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FARMACOTERAPIA DE PACIENTES EM TERAPIA RENAL SUBSTITUTIVA: UM ENFOQUE EM ADESÃO

PHARMACOTHERAPY OF PATIENTS IN SUBSTITUTIVE RENAL THERAPY: AN ADHERENCE APPROACH

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FARMACOTERAPIA DE LOS PACIENTES EN TERAPIA SUSTITUTIVA RENAL: LA ADHERENCIA Y EL ENFOQUE

RESUMO

Avaliar o perfil farmacoterapêutico e a adesão em pacientes com insuficiência renal crónica submetidos à diálise de um hospital grande no centro-oeste de Minas Gerais, Brasil. Trata-se de um estudo transversal conduzido em um hospital filantrópico durante as sessões de diálise. Os questionários de adesão Morisky-Green e Brief Medication Questionnaire foram usados para analisar a adesão dos pacientes; adicionalmente a presença de polifarmácia e o índice de complexidade terapêutica foram avaliados. Foram incluídos 219 pacientes, caracterizados pela predominância de homens, brancos, casados e idade média de 56,5 anos (DP: 13,2). As principais classes de medicamentos em uso foram anti-hipertensivos e aglutinantes de fosfato e 66% dos pacientes apresentaram polifarmácia e o índice de complexidade terapêutica foi considerado alto. Polifarmácia e adesão não são influenciadas por fatores sociais (gênero, etnia, aposentadoria ou plano de saúde privado). O perfil de adesão pelo teste de Morisky-Green resultou em alta adesão em 50,5% dos pacientes enquanto pelo Brief Medication Questionnaire, uma possível baixa adesão foi notada em 80,6% dos pacientes. Ambos os testes concordaram no que diz respeito ao perfil de baixa adesão. A farmacoterapia dos pacientes com insuficiência renal crônica submetidos à diálise é complexa e a adesão pode variar de acordo com o teste usado.

Palavras-chave: perfil farmacoterapêutico; adesão medicamentosa; insuficiência renal crônica.

ABSTRACT

To evaluate the pharmacotherapeutic profile and adherence in patients with chronic renal failure undergoing dialysis from a large hospital in the Midwest of Minas Gerais, Brazil. This is a cross-sectional study carried out in a philanthropic hospital during the dialitic session. The Morisky Medication Adherence Scale - 4 items (MMAS-4) and Brief Medication Questionnaire (BMQ) were used to analyze the patient adherence additionally the presence of polypharmacy and the therapeutic complexity index were assessed. 219 patients were include, characterized by predominantly male, white, married and mean age of 56.5 years old (SD:13.2). The main classes of medications in use were antihypertensive and phosphorus binders and 66% of participants presented polypharmacy and therapeutic complexity was considered high. Neither polypharmacy or adherence are influenced by social factors (gender, ethnicity, retirement or health care insurance). Adherence profile by MMAS-4 corresponded to high adherence in 50.5% while by the BMQ corresponded to likely poor adherence in 80.6%. Both tests agreed concerning low adherence profile). The pharmacotherapy of patients with chronic renal failure undergoing dialysis is complex and adherence may variety according to the test used.

Keywords: drug therapy profile; medication, adherence; kidney failure, chron

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RESUMEN

Evaluar el perfil farmacoterapéutico y la adherencia en pacientes con insuficiencia renal crónica que experimenta diálisis de un hospital grande en el Medio Oeste de Minas Gerais, Brasil. Se trata de un estudio transversal llevado a cabo en un hospital filantrópico durante las sesiones de diálisis. Cuestionarios de miembros MoriskyGreen Breve y Medicamentos cuestionario se utilizó para analizar la adherencia de los pacientes; además Se evaluó la incidencia de la polifarmacia y el índice de complejidad terapéutica. Se incluyeron 219 pacientes, que se caracteriza por el predominio de los hombres blancos, casado y una edad media de 56,5 años (SD:13.2). Las principales clases de medicamentos antihipertensivos y fueron aglutinantes de fosfato y el 66% de los pacientes tenían la polifarmacia y el índice de complejidad

terapéutica se considero alta. La polifarmacia y la pertenencia no están influenciados por factores sociales (de género, etnia, o plan de jubilación privado de salud). El perfil de los miembros mediante la prueba de Morisky-Green ha provocado una elevada adherencia 50,5% de los pacientes, mientras que el Cuestionario Breve medicación, una posible baja adherencia se observó en el 80,6% de las pacientes. Ambas pruebas estuvieron de acuerdo con respecto al perfil bajo cumplimiento. farmacoterapia de pacientes sometidos a diálisis con insuficiencia renal crónica es compleja y la adherencia pueden variar con la prueba utilizada.

