Results of improvement in adequacy of intermittent hemodialysis in uremic patients

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Abstract

Purpose: Increasing number of patients, who need intermittent hemodialysis (IHD), is a great challenge for every society. The aim of study is to look if small increase in IHD adequacy is able to improve standard medical parameters.

Material and methods: In 40 patients, Kt/V was monitored on-line during the middle IHD session in the week, 4 times in each of 6 consecutive months. In the first month of observation Kt/V was lower (1.09±0.02) than in the further months, in which Kt/V was increasing to 1.17±0.01. Blood count was estimated every month. At the beginning of study period, after 3 months and at the end of studies, dry body mass, body mass index (BMI), the blood pH and serum concentration of calcium, phosphate, intact parathormone (iPTH), total protein, albumin, cholesterol, iron, ferritin, urea and creatinine were determined.

Results: The increase in Kt/V was accompanied by rising values of hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume, iron, blood pH before and after IHD session as well as by decreasing values of PTH. Statistically unchanged parameters included dry body mass, BMI, serum concentration of total protein, phosphate, cholesterol and ferritin as well as white blood cells and platelet count. There were correlations between Kt/V and serum concentrations of phosphate, PTH, ferritin, Hb and Hct, indicating that higher IHD doses were provided to patients in more advanced uremic state.

Conclusions: Even small increase in IHD adequacy leads to beneficial changes in management of uremic patients.

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Introduction

Increasing number of uremic patients, who need dialysis treatment, is a great challenge for every society but especially for poor and developing countries. In Poland, number of dialyzed patients increased from 497 in 1981 to 11440 in 2003, that is over 20-times [1]. Estimated number of patients on renal replacement therapy is 27500 in 2010 [2]. Thus, a question how to counterbalance medical expectancies and costs is of special importance.

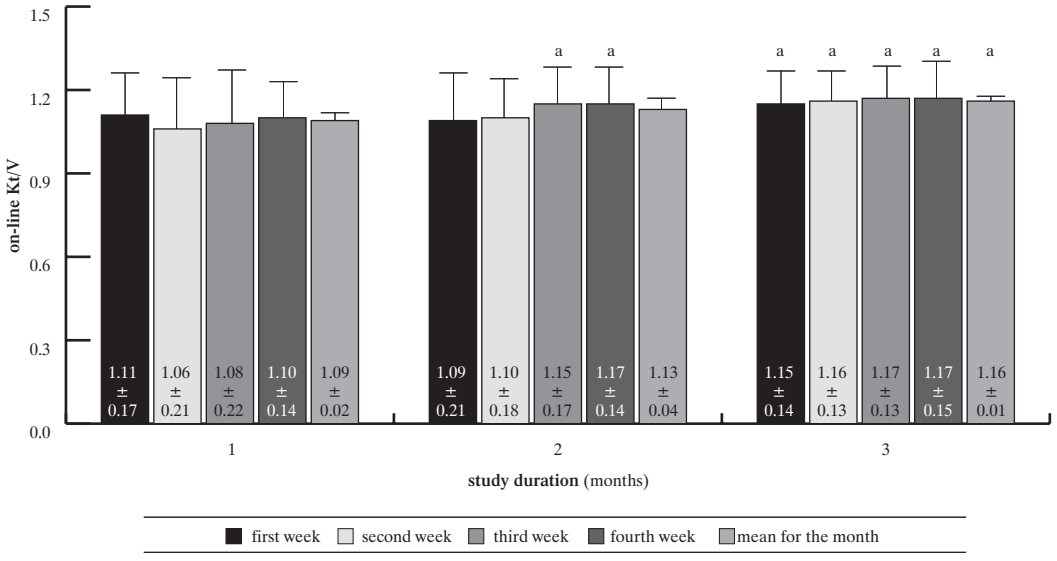
The aim of our study is to look if small (not very expensive) increase in intermittent hemodialysis (IHD) adequacy, expressed by Kt/V, is able to improve standard medical parameters.

