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EVALUATION OF THE COGNITIVE AND AFFECTIVE STATUS IN HEMODIALYSIS PATIENTS WITH CHRONIC RENAL FAILURE

PROCENA OŠTEĆENJA KOGNITIVNOG I AFEKTIVNOG STATUSA KOD BOLESNIKA SA HRONIČNOM BUBREŽNOM INSUFICIJENCIJOM NA HEMODIJALIZI

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Summary

Introduction. Hemodialysis patients with chronic renal failure, suffer from affective dysfunction to a variable extent. The aim of our study was to evaluate the cognitive and affective status in patients before and after hemodialysis. Apart from this, the goal of the study was to examine and compare the cognitive status of patients on dialysis in relation to the control group, but also in relation to laboratory parameters. **Material and Methods.** This research was a prospective study including 30 hemodialysis patients with chronic renal failure treated at the Department of Nephrology of the Health Center in Kosovska Mitrovica. The cognitive status of the subjects was evalueted by determining the simple reaction time to auditory and visual stimuli before and after hemodialysis sessions and using the Mini Mental Status Examination, while the affective status was evalueted by using the Beck Depression Inventory. **Results.** The analysis of the obtained results showed a statistically significantly lower auditory and visual simple reaction times (p = 0.014) after dialysis (p = 0.023). The results have confirmed a statistically significantly decreased simple reaction time to visual stimuli (p = 0.001), while a statistical significance (p = 0.137) was not obtained for the auditory stimuli when compared to the control group. The Mini Mental Status Examination and the Beck Depression Inventory did not indicate a significant cognitive status damage or presence of depression. **Conclusion.** The importance of hemodialysis in the improvement of cognitive function is clearly evident, even though the general state of cognitive status in patients on hemodialysis is lower compared to the healthy population. Evaluation of the cognitive and affective status using simple reaction time, Folstein's Mini Mental State Examination and the Beck Depression Inventory, should be used on daily basis in hemodialysis patients.
Key words: Renal Insufficiency, Chronic; Cognitive Dysfunction; Affective Symptoms; Reaction Time; Neuropsychological Tests; Renal Dialysis; Treatment Outcome

Sažetak

Uvod. Kod pacijenata sa hroničnom bubrežnom insuficijencijom podvrgnutih hemodijalizi kognitivna i afektivna disfunkcija je prisutna u varijabilnom intenzitetu. Cilj istraživanja je procena kognitivnog statusa pacijenata pre hemodijaliznog tretmana i nakon njega, kao i afektivnog statusa. Jedan od ciljeva istraživanja je i sagledati kognitivni status pacijenata na dijalizi u odnosu na kontrolnu grupu, kao i u odnosu na laboratorijske parametre. **Materijal i metode.** Istraživanje je koncipirano kao prospektivna studija koja je obuhvatila 30 pacijenata sa dijagnozom hronične bubrežne insuficijencije hemodijaliziranih na odeljenju nefrologije Zdravstvenog centra u Kosovskoj Mitrovici. Kognitivna funkcija ispitanika procenjena je određivanjem prostog reakcionog vremena na auditivni i vizuelni stimulus pre i nakon hemodijalizne seanse i primenom mini mental testa, dok je afektivni status procenjen primenom Bekovog testa depresije. **Rezultati.** Analizom dobijenih rezultata registrovane su statistički značajno niže vrednosti prostog reakcionog vremena na auditivni (p = 0,014) i vizuelni stimulus nakon dijalize (p = 0,023). Dobijeni rezultati ukazuju na statistički signifikantno značajno smanjenje vrednosti reakcionog vremena na vizuelni stimulus (p = 0,001), dok za auditivni stimulus nije postignuta statistička značajnost (p = 0,137) u poređenju sa kontrolnom grupom. Mini mental test i Bekov test depresije nisu ukazali na signifikantno oštećenje kognitivnog statusa i prisustvo depresije. **Zaključak.** Značaj dijalize u poboljšanju kognitivnih funkcija je jasno evidentan iako je opšte stanje kognitivnog statusa pacijenata na hemodijalizi oštećeno u odnosu na zdravu populaciju. Procena kognitivnog i afektivnog statusa određivanjem prostog reakcionog vremena, primenom Folstejnovog i Bekovog testa depresije, treba da nađe veću zastupljenost u svakodnevnom kliničkom radu sa pacijentima na dijalizi.
Ključne reči: hronična bubrežna insuficijencija; kognitivni poremećaji; afektivni poremećaji; reakciono vreme; neuropsihološki testovi; hemodijaliza; ishod lečenja