Palabras Clave: perfil farmacoterapéutico; adherencia a la medicación; insuficiencia renal crónica.

INTRODUCTION

The increased incidence of chronic conditions in Brazil is a concerning factor in public health, representing in 2013 more than 72 % of the total registered deaths[1]. In this sense, an adequate plan of public politics for patients carrying those conditions is of paramount importance.

Kidney failure, characterized by a slow, progressive and irreversible loss of the kidney functions is among the chronic diseases with higher morbidity and mortality rates[2]. In only one year, 2014, kidney failure assailed 26,515,066 people nationwide, presenting mortality rates of 12.6 %[3]. According to the Brazilian Society of Nephrology Census (2012), a total of 97,586 patients were in dialysis[4].

Dialysis is the most used means of Substitutive Renal Therapy (SRT), and combined with dietetic treatment, hydric restrictions and drug treatment, ensures these patients' life expectancy[5]. Because of its complexity, it is of extreme importance to guide the patient to adhere to the treatment. Nevertheless, treatment adherence is not an easy task; 50 % of patients with chronic diseases do not follow the treatment correctly, especially the drug treatment option. The same result is observed for patients in dialysis, where forgetting to take the medicine is reported as the main reason for non-adherence[6-8].

Thus, it is necessary to know the pharmacotherapy profile and adherence levels in this population to provide subsidies to the healthcare team and assist the patient to understand their condition and treatment. In this context, the present study aimed to evaluate the pharmacotherapy profile and the pharmacotherapy adherence of Brazilian dialytic patients.

METHOD

Study Design

This is a cross-sectional study, developed in a philanthropic hospital from the Center-West region of Minas Gerais state, Brazil, with a hemodialysis clinic offering services to patients with dialytic chronic renal insufficiency. This service is offered from Monday to Saturday in three cycles, being hemodialysis with a duration of up to four hours per patient.

The maximum capacity of the service is 300 patients. A total of 219 patients under treatment were included in the study. All of the patients under hemodialysis present at the time of interview were invited to join the study. Inclusion criteria were: patients aged 18 or older, with physical conditions capable of answering the survey. Data collection occurred from August to November of 2014 through individual interviews performed during the hemodialysis sessions, with an approximate duration of 30 minutes per patient. The patient acknowledged the study through a consent form.

The study was previously approved by the Ethics Committee in Research about Human Beings (CEPES/CCO) from the Federal University of Sao Joao del-Rei under the protocol number 641.045.

Instruments for data collection

To collect the variables of the study, four instruments were used: socioeconomic and demographic formulary, pharmacotherapeutic profile, the Morisky Medication Adherence Scale - 4 items (MMAS-4) and the Brief Medication Questionnaire (BMQ), described as follows.

The socioeconomic and demographic profile formulary to evaluate gender, age, marriage status, dialysis time (years), ethnic group, healthcare plan, transportation means, retirement, registration by the basic unit of health, and socioeconomic level, traced education and income. Education was evaluated according to the school level, and the monthly household income was calculated by the sum of pension funds plus financial aid from relatives, and other income, being calculated the number of minimum wages based on January 2014 (R$ 724.00).

From the pharmacotherapeutic profile it was possible to verify the presence of polypharmacy and the therapeutic complexity index (TCI). Polypharmacy was considered to be the use of five or more medicines by one patient[9]. The TCI was then calculated according to Acurcio et al. (2009)[10], including measurements of the medicine numbers, frequency, and type of actions required for self-administration. The TCI was calculated only for medicines with continuous use dependent on the actions of patients, and medicines used during and/or after dialysis sessions were disregarded. One patient was excluded from the calculus since he was not using any medicine.

