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RESEARCH ARTICLE

DETERMINATION OF HAEMODIALYSIS ADEQUACY BY IONIC DIALYSANCE: CLINICAL APPLICATION AND LIMITATIONS

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ABSTRACT

Background and aim of study: Morbidity and mortality in hem dialysis patients are closely related to dialysis adequacy. Recently, ionic dialysance is becoming more popular as a method to assess the delivered Kt/V of dialysis treatment. The aim of this study was to assess the correlation between Kt/V measured by ionic dialysance (Kt/Vocm) and Kt/V calculated with Daugirdas formula (Kt/V D) taking into account different estimates of urea distribution volume(V) and to assess the variability of treatment dose delivered to individual patients.

Methods: Our prospective study was conducted for 4 weeks period on 40 patients(22 males,18 females) with ESRD on regular hemodialysis.

Hemodialysis treatments for the studied patients were performed using a Fresenius 5008 machine equipped with online clearance monitor (ocm). Ionic dialysance was measured by conductivity monitoring for the studied patients per session. The second generation Daugirdas formula was used to calculate the Kt/V (Kt/V D) per week. Values of V to allow comparison between Kt/Vocm and blood-based Kt/V were determined using Watson formula (Vw) and bioimpedance spectroscopy (Vimp).

Results: There was a significant correlation between Kt/V measured by ionic dialysance with using Watson formula to determine urea volume distribution (Kt/Vw.ocm) and Kt/V calculated by Daugirdas formula (Kt/V.D) in both single and double pool. However, Kt/Vw.ocm underestimated Kt/V.Dsp by 9.0% (−0.139 ± 0.2673 and the Kt/VD. eq by 6.7%(−0.1080 ± 0.2082) The correlation between Kt/Vocm when V values estimated using Vimp and Kt/V.Dsp or Kt/V.Deq became stronger. Kt/Vocm varied greatly within individual patients, but there was no statistically significant difference between the coefficient of variations (CVs), from either method.

Conclusion: Kt/V measured by ionic dialysance appears to be of good clinical interest and adequacy. Accurate estimation of V is required for Kt/V calculated from ocm to be consistent with the blood-based methods. Bioimpedance spectroscopy(Vimp) used for estimating V ensure better correlation between ocm and blood-based Kt/V.Substantial variation in Kt/V implies repeated measures are necessary to gain a true picture of the mean treatment dose being delivered to patients.

INTRODUCTION

An adequate delivery of Haemodialysis (HD) treatment dose is an important factor in the morbidity and mortality of patients treated with HD (Held *et al.,* 1991). Regular evaluation of delivered treatment dose, commonly performed by measurement of Kt/V, is necessary to intervene when the delivered treatment is inadequate. To assess Kt/V, the second generation Daugirdas formula is advocated by both K-DOQI and EDTA guidelines (NKF-K/DOQI 2000; European Best Practice Guidelines Expert Group on Hemodialysis 2002). Both guidelines recommend measurement of HD dose at least once a month. Recent studies suggest that substantial variation in delivery of Kt/V occurs within intra-individual HD treatments on a session-to-session basis (Kloppenburg *et al.,* 1999; McIntyre *et al.,* 2003). Thus, a more frequent assessment of Kt/V is desirable. However, the need for blood sampling makes more frequent assessment of Kt/V by the standard approach, impractical. Techniques based on measurement of ionic dialysance facilitate the evaluation of dialysis dose by online monitoring of the Kt/V **(**Kt/Vocm**)** (Petitclerc *et al.,* 1995; Lindsay *et al.,* 2001; Mercadal *et al.,* 2005). Assessment of dialysis dose based on ionic dialysance was shown to correlate well with Kt/V assessed by traditional urea kinetic modeling (ukm) (Mercadal *et al.,* 2005; Di Filippo *et al.,* 1998). However, despite highly significant correlations, several studies showed either lower or higher values of Kt/Vocm. compared with Kt/Vassessed by ukm. One reason for these differences is the fact that in some studies, Kt/Vocm, which is a single-pool model, was compared with equilibrated