Introduction

Unrecognized and untreated chronic renal diseases lead to chronic renal failure (CRF) and terminal renal failure, and their incidence has increased exponentially over the past two decades. Consequently, more than two million patients in the world are currently treated with one of the three methods of renal replacement therapy – hemodialysis (HD), peritoneal HD and kidney transplantation

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Abbreviations
CRF   – chronic renal failure
HD   – hemodialysis
SRT   – simple reaction time
MMSE   – Mini Mental State Examination
BDI   – Beck Depression Inventory

[1, 2]. The very nature of CRF affects the incidence of cognitive impairment, most often due to uremia, but this may be attributed to any other metabolic disorder caused by the loss of renal function [3]. The presence of global cognitive impairment in people with CRF compared to healthy individuals from the similar or same age group is evident [3, 4]. Among the laboratory parameters that deviate from the reference values, in correlation with cognitive impairment, the indicators of anemia, serum levels of nitrogenous substances and the elevated potassium levels have been established. Patients with good dialysis efficiency have mild cognitive deficits, progressing to moderate impairments associated with lower HD efficiency. Anemia is a crucial factor and its correction may improve the patient's cognitive status. In patients with different stages of CRF, cognitive impairment shows variable intensity, but its incidence is also observed in individuals undergoing HD treatment [4].

Some studies suggest that there is a proportional correlation between the degree of cognitive impairment and the stage of CRF [5]. Patients with elevated urea and other harmful metabolic products in the blood show poor performance on tests, shorter attention span, and lower levels on working memory tasks [6]. In addition, it should be noted that HD treatment can positively impact the cognitive status in patients with end-stage CRF. The comparison of these results with the results of transplant patients in one of the studies showed that HD does not delay the repair of cognitive functions [7, 8]. The research has also shown a significant influence of low hematocrit values, in other words anemia, on the decline in cognitive function [6, 9]. The synergy of several factors that affect the onset of cognitive impairment and its incidence in dialysis patients requires attention as it can be an indicator of HD efficacy, complications related to the treatment itself, as well as the engagement of other factors including comorbid diseases. Cognitive impairment can significantly reduce patients' quality of life, which in turn leads to inadequate medical care due to the patient's difficulty in following the advice on necessary lifestyle, and may also affect the quality of interpersonal relationships, reduce the ability of social adaptation, and partly lead to the decline in quality of life [5, 9, 10].

The very nature of CRF is associated with the prevalence of psychiatric disorders. The multisystemic involvement with a mass of symptoms leads to patients' inadequate mental response. Symptoms from the domain of mental functions are manifested, over time, by the presence of smaller intellectual deficiencies, fatigue, concentration difficulties and apathy. Mood and character disorders also develop during the progression of the disease. During the treatment of CRF by HD, anxiety and depression are only the most frequent manifestations followed by a decreasing libido and insomnia. A kind of "handicap" is being formed, often influenced by an attachment to the apparatus being used at a certain time. In relation to patients' response to medical personnel performing the HD treatment, the reactions range from an apparent cooperation with the ultimate regression to constant demands and conflicts with the rules. Sometimes, even a suicidal behavior may occur [11]. Psychiatric disorders are more frequent in patients with CRF than in the general population. Although depression significantly affects the survival rate of HD patients, a more accurate incidence rate of depression and other psychiatric disorders has not been fully defined [12].

Neurophysiological and neuropsychological methods, such as cognitive evoked potentials (P300) and reaction time, are objective markers of the readiness levels of cognitive mechanisms. Therefore, their registration and analysis are logical steps in assessing the cognitive state of both healthy subjects and those with different pathological conditions. The reaction time is increasingly used as a quantitative method and technique in examining the speed of information processing in humans, during an experimental process. The time interval between the moment of simple or complex stimuli introduction and the subsequent motor response reflects the speed of neurophysiological, cognitive and information processes that result from the effect of the stimulus on subjects' sensory system. Information perceiving and processing, decision making, and responding by motor action are processes that follow one another and comprise what we call reaction time [13, 14]. A simple reaction time (SRT) is a reaction to an already known stimulus, where the same response is expected in all subsequent attempts, so the subject is able to program the movement in advance [15]. In testing, the reaction time method reflects the readiness level of nervous and cognitive mechanisms, making them valid in studying the reaction rate in various situations in subjects on HD.

