Haemodialysis Adequacy: Ultraviolet *vs.* Calculated Methods

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ABSTRACT

Objective: To compare measuring methods of haemodialysis adequacy; realtime urea reduction ratio (RT-URR) and realtime Kt/V (RT-Kt/V) with calculated urea reduction ratio (C-URR) and calculated Kt/V (C-Kt/V), respectively, in end-stage kidney disease (ESKD) patients.
Study Design: Cross-sectional prospective study.
Place and Duration of the Study: Department of Nephrology, Mayo Hospital, King Edward Medical University, Lahore, Pakistan, from July to December 2023.
Methodology: Patients on maintenance haemodialysis for more than 3 months *via* a well-functioning arteriovenous fistula were included, while patients with acute kidney injury and dialysis-related complications were excluded. Pre- and post-dialysis blood samples for urea measurement were sent to the laboratory. RT-URR and RT-Kt/V were measured by the NIKKISO-DBB-EXAES machine using the ultraviolet absorbance method on spent dialysate. By putting pre- and post-dialysis, urea values C-URR and C-Kt/V (Daugirdas formula) were calculated. RT-URR, C-URR, RT-Kt/V and C-Kt/V were analysed for correlation using the Bland-Altman graph.
Results: Fifty patients were included, with a mean age of 45.18 ± 12.25 years. The majority (n = 29, 58%) were male. Major cause of ESKD was hypertension (n = 27, 54%), followed by diabetes mellitus (n = 16, 32%). The mean duration of dialysis was 54.16 ± 31.74 months, and the majority of patients, 29 (58%), were on thrice weekly dialysis. A positive statistically significant correlation was found between C-URR and C-Kt/V with RT-URR and RT-Kt/V, respectively ($p < 0.001$). A significant negative correlation was found for body surface area (BSA) with C-URR ($p < 0.001$) and RT-URR ($p = 0.013$). Also, a significant negative correlation of BSA with C-Kt/V ($p < 0.001$) and RT-Kt/V ($p = 0.008$) was found.
Conclusion: RT-URR and RT-Kt/V, being strongly correlated with C-URR and C-Kt/V, can precisely tell about adequacy of haemodialysis.

Key Words: *Renal dialysis, Haemodialysis, Home, Urea, Ultraviolet rays, Haemodialysis solutions*.

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INTRODUCTION

When patients develop chronic kidney disease (CKD), there is an accumulation of uraemic toxins in the body. Urea is one of the most commonly measured uremic toxins, which is easily measured in an inexpensive way and monitored for therapeutic and prognostic purposes. Appropriate level of urea in the body of patients with end-stage kidney disease (ESKD) represents a parameter of adequacy of dialysis.[1,2] Factors affecting the adequacy of dialysis are duration of session of dialysis, compliance of the patient, vascular access for dialysis, surface area of the dialyser, and interruptions during dialysis.[3]

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There are different tools used for assessing the adequacy of dialysis such as urea reduction ratio (URR), Kt/V, and time average urea concentration (TAC-Urea).[4,5] Adequate dialysis is very important for better survival and quality of life. According to the National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-KDOQI) clinical practical guidelines, a target spKt/V of 1.4 per session is recommended to obtain a minimum delivered spKt/V of 1.2 in a patient on thrice weekly haemodialysis (HD).[6] Achievement of URR of about 65% indicates an effective dialysis.[7] Inadequate dialysis will lead to increased mortality of the dialysis patients.[8] Data show that the mortality rate decreases by about 7% for every 0.1 increase in spKt/V, and for every 5% increase in URR, the mortality decreases by 11%.[9]

There are different formulas for calculating these parameters; such as drawing blood samples (pre- and post-dialysis) to measure serum urea level. Later on after the advancement in technology, HD machines were developed in such a way that instead of measurement of urea in blood samples, online urea removal was measured, which is equivalent to dialysis dose. These online methods are cost-effective, non-invasive, and readily available.[10] Basic principle of these machines was based on sodium dialysance (sodium clearance), also called as online clearance module (OCM) which was assumed as equal to urea clearance.[11]