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Kt/V (Kt/V.Deq) (McIntyre *et al.,* 2003; Petitclerc *et al.,* 1995; Lindsay *et al.,* 2001; Mercadal *et al.,* 2005). However, another factor which is likely to play a major role in the disagreement between Kt/Vocm and Kt/V assessed by traditional modelling is the estimation of urea distribution volume (V). With the ionic dialysance method, **V** has to be inserted in order to calculate the final Kt/Vocm. So far, in the studies which addressed Kt/V, most commonly the Watson formula is used to assess V(Vw) (Mercadal *et al.,* 2005). However, several studies questioned the reliability of these anthropometry-based equations (Kloppenburg *et al.,* 1999; McIntyre *et al.,* 2003; Petitclerc *et al.,* 1995; Lindsay *et al.,* 2001; Mercadal *et al.,* 2005; Di Filippo *et al.,* 1998; Manzoni *et al.,* 1996; Mercadal 1998). Recently, advances in the online monitoring of conductivity during HD sessions have made the repeated measurement of Kt/V on all HD treatment sessions a practical proposition.This method relies on the fact that the diffusive properties of sodium and urea are similar and that sodium flux can be measured noninvasively using conductivity measurements in the dialysate (Petitclerc 1999). Devices using the ionic dialysance method measure both clearance (K) and treatment time (t) but require a precise input value for V for calculating Kt/V (Moret *et al.,* 2007; Lindley *et al.,* 2009).

Aim of the study

The aim of the present study was to assess the correlation between Kt/V measured by ionic dialysance (Kt/Vocm) and Kt/V calculated with Daugirdas formula (Kt/V D) taking into account different estimates of V and to assess the variability of treatment dose delivered to individual patients.

MATERIALS AND METHODS

Our prospective study was conducted for 4 weeks period on 40 patients (22 males, 18 females) with ESRD on regular HD. All patients were stable and have been on HD for more than 6 months. All patients were oliguric-anuric. It was assumed therefore that none of these patients still having a residual renal function. All patients were dialyzing via arterial venous fistula (AVF). No changes were made to any of the dialysis prescriptions over the study period. Informed written conscent was obtained from the studied patients. HD treatments for the studied patients were performed using a Fresenius 5008 machine (Fresenius Medical Care, Hamburg, Germany) equipped with ocm. All HD sessions were done using high permeability polysulfone dialyzers (surface between 1.6 and 2 m^2), bicarbonate buffering and a dialysate sodium concentration of 138 mmol/l and the temperature of dialysate was set at 37°C. All patients dialyzed three sessions per week, 4h for each session. There were no major variations to blood pump during the duration of the study. All data related to the dialysis session were registered to patient specific files at the end of each session for subsequent analysis.

Ionic dialysance

Ionic dialysance (Ktocm) was measured by conductivity monitoring using ocm. The calculation of the mean ionic dialysance is based on differences in inlet and outlet conductivity values every 30 min. Mean ionic dialysance multiplied by the real duration of the session is used to calculate Ktocm. Because conductivity is related to ion concentration and the transfer characteristics of sodium and urea are similar, the ionic dialysance reflects the clearance of urea. The value for V however must be calculated and entered separately. Ktocm was divided by Vw and Vimp, to assess correlation with Kt/V.Dsp and Kt/V.Deq

Urea distribution volume (V)

Total body water, which is assumed to be equal to V, was calculated by the dialysis machine using the empirical formula of Watson (Vw) taking into account post-dialysis weight, height, gender and age (see Appendix A) (Watson *et al.,* 1980). Vw was used to calculate Kt/Vocm (Kt/Vw.ocm). Kt/Vw.ocm was studied as a function of Kt/V.D calculated from ukm based on the Pre- and post-dialysis serum urea/week in midweek dialysis session):

- In single-pool (KT/V.Dsp): by Daugirdas second generation equation calculated from pre- and post-dialysis urea in a single treatment, time of the session and ultrafiltration volume (see Appendix B) (Daugirdas 1993).
- In double pool (Kt/V.Deq): assessed after the correction of (Kt/V.Dsp) using the rate adjustment equation of Daugirdas and Schneditz (see Appendix C) (Daugirdas and Schneditz 1995).

We also compared V calculated by Watson formula (Vw) with that measured directly by bioimpedance spectroscopy using the body composition monitor (Fresenius Medical Care) before HD session. Overhydration was then subtracted from measured total body water to yield total body water at dry weight (Vimp). Food or water was prohibited during the course of HD session and the patients weight was measured before and after session to determine weight loss (ΔP). Determinants of inter-treatment changes in Kt/Vw.ocm, Kt/Vimp.ocm and Kt/V.D were assessed during 4 weeks study period.

Statistical analysis

The data of our study expressed as mean±SD or percentage. Correlation between data was analysed using linear correlation coefficient. Bland–Altman analysis was used for comparison and evaluation methods. Distribution plot histogram for Kt/V of patients over 4 weeks study was analysed. Comparative study was conducted using student t-test We used GraphPad Software, Inc. QuickCalc (www.graphpad.com) for data analysis. P value <0.05 considered to be significant.

