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CLINICAL STUDY

The effect of biocompatible peritoneal dialysis solutions on neutrophil to lymphocyte ratio

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Abstract

Introduction: Long-term exposure to dialysis solutions is an important contributor to the ongoing inflammatory process in peritoneal dialysis (PD) patients. Some studies have shown amelioration of this adverse effect with biocompatible solutions. We aimed to compare the neutrophil-to-lymphocyte (N/L) ratio in PD patients using biocompatible and standard solutions and to find out the association between N/L ratio and peritonitis indices. *Materials and methods*: This was a cross-sectional, multicenter study involving 120 prevalent PD patients. Seventy-one patients (59%) were using biocompatible solutions and 49 patients (41%) were using standard solutions. From blood samples, N/L ratio and platelet-to-lymphocyte ratio were calculated and mean platelet volume, erythrocyte sedimentation rate and hs-CRP values were detected. Data regarding the peritonitis rate and time to first peritonitis episode were also recorded. *Results*: Biocompatible and standard groups were similar regarding age and gender. N/L ratio and hs-CRP levels have been found significantly higher in patients using biocompatible solutions (3.75 ± 1.50 vs. 3.27 ± 1.3, $p = 0.04$ and 3.2 ± 2.5 vs. 1.8 ± 2.0, $p < 0.01$, respectively). Peritonitis rates and time to the first peritonitis episode were found similar in patients using both types of solutions (0.23 ± 0.35 vs. 0.27 ± 0.32, $p = 0.36$ and 32.8 ± 35.8 vs. 21.5 ± 26.9 months, $p = 0.16$, respectively). *Discussion*: N/L ratio was significantly higher in biocompatible solution users in parallel to hs-CRP levels, so biocompatible solutions seem to be related with increased inflammation in PD patients. Although we cannot make a certain explanation, we assume that there may be an association between acidity of the peritoneal content and virulence of microorganisms.

Keywords

Biocompatible solutions, standard solutions, N/L ratio, peritonitis rates, inflammation, peritoneal dialysis

History

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Introduction

Chronic inflammation is a non-traditional cardiovascular risk factor and it contributes to exaggerated mortality rates in chronic kidney disease (CKD) population.[1,2] Sustained exposure to dialysis solutions is an important contributor to the ongoing local and systemic inflammatory process in peritoneal dialysis (PD) patients. The anticipated inflammatory response might differ depending on the contents of the commercially available PD solutions. Preclinical studies on this issue provided that standard (conventional) PD solutions might impair the peritoneal immune defense mechanisms by distorting the function and viability of the mesothelial cells.[3,4] Therewithal, some observational cohort studies have shown amelioration of these adverse effects, characterized by neutral pH and relatively low-glucose degradation products.[5–8] Superior inflammatory marker levels,[5] peritonitis and exit site infection rates[6] and also a superior patient survival[7–9] have been reported by biocompatible PD solutions. However, in terms of peritonitis rates, the data from the randomized controlled trials revealed conflicting results; while some exerted significant benefits[10,11] some other studies reported a neutral effect with the use of biocompatible solutions.[12–14]

In recent years, researchers have focused on the neutrophil-to-lymphocyte (N/L) ratio, as a novel inflammatory marker by virtue of its simply accessible nature. This novel marker has been examined in a wide range of clinical situations; particularly ones having ongoing inflammation.[15–19] Studies subjecting CKD patients have exposed higher N/L ratio in either hemodialysis or PD patients, compared to the healthy subjects.[15,16] Further, one of the latest trials exerted this ratio as a strong predictor of overall and cardiovascular mortality in PD patients.[17] Considering all these data, one could assume to find a difference in N/L ratio between biocompatible solution users and standard solution users. However, there is lack of data in this subject, to the best of our knowledge.

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In the presented study, we aimed to compare N/L ratio in PD patients using biocompatible and standard solutions. Besides, we also intended to find out the association between N/L ratio and some peritonitis indices in PD patients.

