0.41	≥2	0.001 (1.14-1.35)
	12 hrs/wk (n=58)	1.18±0.39	≥1.2	0.35 (1.08-1.28)
TACurea (mg/dl)		83±26	<52	0.001 (78.52-88.00)
nPCR (g/kg/day)		1.29±0.46	≥1	0.001 (1.20-1.37)

*Student t-test was done.

prolong patient survival, reduce morbidity and improve quality of life. However, despite many technical advances made over the last few years, morbidity and mortality of dialysis patients remain unacceptably high and their quality of life is often poor. The delivered dose of dialysis can affect morbidity and mortality of dialysis patients. Moreover, in the last decade, several epidemiological studies, based mainly on longitudinal database registries, have suggested a possible superiority of convective dialysis treatments in improving patient outcome. Inadequate dialysis accounts for the high mortality in patients with end stage renal disease (ESRD). Most of the patients were getting haemodialysis twice per week due to financial and logistic limitations and various other factors[8]. The term "dialysis adequacy" is usually taken to mean nitrogenous solute removal. The measures of urea removal most often used in clinical practice are the Urea Reduction Ratio (URR) and the mathematically-related Kt/V urea.

This study was carried out to determine haemodialysis dose by Urea Kinetic Modeling (UKM). Here observed maximum solute clearance in one session of haemodialysis by measuring predialysis and postdialysis blood urea and applying Kt/V and

Table-IV: *Distribution of participants on the basis of cut off values of haemodialysis adequacy parameters (n=120).*

Adequacy parameters		Cutoff values	Mean ±SD	Frequency	Percent
URR		>65%	72±6	52	43
		<65%	53±9	68	57
Kt/V	8 hrs/wk (n=62)	>2	2.49±0.59	3	5
		<2	1.18±0.29	59	95
	12hrs/wk (n=58)	>1.2	1.54±0.25	26	45
		<1.2	0.89±0.18	32	55
TACurea		<52	43±9	13	11
		>52	88±23	107	89
nPCR		>1	1.48±0.38	86	72
		< 1	0.76±0.15	34	28

Table-V: *Comparisons of clinical, biochemical and dialysis adequacy parameters on the basis of Kt/V cut off values of 8 hours/week haemodialysis group (n=62).*

Variables	Kt/V >2(n=3)	Kt/V <2(n=59)	p-value (95% confidence interval)
Age (years)	53±26	50±14	0.875 (-62.54-68.07)
BMI (kg/m^2)	20.9±2.5	22.5±3.7	0.383 (-7.26- 3.98)
Haemoglobin (g/dl)	8.7±1.9	8.9±2.0	0.911 (-4.79-4.50)
S. Albumin (g/dl)	4.3±0.4	3.6±0.5	0.097 (-0.27-1.68)
S. Calcium (mg/dl)	10.7±0.4	9.2±0.8	0.016 (0.58- 2.49)
S. Phosphate (mg/dl)	5.8±3.5	5.8±1.8	0.979 (-8.44-8.57)
TACurea (mg/dl)	74±31	91±25	0.439 (-93.00-57.89)
URR%	88±4	61±10	0.001 (16.56-32.59)
nPCR (g/kg/day)	1.62±0.74	1.15±0.38	0.391 (-1.35-2.30)

Table-VI: *Comparisons of clinical, biochemical and dialysis adequacy parameterson the basis of Kt/V cut off values of 12 hours/week haemodialysis group (n=58).*

Variables	Kt/V >1.2(n=26)	Kt/V <1.2(n=32)	p-value (95% confidence interval)
Age (years)	51±14	54±12	0.390 (-10.29-4.08)
BMI (kg/m^2)	23.2±3.9	25.3±3.8	0.043 (-4.17- 0.06)
Haemoglobin (g/dl)	10.5±1.9	9.6±2.0	0.110 (0.19-1.87)
S. Albumin (g/dl)	3.6±0.3	3.5±0.6	0.660 (-0.20-0.32)
S. Calcium (mg/dl)	9.2±0.9	9.2±1.5	0.990 (-0.67-0.66)
S. Phosphate (mg/dl)	4.8±2.0	5.2±2.0	0.508 (-1.44-0.72)
URR%	71±5	51±8	0.001 (16.53-23.81)
TACurea (mg/dl)	70±20	79±27	0.173 (-21.28- 3.93)
nPCR (g/kg/day)	1.54±0.39	1.30±0.54	0.060 (0.01-0.48)

Table-VII: *Comparisons of clinical, biochemical and dialysis adequacy parameters on the basis of URR cut off values.*

Variables	URR (%) >65(n=52)	URR (%) <65(n=68)	p-value (95% confidence interval)
Age (years)	51±16	52±15	0.475(-7.14-3.35)
BMI (kg/m^2)	22±4	24±4	0.004(-3.44- -0.65)
Haemoglobin (gm/dl)	10.2±1.82	8.9±2.1	0.001(0.51-1.95)
S. Albumin (gm/dl)	33.7±0.5	3.5±0.5	0.153(-0.05-0.34)
S. Calcium (mg/dl)	9.3±0.9	9.2±1.2	0.769(-0.34-0.46)
S. Phosphate (mg/dl)	5.1±1.8	5.7± 2.1	0.078(-1.39-0.07)
TACurea (mg/dl)	81±25	85±27	0.402(-13.63- 5.51)
Single session Kt/V	1.56±0.33	0.95±0.19	0.001(0.52- 0.71)
nPCR (gm/kg/day)	1.5±0.4	1.2±0.5	0.001(0.13-0.45)

URR formula, calculate the Time Average Concentration of urea (TAC urea) and normalized Protein Catabolic Rate (nPCR). Presenting study showed majority of patients (60%) belonged to >50 years age group and 60% were male. Chandna et al. in a cross-sectional analysis of 1282 patients reported the mean age was >50 years[9]. And another similar study from three haemodialysis centers of Isfahan in Iran on 2016, reported that mean age of the patients was 59.6±14.45 years and out of 202 participants, 135 (66.8%) were male[10].