RESULTS

Demographic characteristics of 40 studied patients are shown in Table 1. HD sessions data for our 40 patients are shown in Table 2.

Mean values of Kt/Vw.ocm, Kt/V.Dsp,Kt/V.Deq and Kt/Vimp.ocm were. 1.35±0.19, 1.49±0.267, 1.46±0.209 and 1.517± 0.294 respectively. There was statistically significant difference between Kt/Vw.ocm and Kt/V.Dsp (p=0.0021) and Kt/V.Deq (p=0.0017). There was no statisticaly significant

difference between Kt/Vimp.ocm and Kt/V.Dsp and Kt/V.Deq (p=0.511;p=0.12 respectively) (Table 3)

Table 1. Demographic characteristics of the studied patients

Variable	
Age(years)	53.7± 11.4
Gender(no.)	
Male	22(55%)
Female	18(45%)
BMI(kg/m^2)	24.5±4.26
Duration on hemodialysis(months)	42.8±23.41
Aetiology of ESRD	
Diabetis mellitus	10(25%)
Hypertension	8(20%)
Glomerulonephritis	8(20%)
Lupus nephritis	6(15%)
Chronic interstitial nephritis	4(10%)
Obstructive uropathy	2(5%)
Unknown	2(5%)

Table 2. Characteristics of hemodialysis treatment

Variable	Mean+SD
Duration of dialysis session(min)	240.8±15.6
Blood flow rate(ml/min)	325.7±17.3
Dialysate flow rate(ml/min)	498.4± 27.8
Total ultrafiltration(ml)	1784.3±786.2
Predialysis weight(Kg)	67.8±14.7
Postdialysis weight(Kg)	66.3±13.8

Kt/V. Deq became better (r=0.6835, p<0.0001; r=0.6943, p<0.0001) (Table 4; Fig.4,5). However, Kt/Vw.ocm underestimated Kt/V.Dsp by 9.0% (−0.139 ± 0.2673 and the Kt/VD.eq by 6.7%(−0.1080 ± 0.2082) There was a high degree of precision between the two measures as illustrated by Bland–Altman plot (Fig.6,7).

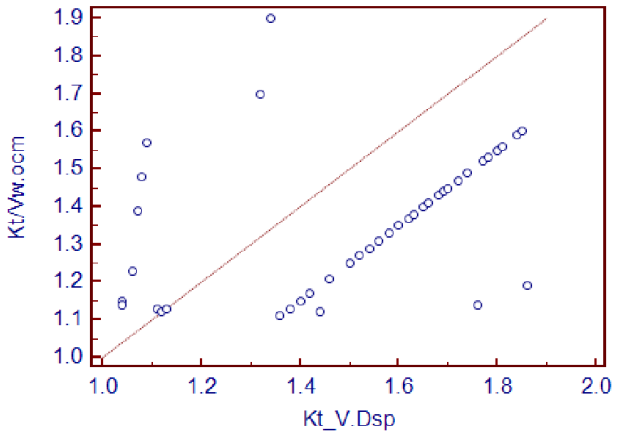

Fig.1.Correlation coefficient between Kt/Vw.ocm and Kt/V.Dsp

Table 3. Comparison of different methods of Kt/V estimation

Variable	N	Mean±SD	95% CI	Minimum	Maximum	P* value	P** value
Kt/Vw.ocm	40	1.354±0.19	1.293-1.415	1.110	1.900		p**=0.006 Sig.
Kt/V.Dsp	40	1.493±0.267	1.408-1.578	1.040	1.860	P*=0.0021. Sig.	p**=0.51 NS
Kt/V.Deq	40	1.462±0.209	1.395-1.592	1.100	1.760	P*=0.0017 Sig	p**=0.12 NS
Kt/Vimp.ocm	40	1.517±0.294	1.423-1.610	1.010	1.890	P*=0.006 Sig.	

P*=Kt/Vw.ocm compared with Kt/V.Dsp,Kt/V.Deq and Kt/Vimp.ocm,p**= Kt/Vimp.ocm compared with Kt/V.Dsp,Kt/V.Deq and Kt/Vw.ocm using student t-test.Sig.=significant. NS=non sig.