The Brazilian Portuguese version of the MMAS-4 and the BMQ were used to evaluate pharmacotherapy adherence. The MMAS-4 is comprised of four questions with answers being "yes" or "no" considering: adherent (no positive answer), moderated adherence (one or two positive answers), low adherence (three or four positive answers)[11].

Meanwhile, the BMQ comprises three domains that identify barriers to adherence regarding regimen, beliefs, and memory in relation to the drug therapy from the patient's perspective. The regimen domain has seven questions and a score ≥1 indicates potential non-adherence; the belief domain has two questions and a score ≥1 indicates positive tracking for belief barriers, and the memory domain has two questions and a score ≥1 indicates a positive score for memory barriers. Hence the final possible results are: adherent (no positive answers), probable adherence (positive answer in one domain), probable low adherence (positive answer in two domains) and low adherence (positive answer in three domains)[11].

For classification purposes, the Anatomic Therapeutic Chemical (ATC) classification system, proposed by the World Health Organization was used[12].

Finally, data were plotted into a database using Excel software. Statistical analysis was performed using SPSS v. 16.0 software, establishing a significance level of 5 % (p<0.05). Statistical tests used were the Chi-square, Mann Whitney and Kruskal-Wallis, and the TCI was correlated to BMQ and expressed as coefficient of correlation (p).

RESULTS

From the 219 patients under dialytic treatment in the study period, 21 patients (9.6 %) opted not to join the study and only one patient was not in a physical condition to answer the survey and sign the consent form, therefore 197 patients were subsequently included in the study.

The study population was characterized predominantly by males, white, married, average age of 56.6 years old (SD: 13.2), retired individuals, incomplete elementary school level, with no health insurance, household income less than two Brazilian minimum wages and having as transportation means a bus/van to go to the treatment site, as seen in Table 1.

Table 1: Socioeconomic and demographic characteristics of a population under dialysis from a large hospital in the Center-West region of Minas Gerais, Brazil (n = 197).

Characteristics	n	%
Gender		
Male	121	61.4
Female	76	38.5
Age (years)		
Average (SD)	56.5(13.2)	
25-48	54	27.4
49-56	45	22.8
57-66	53	26.9
≥ 67	45	22.8
Ethnic Group		
White	142	7211
Black	55	27.9
Marital status		
Single	57	28.9
Married	108	54.8
Widowed	26	13.2
Divorced	6	3
Retirement		
Yes	142	72.1
No	55	27.9
Private Health Insurance		
Yes	65	33
No	132	67
Transportation		
Own vehicle	65	33
Bus/van	120	60.9
Ambulance	4	2.0
On foot	4	2.0
Taxi	2	1.0
No answer	2	1.0
Education Level		
Illiterate	5	2.5
Incomplete elementary school	113	57.4
Complete elementary school	35	18
Complete high school	32	16.2
Complete higher education	10	5.1
No answer	2	0,8
Household income (Brazilian minimum wages)		
< 2 minimum wages	131	66.5
2-5 minimum wages	19	9.6
> 5 minimum wages	3	1.5
No answer	44	22.3

The main comorbidities associated with kidney disease were: (1) systemic arterial hypertension (SAH), (n = 158; 80.2 %); (2) diabetes (n = 59; 29.9 %); (3) congestive heart failure, (n = 48; 24.4 %); (4) ulcer/gastritis (n = 20; 10.2 %); (5) depression (n = 17; 8.6 %); (6) bone diseases (n = 12; 6.1 %); and (7) neoplasms (n = 1; 0.5 %). Most patients were under dialytic treatment for less than five years (n = 111; 56.4 %), 44 (22.3 %) patients for more than five and less than 10 years, 40 (20.3 %) patients were under treatment for 10 years or more and two patients did not answer this question.

The most common drug classes were phosphate binders, beta-blockers, loop diuretics and calcium channel antagonists, as presented in Table 2. The most used drugs during or after the dialysis sessions were recombinant human erythropoietin (n = 104; 52.8 %), iron hidroxyde saccharate (n = 58; 29.4 %) and injectable calcitriol (n = 16; 8.1 %).

Table 2: ATC classes used by patients in dialysis.