Materials and methods

Patients and general characteristics

This was a cross-sectional, multicentered study involving 120 prevalent PD patients (60 men, 60 women). The patients had been on PD therapy for at least three months and under follow-up in one of the outpatient clinics of three different hospital nephrology departments in Turkey. Sixty patients were from Ankara Education and Research Hospital, 40 patients from Isparta Süleyman Demirel University Hospital and the rest 20 patients were from Afyon Kocatepe University Hospital. Patients younger than 18 years and older than 80 years, patients with active infection or inflammation, current malignancy and patients under immunosuppressive therapy were excluded. This trial was conducted in accordance with the principles of Helsinki Declaration and the protocol was approved by local Medical Ethics Committee of Süleyman Demirel University School of Medicine.

Our patients were using PD solutions containing dextrose in different concentrations and icodextrin as osmotic agent. Solutions with buffer status of the neutral pH and solutions with low glucose degradation products were both accepted as ''biocompatible solutions''. Subjects were separated into two groups, according to the types of solutions they had been using in previous three months. Seventy-one patients (59%) were using biocompatible solutions (biocompatible group) and 49 patients (41%) were using standard solutions (standard group). Biocompatible PD solutions were either Physioneal® (Eczacıbası, Baxter Healthcare, Castlebar, Ireland) or Balance® (Fresenius Medical Care, Wendel, Germany). (*Physioneal®*; pH:7.40 Na 132, Ca 1.25, Mg 0.25, Lactate 15 mmol/L, Bicarbonate 25 mmol/L. *Balance®;* pH:7.0 Na 134, Ca 1.25, Mg 0.5, Lactate 35 mmol/L. Standard solutions: pH:5.50 Na 132, Ca 1.25, Mg 0.25 or 0.50, Lactate 40 mmol/L).

Twenty out of 120 patients (16.7%) were performing automated peritoneal dialysis (APD) with continuous cyclic PD regimen. A cycler delivered 1000–1200 ml glucose containing solution into peritoneal space and drained it out at the end of every 90–120 minute period through the night time hours (approximately 10 hours). The remaining 100 patients were on continuous ambulatory peritoneal dialysis (CAPD) regimen and they were performing 4 daily manual exchanges with 1500–2500 ml solutions. Icodextrin containing solutions were used according to the volume status of the patients. For APD patients, the cycler delivered 1500–2000 ml icodextrin containing solution into peritoneal space during day-time hours and drained it out just before the night time exchanges. For CAPD patients, icodextrin was used at night time hours and remained in peritoneal space at least for 8 hours.

Clinical data

Baseline characteristics and medical history of the participants were acquired from hospital records. Age, gender, body weight, height and office blood pressure (BP) measurements were recorded beside primary etiology of CKD, concomitant disorders (hypertension, diabetes mellitus and coronary artery disease), time on PD, weekly peritoneal Kt/V, daily ultrafiltration volumes and daily urine output. Coronary artery disease was defined as having the history of balloon angioplasty, coronary artery stent or coronary artery bypass graft operation. Body mass index (BMI) was calculated with [weight (kg)/height^2 (m^2)] equation. Office BP measurements were repeated using a convenient cuff, two times after 5 minutes resting in sitting position and the average value was noted. Systolic blood pressure (SBP) $\geq$140 mm Hg and/or diastolic blood pressure (DBP) $\geq$90 mm Hg in office measurements, or being on current antihypertensive medications were defined as arterial hypertension (HT).

Peritonitis rates were calculated according to the recommendations of International Society of Peritoneal Dialysis.[20] Examined outcomes were peritonitis rate in terms of peritonitis episode per patient year and time to first peritonitis episode. Relapsed peritonitis was counted as a single episode.

Laboratory measurements

Venous blood samples were drawn from all the subjects after an overnight fasting period, particularly before the first exchange of the day. Complete blood count and biochemistry analysis [serum creatinine, serum albumin, total cholesterol, triglyceride (TG), calcium, phosphorus, parathormone and ferritin] were performed by automated procedures. White blood cell differential was determined as part of complete blood count testing. Volume conductivity scatter method was used in Beckman Coulter AU5800 analyzer machine (Beckman Coulter Inc., Brea, CA) for measurement of complete blood count in all three medical centers participating into the study. N/L ratio was constructed by dividing neutrophil count by lymphocyte count. Similarly, platelet-to-lymphocyte ratio (P/L) ratio was calculated as the ratio of the platelet count to lymphocyte count obtained from the same blood sample. Mean platelet volume (MPV) was calculated as fentoliter from blood samples that were drawn into two ml EDTA tubes. Erythrocyte sedimentation rate (ESR) was measured by spectrophotometric assay and hs-CRP was determined by high-sensitive turbidimetric method.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 15.0 for Windows (SPSS Inc., Chicago, IL). For the presentation of measurable continuous variables; mean and standard deviation were used. Frequencies and percentages were used while presenting the categorical data. For variables which met parametric test conditions, Student's *t* test and for others Mann–Whitney *U* test were used for two group comparisons. For the evaluation of categorical variables, chi-square (χ^2) test and if needed, Fisher's exact test were used. Independent relationships of N/L ratio, hs-CRP and P/L ratio with biocompatibility of PD solutions were examined separately by univariate linear regression analysis with enter method. All probability values were calculated by assuming a