Table 4.Correlation coefficient between Kt/Vocm(Kt/Vw.ocm,Kt/Vimp.ocm)and blood based Kt/V (Kt/V.Dsp,Kt/V.Deq)

		Kt/Vw.ocm	Kt_V.Dsp	Kt/V.Deq	Kt/Vimp
Kt/Vw.ocm	Correlation Coefficient		0.355	0.487	0.419
	Significance Level P		0.0247	0.0014	0.0071
	n		40	40	40
Kt_V.Dsp	Correlation Coefficient	0.355		0.744	0.684
	Significance Level P	0.0247		<0.0001	<0.0001
	n	40		40	40
Kt/V.Deq	Correlation Coefficient	0.487	0.744		0.694
	Significance Level P	0.0014	<0.0001		<0.0001
	n	40	40		40
Kt/Vimp	Correlation Coefficient	0.419	0.684	0.694	
	Significance Level P	0.0071	<0.0001	<0.0001	
	n	40	40	40	

Pearson correlation coefficient

Kt/Vw.ocm versus blood based Kt/V and Kt/Vimp.ocm

There was a significant correlation between Kt/V measured by ionic dialysance with using Watson formula to determine V (Kt/Vw.ocm) and Kt/V calculated by Daugirdas formula (Kt/V.D) in both single and double pool (r=0.3547, p<0.0247; r=0.4868,p=0.0014 espectively) (Table 4; Fig.1,2). There was also a significant correlation between Kt/Vw.ocm and Kt/Vimp (r=0.4189,p=0.0071) (Table 4; Fig.3). The agreement between Kt/Vocm when V estimated using Vimp and Kt/V. Dsp and Kt/Vimp.ocm over derestimated Kt/V.Dsp by only 1.2% (0.0230±0.224) and Kt/V.Deq by 2.7% (0.0547±0.2114) (Fig.8,9)) There was considerable variation in both delivered Kt/Vw.ocm and K/Vimp.ocm and Kt/V.D within individual patients over the 4 weeks study (Fig.10,11,12,13). The mean coefficient of variations (CVs) within individual patients was 0.14±0.12 (0.06–0.14) for Kt/Vw.ocm and 0.12±0.03 (0.1–0.13) for Kt/Vimp.ocm and 0.1±0.02(0.09-0.11) for Kt/V.D. There was no statistically significant difference between the CVs, from either method.