Material and methods

Studies were carried out during six months in 40 uremic patients (23 women, 17 men) in the age of 58.9±14.7 years. All patients were stable in the month proceeding the study beginning. Causes of end-stage renal disease included: diabetic nephropathy (12 patients), chronic glomerulonephritis (7 patients), chronic tubulointerstitial nephritis without renal stones (4 patients) or with renal stones (3 patients), polycystic kidney disease (2 patients), amyloidosis, renal cirrhosis, lupus nephritis, myeloma multiplex, chronic lymphatic leukemia (one case each). In 7 patients etiology of end-stage renal disease remained unknown. Arterial hypertension occurred in 25 patients, cardiovascular disease – in 20 patients, diabetes mellitus type I – in 2 patients, diabetes mellitus type II – in 10 patients.

Patients were treated with dialyses for 21 (1-185) months. One patient before starting IHD program was treated with continuous ambulatory peritoneal dialysis for 14 months. Those, who were dialyzed longer than one month but shorter than 6 months (n=6) were also included into the study, because they

Figure 1. **Values of on-line Kt/V during the first three month of study**



* $p<0.05$ as compared to the mean for the first month of study

had started their IHD program in planned manner with mature arterio-venous fistulas and did not show any problems related to dialysis initiation.

Patients (n=36) were taken erythropoietin beta intravenously in the individual doses ranging from 1 000 to 8 000 units per week (3 375±2 371 units per week including four patients not receiving erythropoietin). Iron was supplemented intravenously in 27 patients in the doses of 100 mg per week (67.5±47.4 mg per week including 13 patients not receiving iron). Alfa-calcidol was applied orally to 12 patients in the individual doses of 0.25 to 100 μg per day. Calcium carbonate was administered in 38 patients in the doses of 1.0 to 9.0 g per day. Doses of intravenous drugs were stable. Prescriptions of oral drugs were also unchanged, but probably influenced by patients' compliance.

In all patients, Fresenius dialysis machines type 4008 S and polysulfone-based membranes were used. Dialyzers were not reused. Composition of dialysis solution was not changed during the study.

On-line monitoring of Kt/V was repeatedly performed during the middle IHD session in the each week in six consecutive months. Measurements of Kt/V based on the conductivity method. Total body water, which is assumed the equal the urea distribution volume, was calculated using the formula of Watson et al. [3] for women and men, respectively.

In the first month of study, IHD schedule was not changed as compared to that used in the few previous months in respect of blood and dialysate flows, duration of IHD session and selection of a dialyzer. Values of on-line Kt/V were stable in weekly evaluations. In the next weeks, efforts were made to obtain significantly higher Kt/V by an increase in blood flow and/or dialysate flow. The increase in blood flow was preferable but not always sufficiently possible due to poor blood access or patients' intolerance. In such cases, an increase in dialysate flow (from 500 ml/min to 800 ml/min) accompanied trials to enhance blood flow.

In the second month of study, on-line Kt/V in the third and fourth week was significantly higher than mean on-line Kt/V for the first month of study, but mean values for both months were still not different.

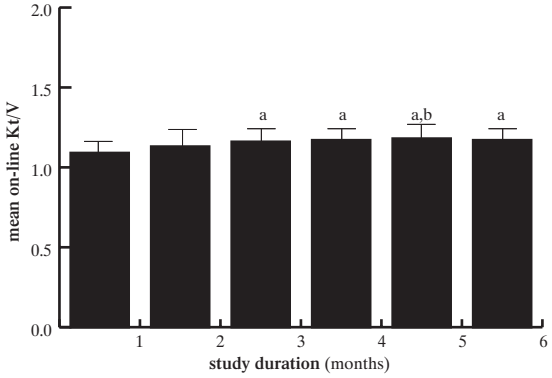
In the third month of study, values of weekly Kt/V estimations and mean monthly Kt/V were stable and significantly higher than mean value for the first month (*Fig. 1*). Thus, our aim to obtain slightly, but significantly higher Kt/V was achieved. During the next three months of study the more effective IHD schedule was maintained, but further efforts to improve adequacy of IHD were not undertaken.

Hemodialyses were performed three times a week. The average duration of IHD session was not significantly different in consecutive months, ranging from 4.19±0.32 hours to 4.24±0.32 hours. The majority of the patients (n=34) were dialyzed through arteriovenous fistulae (85%). Permanent vascular catheters were used in 6 patients (15%). Effective blood flow increased from 216±26 ml/min to 234±15 ml/min. The dialysate flow increased from 545±108 to 665±151 ml/min.