two-sided p value of <0.05 with confidence intervals (CI) at the 95% level.

Results

The mean age of study population ($n = 120$) was 49.1 ± 13.7 years; 60 (50%) of which were male. Biocompatible and standard groups were similar regarding age and gender of the patients [(49.5 ± 14.1 vs. 48.4 ± 13.2, $p = 0.66$); (35 (49%) vs. 25 (51%), $p = 0.85$), respectively]. Two groups were also similar in terms of primary etiologies of kidney diseases ($p = 0.21$). Regarding comorbid conditions; the frequencies of hypertension, diabetes mellitus and coronary revascularization were 82%, 25% and 10% in biocompatible group and 81%, 24% and 12% in standard group, respectively ($p = 0.88$). The demographical characteristics and descriptive data of the groups are shown in Table 1.

Although the neutrophil, the lymphocyte and the total WBC counts were similar between the groups ($p > 0.05$, for all), mean N/L ratio has been found significantly higher in patients using biocompatible solutions ($p = 0.04$). Mean hs-CRP levels were also higher in these patients ($p < 0.01$). The P/L ratio has been found moderately higher in biocompatible solution users compared to that of standard group; however, the difference did not reach statistical significance (176 ± 79 vs. 157 ± 69, respectively; $p = 0.18$). Neither MPV nor ESR values were different between the two groups of patients ($p = 0.37$ and $p = 0.58$, respectively). Peritonitis rates and time to the first peritonitis episode were found similar in patients using both types of solutions. Laboratory results and peritonitis indices of the study participants are shown in Table 2.

Further, we classified the patients into two groups based on median value (3.29) of N/L ratio. The higher N/L ratio group had a trend toward shorter time to first peritonitis episode (21.7 ± 26.7 vs. 33.6 ± 36.6, $p = 0.06$). Peritonitis rates were similar between the patients having higher or lower N/L ratio (0.28 ± 0.39 vs. 0.21 ± 0.27, $p = 0.59$).

In univariate linear regression analysis, when N/L ratio was accepted as the dependent variable, biocompatibility of PD solutions was not found to be an independent predictor (β: 0.158, p: 0.085 and CI: from −0.065 to 0.998). Similarly, the relation between bio-compatibility and P/L ratio was not statistically significant when P/L ratio was the dependent variable (β: 0.119, p: 0.197 and CI: from −9.575 to 45.935). However using biocompatible solution was found to be an independent predictor of serum hs-CRP levels in linear regression model (β: 0.297, p: 0.001 and CI: from 0.576 to 2.303).

Discussion

In the present study, we primarily aimed to compare N/L ratio between biocompatible solution users and standard PD solution users; and assess possible associations between N/L ratio and peritonitis indices. According to our results, mean N/L ratio – a novel measure of inflammation – was significantly higher in biocompatible solution users in parallel to hs-CRP levels. However, we did not manifest a significant relationship between N/L ratio and peritonitis indices.

Long-term PD promotes chronic inflammatory process potentially sourced from catheter access infections, dialysate contamination, inadequate dialysis and high-concentration of uremic toxins and bio-incompatibility of dialysis solutions.[21] It is widely accepted that chronic peritoneal exposure to standard bio-incompatible PD solutions leads to structural membrane alterations which precipitate changes in fluid and solute transport; and eventually peritoneal membrane failure.[22,23] Supporting this issue, Stankovic et al. have showed significantly lower hs-CRP levels and better nutritional status in biocompatible solution users in a single center study.[5] In a parallel manner, Chen et al. have demonstrated reduced

Table 1. Demographic and clinic features of the study groups.