In Pakistan, dialysis dose is measured by the OCM provided in most of the dialysis machine models. The principle of the dialysis dose measurement was based on the sodium dialysance method. The molecular weight of the urea and sodium are very close. So, the rates of diffusion and clearance of the urea and sodium are assumed to be equal while passing through the dialyser membrane. In order to exploit this assumption, the dialysis machine increases the sodium concentration in the dialysate for a short period which crosses the membrane leading to a reduced concentration in the spent dialysate. This reduction in the concentration of sodium is considered as the clearance of sodium. By measuring the conductivity of the dialysate entering and leaving the dialyser, it helps to report pseudo Kt/V. Previous local and international studies have shown strong correlation of online Kt/V and URR measured by dialysis machines with calculated methods using different formulas. This online technique was having few limitations such as intermittent (every 20-30 minutes measurement) nature of the measurement of clearance instead of continuous nature. In this technique, volume is measured by Watson formula which overestimates the volume leading to an under-estimation of Kt/V as compared to Daugirdas formula.[12] So, there was a need for a machine to measure the adequacy of dialysis avoiding these limitations.

First time in Pakistan, the NIKKISO Japan launched a machine measuring adequacy of dialysis by dialysis dose monitor (DDM). The principle of this machine is based on UV absorbance in the spent dialysate instead of sodium dialysance. A light source transmits ultraviolet light through the spent dialysate which detects the urea level by absorbance method. DDM measures the change in UV absorbance of spent dialysis fluid. The obtained UV absorbance values are processed and presented on a computer screen. DDM displays standard dialysis dose (spKt/V) in a graphic form with a projected line. Adequacy of the dialysis measured by the machine is continuous and real-time. DDM uses the Daugirdas formula same as blood analysis reports without the need for information of gender, height, and age. In a country such as Pakistan, the adequacy of dialysis is not assessed on regular basis. This is because; people cannot get and afford blood measurement based assessments of HD adequacy, which increases the extra burden on the healthcare system. HD machines which can provide an assessment of the adequacy of dialysis without the need for blood urea nitrogen measurements can help in improving the morbidity and mortality of dialysis patients.

This study was conducted to find an easy, non-invasive, cost-effective, and readily available real-time method to measure adequacy of haemodialysis. There are no local data available on this important aspect that whether realtime urea reduction ratio (RT-URR) and realtime Kt/V (RT-Kt/V) are equivalent to calculated urea reduction ratio (C-URR) and calculated Kt/V (C-Kt/V), respectively. So this study aimed to compare measuring methods of haemodialysis adequacy; RT-URR and RT-Kt/V with C-URR and C-Kt/V, respectively, in ESKD patients.

METHODOLOGY

This cross-sectional prospective study was conducted at the Department of Nephrology, Mayo Hospital, King Edward Medical University, Lahore, Pakistan, after permission from the Institutional Review Board (IRB No: 209/RC/KEMU; Dated 08/06/2023). Sample size was calculated using a formula based on correlation coefficient.[13] Patients who were on maintenance haemodialysis (MHD) for more than three months and had permanent access to HD were included in the study. The patients who were on temporary access to HD, past history of intra-dialytic complications, ischaemic heart disease, excessive ultrafiltration (>3000ml), and non-compliant with dialysis prescription were excluded from the study. Demographic data (age, gender, marital status, and employment), anthropometric data [weight, height, and body surface area (BSA) using Du-Bois], and clinical data (cause of ESKD, duration and frequency of HD) were collected on predefined proforma. To avoid any variability in the HD prescription, blood flow rate (300 ml/min), dialysate flow rate (500 ml/min), duration of HD session (4 hours), dialyser surface area (1.8 m^2), and conductivity (13.8) were kept constant except ultrafiltration. All patients were dialysed through the permanent access for HD and two blood samples were drawn for measurement of serum urea just at the time of dialysis initiation C_0(pre-dialysis) and at the end of dialysis C (post-dialysis). Pre-dialysis blood samples were drawn from the arterial line before administering any saline or heparin. Post-dialysis blood samples were drawn from arterial tubing by decreasing the blood flow at 50 ml/min for 30 seconds. The values of serum urea were put in the relevant formulas for the determination of C-URR and C-Kt/V.