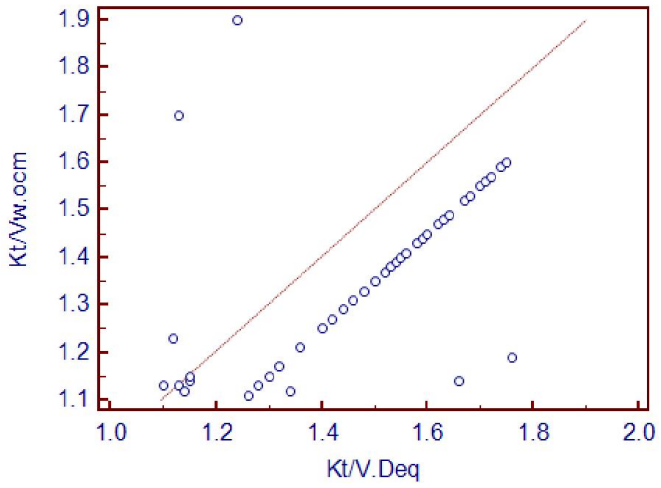

Fig.2. Correlation coefficient between Kt/Vw.ocm and Kt/V.Deq

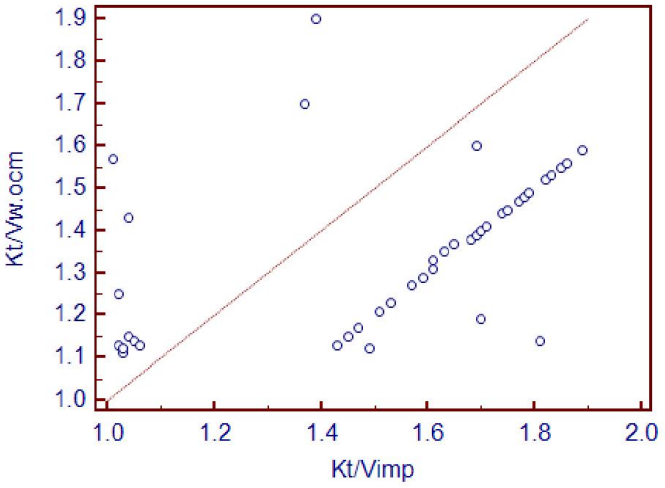

Fig.3. Correlation coefficient between Kt/Vw.ocm and Kt/Vimp

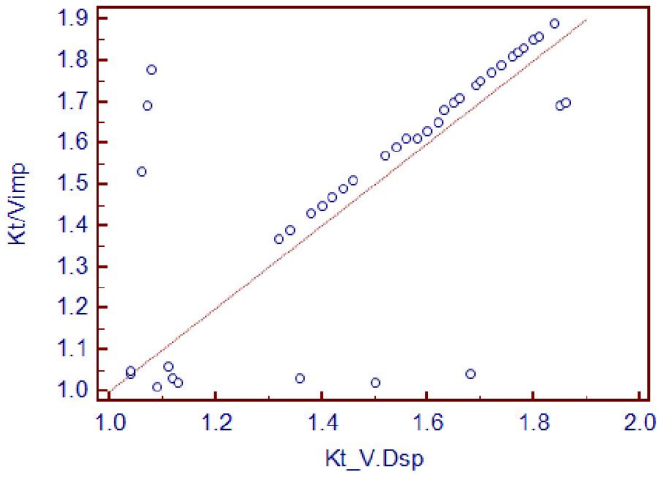

Fig.4. Correlation coefficient between Kt/Vimp and Kt/V.Dsp

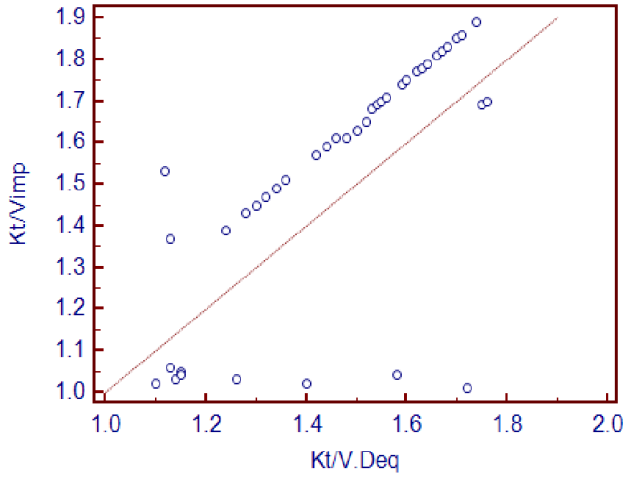

Fig.5. Correlation coefficient between Kt/Vimp and Kt/V.Dsp

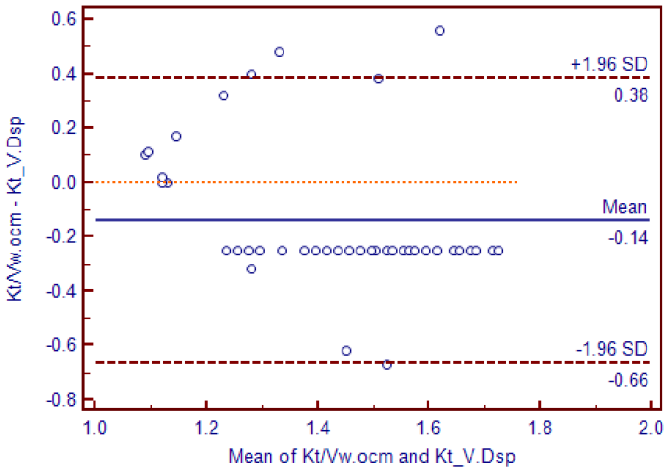

Fig. 6. Bland-Altman plot for comparison and evaluation of Kt/Vw.ocm and Kt/V.Dsp