	Patients with Biocompatible Solutions (n: 71)	Patients with Standard Solutions (n: 49)	p Value
Age (years)	49.5 ± 14.1	48.4 ± 13.2	0.66
Female/Male	36/35	24/25	0.85
BMI (kg/m^2)	27.3 ± 5.8	26.4 ± 4.8	0.36
Office SBP (mmHg)	133.7 ± 19.6	138.9 ± 23.7	0.37
Office DBP (mmHg)	84.3 ± 9.8	84.8 ± 14.3	0.86
Primary etiology of CKD			0.21
Diabetic nephropathy	17 (23.9%)	13 (26.5%)	
Hypertensive nephrosclerosis	19 (26.8%)	7 (14.3%)	
Chronic glomerulonephritis	11 (15.5%)	7 (14.3%)	
Polycystic kidneys	2 (2.8%)	2 (4.1%)	
Reflux nephropathy	4 (5.6%)	–	
Others or unknown	18 (25.4%)	20 (40.8%)	
PD characteristics			
Time on PD (months)	59.8 ± 39.0	52.4 ± 28.7	0.23
Peritoneal Kt/V per week (units)	2.73 ± 1.23	2.63 ± 0.77	0.90
Daily UF volume (ml)	574 ± 73	540 ± 78	0.63
Daily urine volume (ml)	721 ± 86	502 ± 73	0.06

Abbreviations; BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CKD: Chronic kidney disease, PD: peritoneal dialysis, Kt/V: Urea clearance index used to represent weekly dialysis dose; where K is the clearance of urea, t is the dialysis time and V is the volume of distribution of urea, UF: Ultrafiltration. Values expressed with a plus/minus sign are the mean ± standard deviation. All other values are the number (percentage) of patients.

Table 2. Laboratory findings and peritonitis indices of the study groups (mean ± SD).

	Patients with Biocompatible Solutions (*n*: 71)	Patients with Standard Solutions (*n*: 49)	*p* Value
Creatinine (mg/dl)	8.3 ± 2.9	8.8 ± 2.9	0.39
Albumin (g/dl)	3.7 ± 0.4	3.6 ± 0.5	0.15
Calcium (mg/dl)	8.9 ± 0.9	8.7 ± 0.8	0.52
Phosphorus (mg/dl)	4.9 ± 1.3	4.6 ± 1.3	0.13
Parathormone (pg/ml)	535 ± 464	595 ± 421	0.48
Ferritin (mg/dl)	588 ± 325	540 ± 362	0.45
Total cholesterol (mg/dl)	200 ± 44	195 ± 49	0.55
Triglyceride (mg/dl)	207 ± 110	204 ± 142	0.92
Hemoglobin (g/dl)	11.0 ± 1.5	10.6 ± 1.8	0.11
WBC count (cell/mm^3)	7895 ± 1910	7520 ± 1788	0.28
Neutrophil count (cell/mm^3)	5416 ± 1583	5026 ± 1504	0.18
Lymphocyte count (cell/mm^3)	1547 ± 444	1640 ± 493	0.28
Platelet count ($\times 10^3$ cell/mm^3)	251 ± 75	240 ± 83	0.52
MPV(fL)	7.98 ± 0.97	7.92 ± 1.08	0.58
N/L ratio	3.75 ± 1.50	3.27 ± 1.34	0.04
P/L ratio	176 ± 79	157 ± 69	0.18
ESR (mm/h)	51.9 ± 32.7	44.1 ± 25.7	0.37
hs-CRP (mg/dl)	3.2 ± 2.5	1.8 ± 2.0	<0.01
Peritonitis rates (episodes per patient year)	0.23 ± 0.35	0.27 ± 0.32	0.36
Time to first peritonitis episode (months)	32.8 ± 35.8	21.5 ± 26.9	0.16

Abbreviations; WBC: White blood cell, MPV: Mean platelet volume, N/L ratio: neutrophil-to-lymphocyte ratio, P/L ratio: platelet-to-lymphocyte ratio, ESR: Erythrocyte sedimentation rate, hs-CRP: High sensitive C-reactive protein. Values expressed with a plus/minus sign are the mean ± standard deviation.