The cognitive status of CRF patients on HD expressed through the mean value of SRT is not the same before and after dialysis treatment, and it is affected by the values of biochemical laboratory parameters characteristic for CRF. The more pronounced the parameters of anemia, electrolyte imbalance, and elevated levels of nitrogenous substances, the poorer the achievement in tasks requiring preserved writing ability and constructive activity, which in turn can be estimated by using Mini Mental State Examination (MMSE) by Folstein, 1975 [4, 16–18].

The aim of this study was to determine the cognitive and affective status of patients with CRF on HD treatment by examining SRT before and after dialysis treatment using the neuropsychological MMSE test, as well as the Beck Depression Inventory (BDI). One of the objectives of the study was to evaluate the cognitive status of patients with CRF on HD treatment compared to the control group, in relation to laboratory parameters.

The study was based on the assumption that HD treatment contributes to the improvement of cogni-

Table 1. Auditory and visual SRTs before and after hemodialysis
Tabela 1. Vrednosti prostog reakcionog vremena na vizuelni i auditivni stimulus pre i posle hemodijalize

Simple reaction time/*Prosto reakciono vreme*	Before HD/*Pre HD*	Post HD/*Posle HD*	p - value/*p - vrednost*
Auditory stimuli/*Auditivni stimulus*	332.9 ± 94.1	313.8 ± 67.1	0.014
Visual stimuli/*Vizuelni stimulus*	429.2 ± 147.8	385.1 ± 121.8	0.023

HD - hemodijaliza

Table 2. Mean auditory and visual reaction times compared to the control group
Tabela 2. Prikaz srednjeg reakcionog vremena na auditivni i vizuelni stimulus u odnosu na kontrolnu grupu

Simple reaction time/*Prosto reakciono vreme* Post HD/*Posle HD*	Control group/*Kontrolna grupa*	p – value/*p - vrednost*
Auditory stimuli/*Auditivni stimulus*	313.8 ± 67.1	293.8 ± 34.7	0.137
Visual stimuli/*Vizuelni stimulus*	385.1 ± 121.8	300.9 ± 50.5	0.001

HD - hemodijaliza

tive and affective status of patients and that the cognitive and affective status of patients with CRF differs from the one of the patients without CRF.

Material and Methods

This prospective study included a total of 30 volunteer patients (22 men and 8 women) aged 29 to 75 (54.3 ± 14.51), with 4 to 16 years of formal education, suffering from CRF on hemodialysis in the period from May to July 2017 at the Department of Nephrology of the Health Center in Kosovska Mitrovica. The subjects were treated by hemodialysis about four hours, three times a week. The study included a control group of 50 healthy volunteers (20 men and 30 women), aged 35 to 69 (56.1 ± 9.5), with 8 to 16 years of formal education.

Using a special computer program, SRT testing was performed in each patient individually, before and immediately after HD treatment. The SRT was measured using a combination of two tasks, one including visual and the other auditory stimuli.

The MMSE (Folstein, 1975) was used as a screening test for the assessment of cognitive decline, that is the existence and the severity of dementia, while BDI (Beck, 1996) was used for assessing the affective status, i.e. the severity of depression.

The obtained data were processed using the Statistical package for the social sciences (SPSS) (version 25) (IBM Corporation, Armonk, NY, USA). The data are shown as percentages and mean values with standard deviation. The T-test was used for testing statistical hypotheses for two dependent and two independent samples. The correlation between the variables was estimated by Pearson's and Spearman's correlation coefficient. Statistical hypotheses were tested at the level of statistical significance (alpha level) of 0.05.

The study was conducted with the approval of Ethics Committee of Health Center Kosovska Mitrovica.

Results

The most common causes of CRF in our subjects were chronic glomerulonephritis (26.7%) and diabetic nephropathy (20.0%). The average duration of

HD treatment was 4.25 ± 4.09 years, with a range of 0.07 to 14.57. In the survey sample, the highest incidence of subjects on HD (56.3%) was recorded in four municipalities of the northern part of Kosovo and Metohija (Kosovska Mitrovica, Leposavić, Zvečan and Zubin Potok). Patients from municipalities in the south of the province had a lower incidence (43.7%).