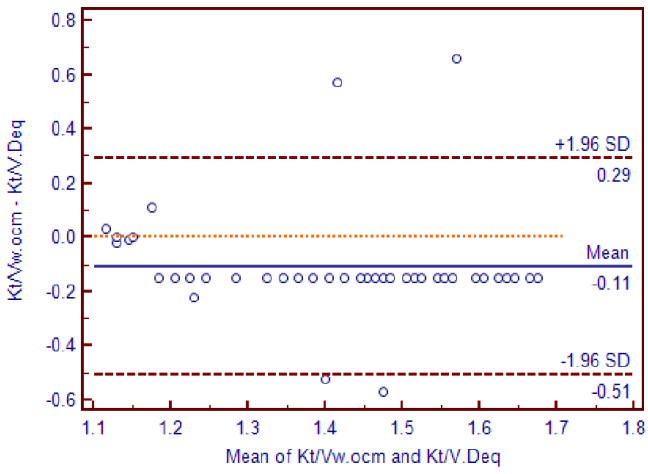

Fig.7. Bland-Altman plot for comparison and evaluation of Kt/Vw.ocm and Kt/V.Deq

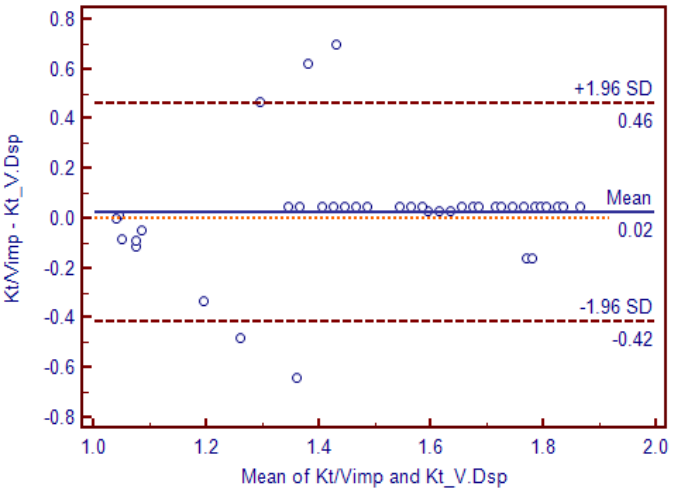

Fig.8. Bland-Altman plot for comparison and evaluation of Kt/Vimp.ocm and Kt/V.Dsp

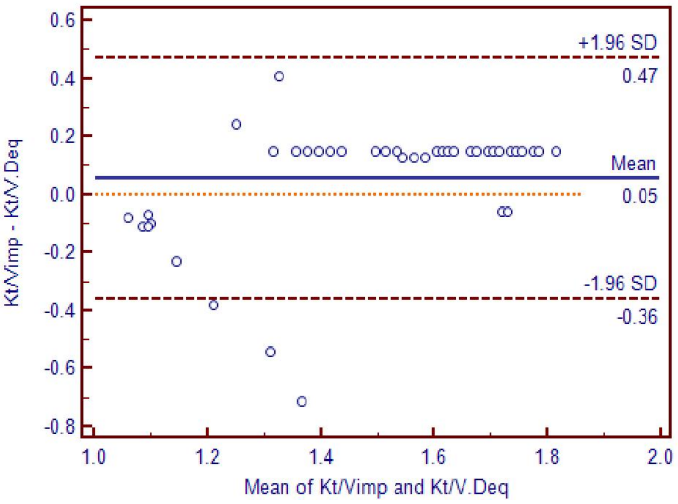

Fig.9. Bland-Altman plot for comparison and evaluation of Kt/Vimp.ocm and Kt/V.Deq