proinflammatory cytokines like IL-6 and β_2-microglobulin and improved effluent markers of peritoneal membrane integrity in a prospective study.[24] On the other hand, in a cross-sectional study, Maksic et al. detected similar concentrations of serum and intra-peritoneal IL-1β and TNF-α in patients using biocompatible and standard solutions. However, the authors observed a trend toward a lower intraperitoneal IL-6 level in biocompatible users.[25] Regarding peritonitis as a clinical outcome, Lee et al. have shown similar peritonitis rates, but significantly superior survival rates in patients on biocompatible solutions compared to those on standard PD solutions.[7] Herein, the results of the presented study are a little bit surprising and somewhat different from the ones of previous observational and retrospective studies.[5–7–] Serum hs-CRP levels and N/L ratio were significantly higher in biocompatible group compared to those in standard group in our study.

The calculated peritonitis rates of our patients are at levels much lower than accepted by the International Society of Peritoneal Dialysis guidelines.[20] The association between biocompatible solutions and peritonitis rates has been evaluated in a recently published randomized clinical trial named as BalANZ.[26] This well-designed larger sample sized investigation suggested that biocompatible solutions might reduce the incidence of peritonitis rates compared with conventional ones.[26] Conversely, in an observational study based on ANZDATA registry, Cho et al. have reported that, although the outcomes after peritonitis episodes were similar, the use of biocompatible PD solutions was found to be associated with higher overall peritonitis rates and shorter time to first peritonitis.[27] It was the first study reporting an increase in the peritonitis rates with the use of biocompatible solutions. The results of this study are rather strong and important because of its large sample size – a total of 2245 incident PD patients – and long follow-up, for a median time of 1.1 years. Actually, we did not show a significant difference in neither peritonitis rates nor time to first peritonitis episode between biocompatible solution users and standard solution users. These indices have also been found to be similar between redefined groups according to the median of N/L ratio. Hence, by virtue of our results, we cannot make an interpretation concerning a favorable effect by neither of the solutions on peritonitis indices. However, according to our knowledge we consider that our results have given a valuable contribution to the data in this field; since this is the first study that investigates the N/L ratio in regard to different PD solutions.

Although we cannot make a certain or a biologically reasonable explanation for our results, we can speculate that there may be an association between acidity of the peritoneal content and virulence of microorganisms. This assumption may explain the unfavorable effects of PD solutions with neutral pH on increased level of inflammatory markers or peritonitis rates. There is some recently published evidence in the literature supporting this hypothesis.[28–30] Schwan et al. showed that urine is slightly less acidic in the bladder than in the kidneys and the osmolality in the bladder is lower than the osmolality in the kidneys.[28] They suggested that lower acidity (higher pH) and lower osmolality increases type 1 pilus expression in uropathogenic *E. coli*.[28] Similarly, Gonzales et al. showed that the exposure to high pH induces the secretion of the heat labile enterotoxin of enterotoxigenic *E. coli*.[29] Other than gram negative bacteria, such an association was also reported for *S. aureus* and *S. epidermidis*. It is suggested that, acidic environment could have important implications for preventing bacterial colonization and control biofilm formation.[30] Based on this evidence, one may assume that there may be a casual relation or facilitative effect between acidity of biological media and tendency to bacterial infections.

There were several limitations of our study. First limitation was the somewhat small number of the study patients.

Unfortunately, a considerable number of patients have not been included because of the strict exclusion criteria regarding inflammatory processes. Secondly, this study was of cross-sectional design and lacked long-term clinical follow-up. We have not investigated the effects of biocompatible solutions on inflammation in a prospective manner.

In conclusion, biocompatible solutions seem to be related with increased inflammation in PD patients. According to our results and the consistent evidence, we speculate that the term of ''biocompatibility'' needs a newer definition. N/L ratio might be a useful marker in determining the rate of ongoing inflammatory process in PD patients. In order to make precious inferences about the impact of biocompatibility on inflammation and the role of N/L ratio in predicting peritonitis episodes, randomized-controlled clinical trials with larger patient populations are warranted.

Declaration of interest

The authors have no financial disclosures to declare and no conflicts of interest to report. The authors alone are responsible for the content and writing of the paper.

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