The mean SRT to auditory stimuli before HD was 332.9 ± 94.1 and post HD treatment it was 313.8 ± 67.1, which shows a statistically significant difference (p = 0.014). There was a significant reduction in the mean SRT to the auditory stimuli post HD treatment. The mean SRT to visual stimuli before HD was 429.2 ± 147.8, while post HD treatment it was 385.1 ± 121.8, which also shows a statistically significant difference (p = 0.023). There was a significant reduction of SRT to visual stimuli post HD **(Table 1)**.

The mean SRT to auditory stimuli in subjects with CRF after HD treatment was 313.8 ± 67.1, while in the control group it was 293.8 ± 34.7, which was not a statistically significant difference (p = 0.137). The mean SRT to visual stimuli in subjects after HD treatment was 385.1 ± 121.8 while in the control group it was 300.9 ± 50.6, which was a statistically significant difference (p = 0.001) **(Table 2).**
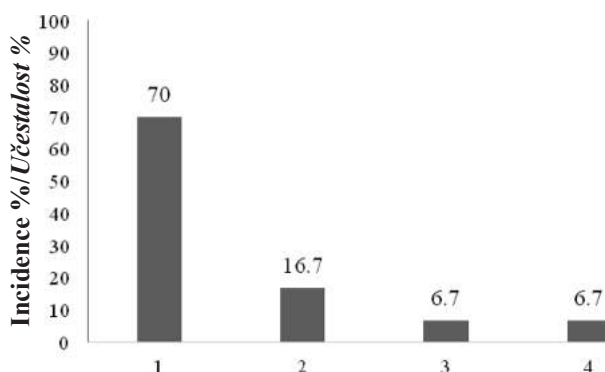
Graph 1. Beck Depression Inventory in the studied group of patients
Grafikon 1. Bekov indikator depresije kod ispitivane grupe pacijenata

Based on the results of our study, the incidence of patients with CRF on HD examined by the Folstein's MMSE showed no statistically significant predictive value affecting their cognitive status. The total score reported normal functioning in 27 patients (90%), and a minimal cognitive deficit in 3 patients (10%).

The BDI was used to examine the degree of depression in patients with CRF on HD, or the lack thereof. The results of examination showed 9 positive cases, 2 patients with severe, 2 with moderate, and 5 with mild depression, while no depression was detected in 21 patients. The statistical analysis of the obtained data revealed that there was no correlation between depression and mean SRT **(Graph 1).**

Laboratory indicators of anemia in patients on HD showed decreased mean erythrocyte (3.4 ± 0.6), hemoglobin (104.7 ± 18.2) and hematocrit (316 ± 55.04), while the mean value of iron was 11.8 ± 6.5. The level of glycemia in patients undergoing HD was 6.02 ± 2.8.

By reviewing the average range of laboratory parameters that indicate serum levels of nitrogenous substances, in patients with CRF on HD, there were significant increases of urea (26.14 ± 5.75), creatinine (1111.55 ± 1327.88) and uric acid (403.17 ± 73.21) before HD, while the values of azotemia were, as expected, within the reference values (urea: 11.25 ± 3.13, creatinine: 444.16 ± 124.88, uric acid: 165.8 ± 59.25) after HD treatment. The review of the electrolyte status before HD indicated an electrolyte imbalance, which contributes to hyperkalemia, a mild elevation of phosphorus before HD treatment, as well as calcium after HD treatment, with approximate reference values for serum concentrations of other electrolytes (Na^+, Cl^-). The parameters of hepatic parenchymal damage, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase, were within the reference values, whereas the average leukocyte and sedimentation values did not indicate an inflammatory disease.

Using the correlation tests, we found that there was a statistically significant, medium negative association between the levels of urea before HD and the values of SRT to auditory stimuli before HD (r = -0.399; p = 0.029). Also, there was a statistically significant medium negative correlation between post HD creatinine values and post HD values of SRT to auditory stimuli (r = -0.448; p = 0.013).

The correlation between the duration of dialysis and the values of SRT to auditory and visual stimuli did not prove to be statistically significant.