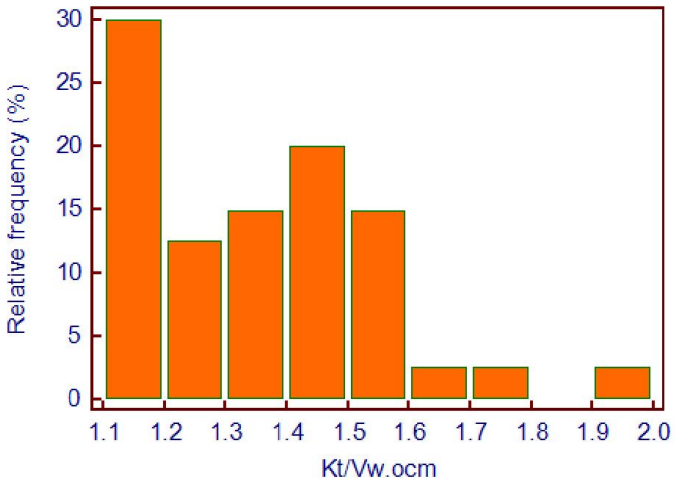

Fig.10. Hisogram distribution plot for Kt/Vw.ocm over the 4 weeks study

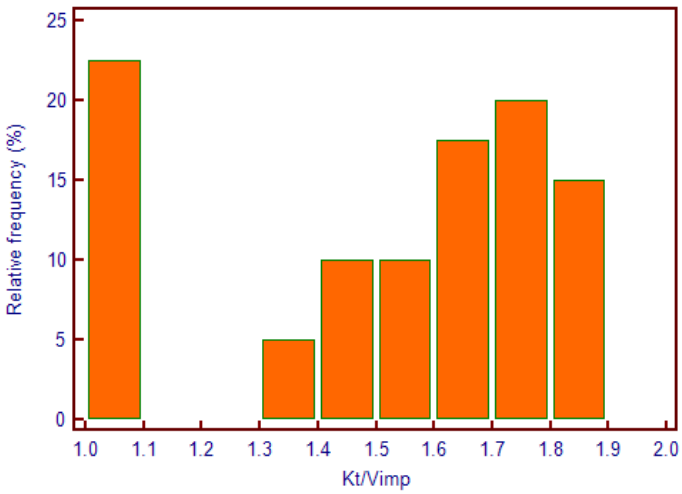

Fig.11. Hisogram distribution plot for Kt/Vimp.ocm over the 4 weeks study

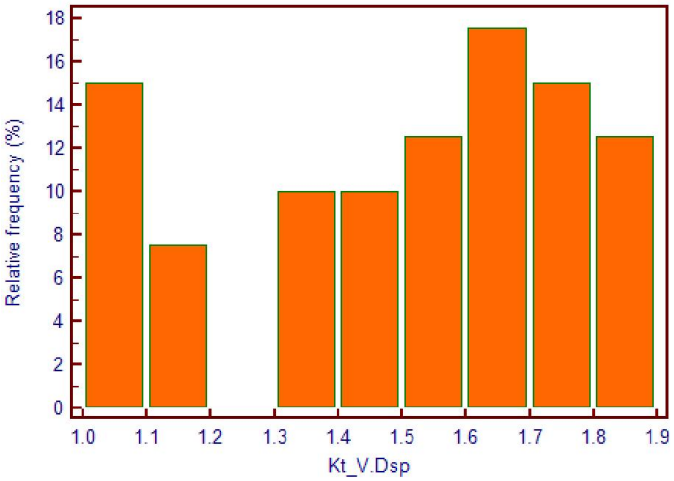

Fig 12. Hisogram distribution plot for Kt/V.Dsp over the 4 weeks study

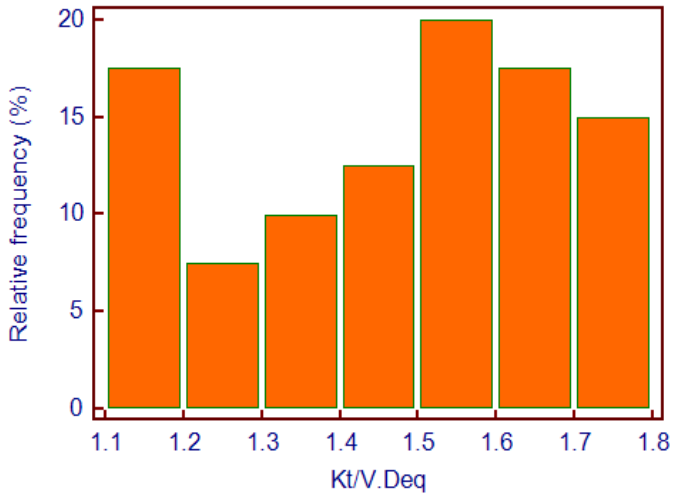

Fig 13. Hisogram distribution plot for Kt/V.Deq over the 4 weeks study

DISCUSSION

Our study confirms the clinical usefulness and application of continuous ocm to assess the delivered dose of HD in chronic HD patients. The ability to assess Kt/V on each treatment also gives some insight into the significant variability of delivered dose that each individual patient is subjected to. Ionic dialysance derived Kt/V (Kt/Vocm) has been validated as an effective and accurate system for the assessment of dialysis adequacy (as measured by Kt/V) (Coyne *et al.,* 1997; Watson *et al.,* 1980). In our study, there was a significant correlation between Kt/V measured by ionic dialysance (Kt/Vw.ocm) and Kt/V calculated by Daugirdas formula (Kt/V.D) in both single and double pool. However, Kt/Vw.ocm underestimated Kt/V.Dsp by 9.0% (−0.139 ± 0.2673 and the Kt/VD.eq by 6.7% (−0.1080 ± 0.2082) Our results are consistent with previously published data (20-25). All these studies also demonstrated a small underestimate of Kt/V when measured by ionic dialysance. Gotch *et al.* (2004) have postulated that ionic dialysance may underestimate effective urea clearance due to the effects of systemic salt loading during the ionic dialysance measurements, resulting in a reduced conductivity diffusion gradient across the dialyser, especially when urea clearance is >150 ml/min and the Kt/V also depends on the effective duration of dialysis (t) (Gotch *et al.,* 2004). In our study we prohibited salt and water intake during HD sessions and the duration of session is constant when considering the cases related to alarms and bypass. Therefore salt loading and duration of dialysis could not explain the underestimated Kt/V by ocm in our study, but has been postulated to be as a result of the effect of cardiopulmonary recirculation, that differences between study populations and nature of conductivity methods (Moret *et al.,* 2007**)** and that anthropometrically estimated V volumes in our study were significantly larger than V volumes determined from ukm or bioimpedance. This has been consistent with other published studies (Wuepper *et al.,* 2003; Cooper *et al.,* 2000; Chertow *et al.,* 1995; Kloppenburg *et al.,* 2001; Dumler 2004).