URR is one of the measures of how effectively an HD treatment removes waste products from the body and is expressed as percentage. URR may vary considerably from treatment to treatment.[14]

$$URR = \frac{(C_O - C)}{C_O} \times 100$$

Where C_0 is concentration of predialysis urea and C is concentration of post-dialysis urea.

Urea kinetic modelling (Kt/V) is the method for verifying the amount of dialysis delivered by the Daugirdas equation.[12]

$$sp\frac{Kt}{V} = -ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times 0.55 \times \frac{UF}{V_{urea}}$$

ln = Negative natural logarithm.
R = Predialysis urea/postdialysis urea.
K = Dialyser clearance (ml/min or litres/hour).
t = Dialysis time in hours.
V = Anthropometric urea distribution volume in litres.
UF = Weight loss in kilograms.

Recently an HD manufacturing company from Japan (NIKKISO) launched a machine (model DBB-EXA ES) in Pakistan with DDM (dialysis dose monitor). This machine measures real-time urea clearance on the basis of UV absorbance technique during the dialysis session. On the basis of urea measurement in the spent dialysate, it determines RT-URR and RT-Kt/V.

Data were analysed by using SPSS version 23. The continuous variables (age, duration of dialysis, and adequacy parameters) were tested for normality and expressed as Mean ± SD, whereas categorical variables (gender, cause of ESRD, and frequency of dialysis) were expressed as frequencies. Independent t-test was used to compare all adequacy parameters between groups (gender, vascular access, and UF). Mean difference of 95% consistency limits between dialysis adequacy methods was displayed by Bland Altman graphs. Pearson's intra-class correlation coefficient (ICC) was employed to find significant relationship between paired measurements. A p-value less than <0.05 was assumed for statistical significance.

RESULTS

Fifty patients were included in the study who met the inclusion criteria. The mean age of patients was 45.18 ± 12.25 years, and the majority of them were male (n = 29, 58%) and unemployed (n = 30, 60%). Major cause of ESKD was hypertension (n = 27, 54%) followed by Diabetes mellitus (n = 16, 32%). Mean duration of dialysis was 54.16 ± 31.74 months. The majority of the patients (n = 29, 58%) were on thrice weekly MHD. Blood flow rate, dialysate flow rate, and duration of dialysis were kept constant for all the participants with values of 300 ml/min, 500 ml/min, and 4 hours, respectively. Mean ultrafiltration during dialysis was 1604 ± 780 ml with a range of 200 to 3000 ml. In this study, mean RT-URR, mean RT-Kt/V, mean C-URR, and mean C-Kt/V were 71.92 ± 6.04%, 1.48 ± 0.26, 75.81 ± 5.50%, and 1.68 ± 0.30, respectively. There was high ICC between RT-URR and C-URR, (ICC = 0.821, p <0.001), also good consistency was found between RT-Kt/V and C-Kt/V (ICC = 0.862, p <0.001). Bland Altman graph showed the correlation between RT-Kt/V and RT-URR with C-Kt/V and C-URR, respectively, with 95% consistency limits as shown in Figure 1 and 2. A significant negative correlation was found for BSA with RT-URR (r = -0.351, p = 0.013) and C-URR (r = -0.531, p <0.001).

Table I: Independent t-test results between means of adequacy parameters based on gender.

Adequacy parameters	Mean ± SD	p-value
C-Kt/V		0.001
Male	1.56 ± 0.24	
Female	1.85 ± 0.31	
C-URR		0.001
Male	73.73 ± 4.55	
Female	78.68 ± 5.51	
RT-Kt/V		0.017
Male	1.41 ± 0.24	
Female	1.58 ± 0.27	
RT-URR		0.040
Male	70.44 ± 5.57	
Female	73.98 ± 6.21	

Statistical test applied: Independent t-test.
C-Kt/V: Calculated Kt/V; C-URR: Calculated urea reduction ratio; RT-Kt/V: Real-time Kt/V; RT-URR: Real-time urea reduction ratio.