Discussion

During our study, we have performed two separate measurements of SRT (before and after HD) in patients with CRF on HD treatment. The analysis of the results clearly indicated a longer reaction time prior to HD treatment, both to visual and auditory stimuli, and the difference was statistically significant (p < 0.001). A statistically significant difference was also found when comparing the mean SRT to visual stimuli in the control and the HD group (after

HD), but the difference did not reach the statistical significance for the auditory stimuli.

Longer reaction times to visual stimuli were clearly noticeable compared to auditory stimuli. This is probably caused by the fact that auditory stimuli require only 8 to 10 ms to reach the temporal lobe, while visual stimuli require 20 – 40 ms to reach the occipital cerebral lobe [19].

Among patients undergoing HD treatment, the cognitive changes were clearly reversible after HD, transplantation, or introduction of erythropoietin therapy [10]. Due to kidney's inability to maintain the homeostasis of the body fluids and biochemical composition, accumulation of nitrogenous substances and other decomposition products occurs. One of the effects of uremia is the deficit of cognitive strategy. In cases where transplantation is not an option, HD is the main therapeutic method that keeps patients alive. It is a proven fact that HD improves the cognitive status of patients, but the fluctuations of cognitive status related to HD duration, HD type, the frequency of dialysis sessions, including the period between two HD sessions, are slightly less known [20–22]. The parameters for anemia indicate its clear presence in a group of patients on HD, which is supported by lower mean levels of erythrocytes, hemoglobin, and hematocrit. The effects of hematocrit and anemia on neurocognitive performance in patients with CRF on conservative or HD treatment have been investigated in many studies [9, 23–25].

The MMSE is a rapid mental status test which is a good predictor of possible disorders of serum electrolytes [17]. In our study, serum levels of electrolytes indicated a predominantly elevated level of potassium, with no statistically significant correlation. Therefore, the isolated hyperkalemia cannot be a predictor of cognitive dysfunction, which is reflected in the extended SRT values to visual and auditory stimuli prior to HD treatment. Since other relevant electrolytic parameters that are characteristic for HD patients with CRF are within approximate reference ranges, the potassium values are most likely a reflection of the failure of patients on HD to follow the recommended nutritional-hygienic regimen [26]. Our research has shown a correlation between the urea levels before HD and values of SRT to auditory stimuli before HD, as well as a correlation between the creatinine levels after HD and values of SRT to auditory stimuli after HD, while no statistical significance was noted for anemia and electrolyte status parameters.

In our study, we obtained statistically significant values by determining SRTs before and after dialysis and compared them to the results of the MMSE test, which confirmed that determination of SRTs to auditory and visual stimuli is a more sensitive indicator of cognitive deficit.

Patients on HD often feel and look "chronically tired", which means that the fluctuations in memory resources and reaction time are interpreted differently. Specifically, serotonin levels are reduced in patients with CRF, and serotonin is known for its

effects on the affective status and working memory [27]. Psychiatric disorders are more common in patients with CRF than in the general population. A more precise incidence rate of depression and other psychiatric disorders has not been fully defined [12].

Conclusion

Our study showed that there was a significant reduction in the mean simple reaction time to the auditory and visual stimuli post hemodialysis treatment. The importance of hemodialysis in the im-

provement of cognitive functions is clearly evident, even though the general state of cognitive status in patients with chronic renal failure on hemodialysis is impaired compared to a healthy population.

There is a correlation between the levels of urea before hemodialysis as well as creatinine levels post hemodialysis and simple reaction time to auditory stimuli.

Sporadic cases that indicate an impaired affective status and depression of hemodialysis patients require application of preventive psychiatric tests and assessments.

References

1. Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. J Am Soc Nephrol. 2002;13 Suppl 1:S37-40.

2. Bello AK, Nwankwo E, El Nahas AM. Prevention of chronic kidney disease: a global challenge. Kidney Int Suppl. 2005;98:S11-7.

3. Graham JE, Rockwood K, Beattie BL, Eastwood R, Gauthier S, Tuokko H, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. Lancet. 1997;349(9068):1793-6.

4. Kopitović A. Algoritam za rano otkrivanje poremećaja više nervne delatnosti kod bolesnika na hroničnoj hemodijalizi [dissertation]. Novi Sad: Univerzitet u Novom Sadu; 2009.

5. Kurella M, Chertow G, Luan J, Yaffe K. Cognitive impairment in chronic kidney disease. J Am Geriatr Soc. 2004;52(11):1863-9.