A possible explanation for our observation that V calculated from anthropometric data may overestimate total body water is that a significant depletion in muscle mass is present in many dialysis patients (Wuepper *et al.,* 2003; Goldau 2002). Because of this overestimation of V, McIntyre *et al.* (2003) who studied a more homogeneous group of patients**,** showed a better agreement between Kt/Vw.ocm and Kt/V.Deq, in contrast to the data of Di Filippo *et al.* (2001) who showed higher values for Kt/V measured by ionic dialysance compared with Kt/V.Deq. The bioimpedance has been found to agree closely with body water calculated from deuterium-oxide dilution and by direct quantification of dialysis studies in HD patients **(**Koubaa *et al.,* 2010; Cooper *et al.,* 2000**)**. However the results differ according to the technique (mono or multi frequency impedance) and to the mathematical model used (Koubaa *et al.,* 2010). The reproducibility of Vimp depends on electrode positioning and contact, and various patient-related factors that are relatively easy to control (Koubaa *et al.,* 2010). Our study indicated that bioimpedance volume offers better correlation between ionic dialysance and the Kt/V.Dsp or Kt/V.Deq and there was no statistically significant difference between Kt/Vimp.ocm and Kt/V.Dsp and Kt/V.Deq (p=0.511; p=0.12 respectively). There was considerable variations in both delivered Kt/Vw.ocm and K/Vimp.ocm and Kt/V.D within individual patients over the 4 weeks study and all methods demonstrated a similar inter- and intra-patient variability There was no statistically significant difference between the CVs, from either method. If a theoretical level of 'adequate' dialysis was set at 1.1, then 70% of Kt/Vw.ocm,78% of Kt/Vimp,75% Kt/V.Dsp,87% of Kt/V.Deq of the patients studied had variation within the 4 weeks study period that, depending on when a single Kt/Vocm had been measured, their status as adequately or inadequately dialysed could have been altered. Kloppenburg *et al.* (1999) undertook multiple assessments of Kt/V using serum urea reduction. This study concluded that multiple measurements were necessary to produce an averaged delivered dose and that basing clinical decisions of dialysis prescription on a single (usually monthly) urea-based Kt/V was an unjustified practice and should be abandoned. Our study showed that the use of Kt/Vocm particularly Kt/Vimp.ocm gives a convenient and reliable method of fulfilling this ideal.

Conclusion

Kt/V measured by ionic dialysance appears to be of good clinical interest and adequacy. Accurate estimation of V is required for Kt/V calculated from ocm to be consistent with conventional blood-based methods. Bioimpedance spectroscopy (Vimp) used for estimating V values ensure better correlation between ocm and blood-based Kt/V.Substantial variation in Kt/V implies repeated measures (ideally for all treatments) are necessary to gain a true picture of the mean treatment dose being delivered to patients.

Appendex A: Watson equation: (Watson *et al.,* 1980):

Males : Vwatson = + 2.447 + 0.3362 x weight (kg) + 0.1074 x height(cm) – 0.09156 x age (years)
Female :Vwatson = - 2.097 + 0.2466 x weight (kg) + 0.1069 x height (cm)

Appendex B: The Daugirdas Second generation equation: (Daugirdas 1993):

$$(Kt/V)_{sp} = -\ln\left[(c_{end}/c_0) - 0,008t\right] + \left[4 - 3,5(c_{end}/c_0)\right]\Delta P/P$$

ΔP : weight loss by ultrafiltration - P : post-dialysis weight - t : duration of the session.

Cend andCo: the urea concentrations at the start and end of the interdialytic interval.

To avoid dilution when obtaining the postdialysis sample (ct), the ultrafiltration rate was set to zero and the blood pump rate was reduced to 100 mL/min.Ten seconds after reducing the blood flow, the blood pump was turned off. The sample was then drawn from the arterial needle tubing.
Plasma urea concentrations were corrected for plasma water according to this equation:
C(g/Kg water)= C(g/l) (1-0,001*Protidemia(g/l))

Appendix C: Equation of Daugirdas and Schneditz (The rate equation to convert single-pool Kt/V into equilibrated:

(Daugirdas and Schneditz 1995) (Kt/V)eq = (Kt/V)Dsp – (0.6/t) (Kt/V)Dsp+ 0.03.

The authors declared that there is no conflict of interest

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