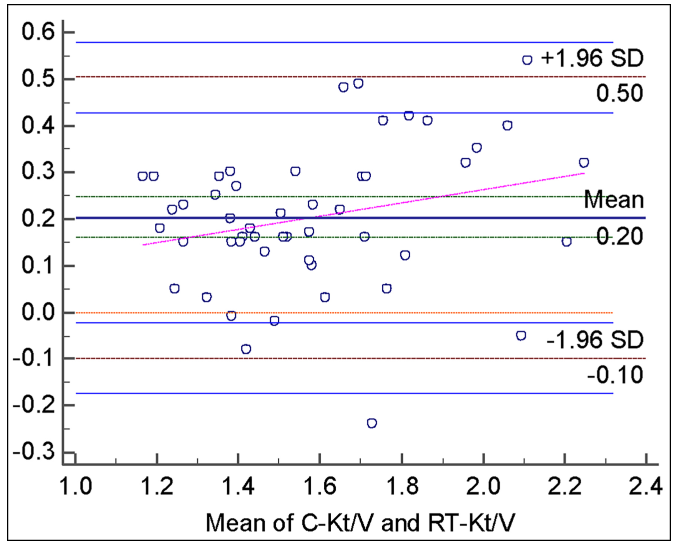

Figure 1: Bland-Altman plot showing a positive correlation between C-Kt/V and RT-Kt/V having just one outlier.
C-Kt/V: Calculated Kt/V; RT-Kt/V: Real-time Kt/V.

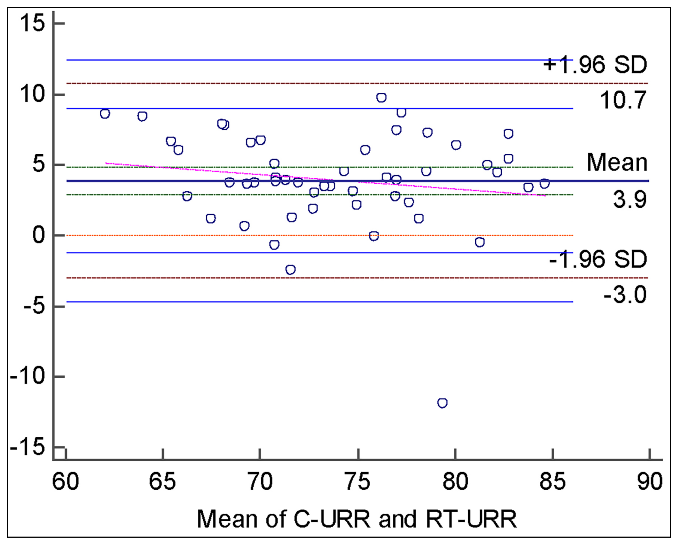

Figure 2: Bland-Altman plot showing a positive correlation between C-URR and RT-URR having just one outlier.
C-URR: Calculated urea reduction ratio; RT-URR: Real-time urea reduction ratio.

There was a significant negative relationship of BSA with RT-Kt/V (r = -0.371, p = 0.008) and C-Kt/V (r = -0.551, p <0.001). There was a significant difference in all adequacy parameters between males and females (p <0.05, Table I), while there was no significant difference in all adequay parameters on the basis of vascular access and UF.

DISCUSSION

This study shows a strong correlation of RT-URR and RT-Kt/V with C-URR and C-Kt/V as observed in other studies. Also, a negative correlation was observed between body surface area (BSA) and delivered dialysis dose *via* both calculated and real-time methods.

Mortality is higher in ESKD patients as compared to the normal population,[15] and HD adequacy is one of the factors affecting mortality in ESKD patients along with many other factors. Dialysis adequacy is primarily defined as an appropriate dialysis dose reflecting urea clearance.[16] Mortality is reduced by delivering adequate dialysis dose.[17] Assessment and reporting of dialysis adequacy indicators vary globally, influenced by historical factors, local norms, reimbursement structures, and preferences of nephrologists. The ability to provide quality dialysis care, along with measuring its effectiveness, is heavily influenced by a country's economic status and the public policies set by its government.[18]