In this study, approximately 52% of patients were on 8 hours per week (2 times/week) haemodialysis session (figure-1). Muhammad Anees from Lahore showed that 1, 2 and 3 times per week dialysis were 7.2%, 77.6% and 15.2% respectively[11]. In less developed Asian countries, a twice weekly pattern is common, sometimes with dialyzer reuse. A majority of patients decrease session frequency or discontinue the program due to financial constraint[12]. The KDOQI guidelines, 2006 recommended that twice-weekly haemodialysis is not appropriate in patients who have residual renal function <2 ml/min/1.73 m^2 body surface area and thrice-weekly HD is a standard renal replacement therapy (RRT) for maintenance dialysis[13].

Our study showed the mean Kt/V, URR, TACurea and nPCR of all study populations were 1.21±0.40, 62±12, 83±26 and 1.29±0.46, respectively. A cross-sectional study of 137 patients of the Military Hospital of Dhaka, Bangladesh, to see the adequacy of haemodialysis and reported mean URR, Kt/V, TAC urea and nPCR were 64.68±17.07, 1.63±0.45, 76.55±25.73 and 1.43±0.55, respectively[18]. Poyyapakkam et al. in their study showed mean nPCR 1.17±0.31 g/kg/day[14]. Aarne Vartia from Finland showed TAC urea (mmol/L) was 17.7±5.2 and nPCR was (g/kg/day) 1.09±0.27 (range 0.48-2.34)[15].

In this study, the mean URR (62±12) of the study population was significantly lower than the target value (≥ 65%) (p-value 0.003). Kt/V of 8 hours per week haemodialysis group (1.24±0.41) significantly lower than target value (≥2) (p-value 0.001) but no significant difference in 12 hours per week haemodialysis group (1.18±0.39) from target Kt/V (≥1.2) (p-value 0.35) at 95% confidence interval. Mean TACurea significantly higher (p-value 0.001) than target value (<52 mg/dl) and mean nPCR significantly higher (p-value 0.001) than target value. Target URR >65%, TACurea <52 mg/dl and nPCR >1 g/kg/day were achieved at 43%, 11% and 72%, respectively. Eight hours per week haemodialysis group achieved Kt/V >2 only 5% and on the other hand, 12 hours per week haemodialysis group achieved Kt/V >1.2 only 45%. A cross-sectional study on 3039 patients over the five European countries shown, Kt/V <1.2 of thrice per week dialysis patients was 16%, 40%, 34%, 35%, 28% and 30% of France, Germany, Italy, Spain, UK and all study population, respectively[16]. The NECOSAD study by Karin E. Moret et al. in 2012, showed mean haemodialysis treatment time was 10.29±1.97 h/week (3 sessions/week) and their mean KtV 1.18±0.26 and URR 63±8%[17]. Similar mean KtV and URR were found in our study.

In this study, the 8-hour per week haemodialysis group showed URR% was significantly higher in patients with Kt/V >2 but serum calcium was better maintained in patients with Kt/V <2 and 12-hour per week haemodialysis group showed only URR% was significantly higher in patients with Kt/V >1.2 but BMI was significantly higher in patients with Kt/V <1.2. A similar study of the Military Hospital in Dhaka, Bangladesh, showed that in the 8-hour/week group, those who achieve target Kt/V also achieve target URR and were statistically significant. And there is a significant difference among the two groups (Kt/V >2 Vs Kt/V <2) in relation to TACurea and nPCR ($p<0.05$) and in the case of 12 hours per week haemodialysis group URR, TAC urea and nPCR were significantly better in patients with Kt/V>1.2 group[18]. In our study, TAC urea and nPCR not significantly different between who achieved target Kt/V or not as because we ignore residual renal function which calculate from 24 hours urine collection. In this study we found haemoglobin, Kt/V and nPCR significantly higher in URR more than 65% groups but BMI significantly higher in URR less than 65% groups. A study from Taiwan of 2651 incident HD patients showed higher URR and Kt/V levels were both associated with higher nutritional markers (haemoglobin, nPCR and total cholesterol) but lower WBC count and serum creatinine[19]. Another study from CMH, Dhaka, Bangladesh showed TAC urea, nPCR and Kt/V, significantly better in URR more than 65% groups[18].

CONCLUSION

The majority of our end stage renal disease (ESRD) patients on haemodialysis didn't achieve the target dialysis dose. Only 45% of 12 hours per week (3 session/week) haemodialysis patients achieved target Kt/V. On the other hand, only 5% of 8 hour per week (2 session/week) haemodialysis patients achieved target Kt/V. Only 13 (11%) achieved target TACurea <52 mg/dl, 86 (72%) nPCR>1 g/kg/day and 43% patients achieved URR > 65%. To achieve haemodialysis adequacy, the KDOQI 2006 recommendation needs to increase the frequency of HD to 3 sessions per week (12 hours /week) and should give more attention to other factors that increase urea clearance like blood flow, dialyzer surface area and high flux dialyzer, dialysate flow, adequate vascular access and optimum anticoagulation.

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