Results of white blood cell (WBC) count, hemoglobin – Hb, hematocrit – Hct, mean corpuscular volume – MCV and platelet (PLT) count were analyzed every month. At the beginning of study, after 3 months and at the end of studies, dry body mass, body mass index (BMI), the blood pH and serum concentration of ionized calcium, phosphate, intact parathormone (iPTH), total protein, albumin, cholesterol, iron, ferritin, urea and creatinine were determined. Standard laboratory methods were applied for blood analysis. BMI was calculated by the formula of post-dialysis weight in kilograms per height in square meters.

Results are expressed as mean and one standard deviation or median and range of values. Distribution of values was

Figure 2. **Values of mean on-line Kt/V during six months of study**



[a]p<0.0009 as compared to result obtained in the first month of study
[b]p<0.041 as compared to result obtained in the second month of study

checked using Kołmogorow–Smirnov test. Statistical analysis included ANOVA test for repeated evaluations and ANOVA Friedman test with post hoc Scheffe test. Results of examined parameters were correlated to Kt/V values, using Spearman or Pearson correlation coefficients as appropriate. Two values of on-line Kt/V were used for correlations: simultaneously obtained Kt/V (simultaneous Kt/V) and mean Kt/V shown in the month proceeding blood analysis. A p value below 0.05 was considered as statistically significant.

Results

Values of Kt/V, obtained during six months of studies, are presented on *Fig. 2*. Mean on-line Kt/V was increasing from 1.09±0.16 in the first month to 1.16±0.13 in the third month (*Tab. 1*) and this higher value was maintained in the next three months of study. As assumed, there were no further significant changes in the mean on-line Kt/V after the second month of study.

The increase in Kt/V over six months period was accompanied by rising values of Hb, Hct, MCV, serum iron concentration, blood pH before and after IHD session as well as by decreasing values of serum iPTH. Statistically unchanged parameters included dry body mass, BMI, serum concentration of total protein, albumin, ionized calcium, phosphate, cholesterol, urea, creatinine and ferritin as well as WBC and PLT (*Tab. 2*).

There were correlations between Kt/V and serum concentration of examined parameters. For one parameter only the highest significant correlation coefficient shown with respective Kt/V during the entire study is presented. Positive correlations were found for phosphate (r=0.324, p=0.041 for simultaneous on-line Kt/V; r=0.370, p=0.019 for mean on-line Kt/V), iPTH (r=0.312, p=0.049 for simultaneous Kt/V; r=0.314, p=0.048 for mean Kt/V) and ferritin (r=0.417, p=0.007 for simultaneous Kt/V), whereas negative correlations – for Hb (r=-0.369, p=0.019 for simultaneous Kt/V; r=-0.376, p=0.017 for mean Kt/V) and Hct (r=-0.365, p=0.021 for simultaneous Kt/V; r=-0.374, p=0.017 for mean Kt/V).

Table 1. **Changes in effective blood flow and dialysate flow during three months of studies**