This study shows strong correlation between the methods of HD adequacy measurement *via* real-time and calculated ways. Although the RT-Kt/V and RT-URR have strong association with C-Kt/V and C-URR, respectively, but values measured by calculated method are more as compared to real-time values. These results are consistent with the results of many studies done in past. Baloglu *et al*.[19] found that the mean Kt/V value was significantly higher with Daugirdas formula than what was measured by ionic dialysance. Although this study also showed a bit higher values of C-Kt/V as compared to RT-Kt/V but the difference was not statistically significant. A similar study was conducted in Sweden in 2001 by Fridolin *et al*. who measured urea and creatinine concentrations in spent dialysate using the UV absorbance method and by simply measuring their concentrations using the biochemical method in 44 HD sessions of 6 ESKD patients.[20] It showed a significant correlation between both the methods similar to this study. A study done on Chinese population by Yang *et al*. who calculated the Kt/V and URR values using the assessment method (a novel method that uses a urea kinetic model requiring lesser blood sampling) and the classical method using the second generation Daugirdas formula.[21] It showed significant agreement in both methods. So, both methods can be used to effectively assess the adequacy of HD in patients undergoing MHD. These results are consistent with the results of this study which also show significant consistency between calculated and real-time methods of measuring dialysis adequacy. Similar results were also found in Raimann *et al*.'s study which was conducted over a period of two years. It reported the preliminary results of the concordance between a new method of calculating Kt/V that requires fewer post-dialysis serum urea nitrogen measurements and a conventional method of calculating URR.[22]

In this study, RT-URR, C-URR, RT-Kt/V, and C-Kt/V, all are negatively correlated with BSA which is statistically significant. Meaning that as BSA increases, the parameters of adequacy of dialysis are decreased. The major variable affecting Kt/V is the volume of urea distribution (V) of the dialysis patients. The patients with small BSA will obviously have a small volume of distribution of urea. When V the denominator is decreased in value, it will lead to a high Kt/V. Further analysis showed that this difference was not only related to BSA but it was also affected by the gender of the patients (Table I). Female patients had small BSA as compared to male patients who had more surface area. So, it was easy to achieve adequacy of dialysis in female patients as compared to male patients. These findings are contrary to Marrocos *et al*. which showed relatively lower V/BSA values in females, thin patients, and elderly population (>65 years) as compared to their counterparts i.e. males, obese, and younger patients (<65 years), respectively.[13] There was no agreement between calculated Kt/V and Kt/BSA. This means that a higher dialysis dose is required to achieve adequacy in females, thin, and elderly patients if adequacy is to be measured on the basis of Kt/BSA. This finding can be explained by the fact that a female has a higher basal metabolic rate (BMR), she has a bit higher BSA (which is dependent on BMR) as compared to males of the same weight. This ultimately leads to relatively lower Kt/BSA in females than males, applying the condition of the same weight and keeping all parameters of dialysis the same. Similar is the case for thin and elderly patients.

This study had some limitations. First, all of the patients who were enrolled in the study were of Pakistani ethnicity, so these results may not be applicable to other races. Second, it was a single-centre study with a relatively smaller sample size. The enrolled patients, being relatively younger and mainly males with arteriovenous fistula for vascular access, might not fully represent the current population on dialysis in other countries.

CONCLUSION

Parameters of adequacy of dialysis, such as RT-URR and RT-Kt/V being strongly correlated with C-URR and C-Kt/V, can precisely tell about the adequacy of haemodialysis. It is also easy to perform, cost-effective, readily available, and does not require blood sampling.

ETHICAL APPROVAL:
Ethical approval was obtained from the Institutional Review Board of Mayo Hospital Affiliated with King Edward Medical University, Lahore, Pakistan (IRB No: 209/RC/KEMU; Dated 08/06/2023).

PATIENTS' CONSENT:
Informed consent was obtained from the patients to publish the data concerning this study.

COMPETING INTEREST:
The author declared no conflict of interest.

AUTHORS' CONTRIBUTION:
MA: Manuscript writing.
NB: Manuscript editing and maintaining the integrity of research.
IE: Data entry.
MSP: Statistical analysis.
FSB: Data collection.
All authors approved the final version of the manuscript to be published.

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