6. Hart RP, Pederson JA, Czerwinski AW, Adams RL. Chronic renal failure, dialysis, and neuropsychological function. J Clin Neuropsychol. 1983;5(4):301-12.

7. McKee DC, Burnett GB, Raft DD, Batten PG, Bain KP. Longitudinal study of neuropsychological functioning in patients on chronic hemodialysis: a preliminary report. J Psychosom Res. 1982;26(5):511-8.

8. Kiolbasa T. Adequacy of hemodialysis compared to kidney transplantation: A neuropsychological perspective [dissertation]. Chicago: University of Illinois; 1998.

9. Lee SY, Lee HJ, Kim YK, Kim SH, Kim L, Lee MS, et al. Neurocognitive function and quality of life in relation to hematocrit levels in chronic hemodialysis patients. J Psychosom Res. 2004;57 (1):5-10.

10. Pereira AA, Weiner DE, Scott T, Sarnak MJ. Cognitive function in dialysis patients. Am J Kidney Dis. 2005;45(3):448-62.

11. Porot A, Adamović V, Beštić M. Enciklopedija psihijatrije. Beograd: Nolit; 1990.

12. Kimmel PL, Weihs K, Peterson RA. Survival in hemodialysis patients: the role of depression. J Am Soc Nephrol. 1993;4 (1):12-27.

13. Pachela RG. The interpretation of reaction time in information-processing research. In: Kantowitz BH, editor. Human information processing tutorials in performance and cognition. Hillsdale: Lawrence Ertlbaum Associates; 1974. p. 41-82.

14. Mišolić M, Ivetić V, Nestorović V, Milanović Z, Radović D, Biševac B, et al. Uticaj funkcionalnog stanja organizma na vreme reakcije studenata. Praxis Medica. 2008;36(3-4):53-6.

15. Kohfeld DL. Simple reaction as a function of stimulus intensity in decibels of light and sound. J Exp Psychol. 1971;88(2):251-7.

16. Folstein MF, Folstein SE, McHugh P. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98.

17. Todorovski Z, Salević-Obradović J, Slankamenac P. Mini Mental State Examination (MMSE) – valjanost prema kriterijumu patoloških promena u endokranijumu definisanih kompjuterskom tomografijom. In: 54. Naučno stručni skup psihologa Srbije – Sabor, Izazovi za primenjenu psihologiju u Srbiji: knjiga rezimea; 2006 maj 24-27; Zlatibor, Srbija. Beograd: Društvo psihologa Srbije; 2006. p. 46.

18. Rondanelli M, Solerte SB, Ferrari E. Electrolytes and cognitive function in the elderly: relationship between serum sodium and chloride concentrations and psychometric test scores. Panminerva Med. 1998;40(3):191-5.

19. Kemp BJ. Reaction time of young and elderly subjects in relation to perceptual deprivation and signal-on versus signal-off conditions. Dev Psychol. 1973;8(2):268-72.

20. Kutlay S, Nergizoglu G, Duman N, Atli T, Keven K, Ertürk S, et al. Recognition of neurocognitive dysfunction in chronic hemodialysis patients. Ren Fail. 2001;23(6):781-7.

21. Evans JD, Wagner CD, Welch JL. Cognitive status in hemodialysis as a function of fluid adherence. Ren Fail. 2004;26(5): 575-81.

22. Pliskin NH, Yurk HM, Ho LT, Umans JG. Neurocognitive function in chronic hemodialysis patients. Kidney Int. 1996;49(5): 1435-40.

23. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339(9): 584-90.

24. Drucke TB, Eckardt KU, Frei U, Jacobs C; Kokot F; McMahon LP, et al. Does early anemia correction prevent complications of chronic renal failure? Clin Nephrol. 1999;51(1):1–11.

25. Martin-Lester M. Cognitive function in dialysis patients: case study of the anemic patients. ANNA J. 1997;24(3):359–66.

26. Harrison T, Kasper D, Braunwald E, Fauci A. Harrison's principles of internal medicine. New York: McGraw-Hill; 2008.

27. Oaksford K, Oaksford M, Ashraf M, Fitzgibbon G. Comparing neuropsychological function before and during haemodialysis: a habituating selective deficit for prose recall. Br J Health Psychol. 2008;13(Pt 2):273-89.