	First month			Third month		
Patient	Effective blood flow ml/min	Dialysate flow ml/min	Mean monthly Kt/V	Effective blood flow ml/min	Dialysate flow ml/min	Mean monthly Kt/V
1	237	500	1.09	239	800	1.10
2	190	500	1.06	234	500	1.07
3	190	500	0.98	233	500	1.03
4	233	500	1.06	250	500	1.08
5	207	800	1.19	233	800	1.30
6	234	500	1.15	236	800	1.23
7	237	500	1.42	240	800	1.45
8	234	500	1.01	237	800	1.11
9	188	500	1.11	206	500	1.17
10	235	500	1.19	237	800	1.24
11	244	500	1.27	245	800	1.37
12	228	500	0.94	232	800	1.06
13	188	500	0.88	208	500	1.00
14	237	500	1.16	242	800	1.17
15	235	500	1.09	247	800	1.11
16	188	500	1.22	210	500	1.30
17	235	500	1.24	236	800	1.36
18	235	500	1.03	242	800	1.06
19	242	500	0.94	243	800	1.07
20	186	800	1.14	225	800	1.32
21	236	500	1.22	248	800	1.32
22	225	500	1.40	231	500	1.38
23	200	500	1.11	214	500	1.12
24	227	500	1.06	231	800	1.09
25	187	500	0.59	222	500	0.87
26	138	500	0.91	187	500	1.02
27	189	500	0.84	231	500	1.02
28	185	500	1.01	232	500	1.11
29	234	500	1.22	249	800	1.36
30	224	500	0.84	232	500	1.10
31	234	800	0.96	256	800	1.05
32	190	500	1.22	233	500	1.19
33	239	500	1.05	257	500	1.07
34	244	500	1.24	260	500	1.28
35	172	500	1.08	208	500	1.13
36	191	800	1.05	234	800	1.19
37	228	800	1.11	234	800	1.14
38	236	500	1.09	261	500	1.12
39	227	500	1.11	234	800	1.14
40	239	800	1.32	234	800	1.33
mean	216	545	1.09	234	665	1.16
SD	26	108	0.16	15	151	0.13
median	228	500	1.09	234	800	1.125
range	138-244	500-800	0,59-1,42	187-261	500-800	0,87-1,45

Simultaneous on-line Kt/V showed correlation with the difference between post- and pre-dialysis serum creatinine level (r=0.354, p=0.025).

A positive correlation was shown between duration of treatment with IHD and on-line Kt/V (r=0.572, p=0.000 for simultaneous Kt/V; r=0.606, p=0.000 for mean Kt/V) and ultra-

Table 2. **Changes in examined parameters in the course of treatment with intermittent hemodialysis (IHD) with increasing values of on-line Kt/V**

Parameter	The beginning of study	The end of study	p value
hemoglobin (g/l)	99.1±16.6	105.1±12.5	0.002
hematocrit (%)	31.6±5.2	33.8±3.6	0.004
mean corpuscular volume (fl)	95.9±7.7	100.7±5.7	0.000
iron (μg/dl)*	58.2±29.6	73.2±27.8	0.002
pH before IHD session	7.26±0.04	7.41±0.04	0.000
pH after IHD session	7.34±0.05	7.48±0.05	0.000
intact parathormone (pg/ml)*	918 (38-3500)	420 (15-4341)	0.036
total protein (g/l)*	69.1±5.7	70.9±4.8	NS
albumin (g/l)	40.0±3.3	40.9±3.2	NS
ionized calcium (mmol/l)*	1.13±0.13	1.13±0.10	NS
phosphates (mmol/l)*	1.85±0.48	1.74±0.65	NS
cholesterol (mmol/l)*	5.26±1.27	4.95±1.60	NS
urea (mmol/l)*	19.1±4.0	17.9±3.7	NS
creatinine (μmol/l)*	752±179	742±178	NS
ferritin (ng/dl)*	740±558	632±346	NS
white blood cells (K/ml)	8.60±3.89	6.52±1.50	NS
platelet count (K/ml)	251±91	195±60	NS
dry body mass (kg)	70.4±15.6	70.9±16.1	NS
body mass index (kg/m^2)	28.2±6.7	28.2±6.8	NS

* serum concentration
NS – non significant

filtration volume per dialysis session (r=0.370, p=0.018). Duration of dialysis session was positively related to patients' height (r=0.428, p=0.006) and dry body mass (r=0.547, p=0.0001).

Inverse correlations were found for adequacy parameters and patient's characteristics: height (r=-0.510, p=0.000 for simultaneous Kt/V; r=-0.436, p=0.005 for mean Kt/V) and dry body mass (r=-0.362, p=0.021 for simultaneous Kt/V; r=-0.399, p=0.011 for mean Kt/V).

Discussion

The technique of Kt/V estimation, based on the use of a conductivity method, is at present possible in the newer dialysis machines. It enables frequent precise Kt/V monitoring, adjusted to patient's needs. In our study we could observe beneficial blood changes, occurring with the Kt/V increase.

Already, in 1983, Harter [4] have found that reducing dialysis dose as reflected by increasing the blood concentration of urea nitrogen averaged with respect to time (TAC_{urea}) significantly reduced Hct and Hb and increased the transfusion requirements. In 1996 Ifudu et al. [5] showed positive effect of higher URR (72%) on Hct compared to their standard URR (61%). Like in our study, patients were treated with a fixed dose of erythropoietin. Ifudu et al. [5] analyzed two different groups of patients with similar Hct at the start of observation, whereas in our study the dialysis dose was increasing in the same patients. Results from the United States Renal Data System, published in 1997, confirmed a correlation between dialysis dose and Hct level in IHD patients treated with erythropoietin [6]. In 2001, it was shown that adequate IHD diminished requirement for recombinant erythropoietin, even in cases in which celulose dialysis membranes were used [7]. In mentioned study, Hct did not correlate with Kt/V, whereas erythropoietin dose and Kt/V were inversely correlated [7]. In 2003, Salahudeen et al. [8] presented data showing Hct in patients with second generation spKt/V ranging from <1.23 to >1.68. There were no significant differences in Hct between groups, however, patients with highest Kt/V had significantly lower serum concentration of creatinine and pre-albumin, what may indicate undernutrition, although serum albumin level was also similar in all spKt/V groups [8]. In our study, an increase in Kt/V was not accompanied with decreased nutritional parameters like dry body mass, BMI, or serum concentration of total protein, albumin, urea, creatinine and cholesterol. Serum ionized calcium concentration was also insensitive to changes in Kt/V. In studies of Harter [4] plasma calcium, cholesterol and triglyceride levels did not show significant changes with higher TAC_{urea}, but less adequate IHD correlated with increased risk from cardiovascular morbidity.

When patients with known causes of resistence to erythropoietin treatment (iron depletion, aluminium overload, severe hyperparathyroidism, acute or chronic infections) are excluded from the study, the beneficial effect of higher IHD adequacy on Hct may be related to removal of dialysable low-molecular-weight inhibitors of erythropoiesis, like spermine and/or polyamine [9,10]. In our study, this effect is also possible, but additionally the influences of serum iPTH decrease, serum iron concentration increase and less pronounced metabolic acidosis have to be considered as contributing factors. Beneficial effects of more effective IHD on plasma PTH and correction of metabolic acidosis were also seen by Harter [4], when results obtained with high TAC_{urea} (100 mg/dl) were compared to respective values shown with TAC_{urea} of 50 mg/dl.

Significant increase in MCV may be related to higher serum iron level as well as to probably greater removal of folic acid with higher IHD adequacy, but with fixed vitamin supplementation.

Correlations between Kt/V and below mentioned parameters indicate that higher IHD adequacy was applied to uremic patients in poorer clinical status. These patients showed higher serum concentrations of phosphate, iPTH, and ferritin as a marker of inflammation, and lower Hb concentration and Hct. Greater IHD adequacy in underdialyzed patients could evidently contribute in clinical improvement.

In our study, higher doses of dialysis and greater ultrafiltration volumes per session were provided to patients treated longer with IHD than those being on IHD on shorter period of time. Such clinical intervention may be related to decrease in residual renal function and to increase in inflammatory catabolic state over time.

In IHD patients, dry body mass and BMI were progressively lower with values of the second generation spKt/V increasing from <1.23 to >1.68 [8]. In other study, overweight patients received less dialysis as measured by spKt/V, and conversely, those with lower BMI received higher spKt/V [11]. In our study, Kt/V was inversely correlated with dry body mass and height, what is in agreement with cited data. Such negative correlation occurred despite longer dialysis sessions provided to patients

with greater dry body mass and height. As expected, Kt/V was greater in patients who received longer dialysis sessions.

Increases in dialysate flow and/or in dialysis duration lead to higher costs of IHD session, but optimizing erythropoietin responsiveness and iron utilisation an adequate dialysis treatment can contribute to a reduction of the costs of maintenance dialytic therapy.

In summary, our results indicate that even small increase in IHD adequacy may be accompanied by beneficial changes in management of uremic patients (better response on erythropoietin, diminished laboratory features of secondary hyperparathyroidism, better iron utilisation). Correlation between Kt/V and examined parameters indicate that higher IHD doses were provided to patients in more advanced uremic state. It may partially explain advantages observed with incremental IHD adequacy.

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