Drug classes	Patient number (n=197)	Frequency (%)
Phosphate binder	179	90.7
Beta blocking	130	66.0
Diuretics	98	49.7
Calcium channel blockers	74	37.6
Angiotensin II antagonists	71	36.0
Platelet aggregation inhibitors	58	29.4
HMG CoA reductase inhibitors	53	26.9
Adrenergic agents	50	25.4
Benzodiazepines	50	25.4
Proton bomb inhibitors	48	24.4
Pancreatic hormones	43	21.8
ACE inhibitors	40	20.3
Others	121	61.4

The presence of polypharmacy was found in 130 patients (66.0 %). The TCI ranged from two to 34, with a median of 15 (IQ 10-20). Additionally, with evaluation therapy adherence via MMAS-4, it was verified that 99 patients showed high (50.5 %) while 30 patients showed low adherence (15.3 %). Controversially, through BMQ, 158 (80.6 %) patients were found to have probable low adherence, 22 (11.2 %) patients with low adherence, and only 16 (8.2 %) presented probable adherence.

Considering BMQ, scores equal to or higher than one indicate potential barriers regarding the regimens, and scores equal to zero indicate no barrier. The regimen domain comprises seven questions and 182 (92.8 %) patients showed potential non-adherence results; it is important to mention that two questions of this domain showed crucial results, as one of the questions was about the failure of the patient to mention spontaneously their prescribed medicine, being 68.4 % of patients presenting this issue. The other question showed that 83.2 % of the patients omitted to reduce the dose of any prescribed medicine. In the beliefs domain, comprising two questions, 171 (87.2 %) patients showed no barriers, and the recall domain comprising two questions, showed that 190 (96.9 %) patients achieved scores equal to or higher than 1. Hence, the belief domain did not influence adherence to the drug therapy in dialytic patients.

For the influence of socioeconomic and demographic variables (gender, ethnicity, retirement and healthcare insurance) in polypharmacy, the high and low adherence profile from MMAS-4 and BMQ domains were evaluated. No difference between the presence of polypharmacy or adherence profile over social factors was found (p>0.05; chi-square).

The influence of polypharmacy on comorbidity numbers, TCI value, dialysis time and adherence profile was evaluated, as shown in Table 3; both comorbidity numbers and TCI value showed direct influence upon the presence of polypharmacy. On the other hand,

the time of dialytic treatment did not influence the presence of polypharmacy. Concerning the adherence profile, polypharmacy showed no influence on adherence in the MMAS-4 test; in contrast, the BMQ score seems to be influenced, with higher values in the presence of polypharmacy.

Table 3: Influence of comorbidity numbers, TCI value and dialysis time upon polypharmacy

	Polypharmacy		p-value *
	Yes (n=130)	No (n=67)	
Comorbidity numbers	2 (1;3)	1 (1;2)	<0.0001
TCI	18 (14;22)	8 (6;12)	<0.0001
Dialysis time (years)	4 (1.5; 8)	4.5 (2;10.75)	0.584
Brief medication Questionnaire			
Regimen	2.0 (0;5)	2.0 (0;4)	0.010
Beliefs	0.0 (0;2)	0.0 (0;1)	0.037
Recall	1.0 (1;2)	1.0 (0;2)	0.004
Morisky Medication Adherence Scale - 4 items			
Low	21 (10.7 %)	9 (4.6 %)	0.582**
Medium	41 (20.8 %)	26 (13.2 %)	
High	68 (34.5 %)	32 (16.2 %)	

*Mann Whitney; Data expressed as Median (Max;Min); ** Pearson Chi-square; data expressed as number (%).

When comparing the TCI value with the adherence profile, no influence of therapy complexity on MMAS-4 for patients with high (TCI median of 16.0), medium (13.0) or low (13.5) adherence (p=0.136) was observed. Additionally for BMQ a depreciable correlation was obtained for regimen (p=0.262), beliefs (p=0.094) and recall (p=0.224)

In Table 4, the variation of scores yielded by BMQ in different domains relating to the adherence profile from MMAS-4 was evaluated. Since the belief domain does not change according MMAS-4 profile, no difference was found between the groups. On the other hand, BMQ scores representing low adherence match the same result found using MMAS-4. Additionally, the probable non-adherence identified in BMQ was not observed in MMAS-4. In this way, MMAS-4 when compared to BMQ showed to be an important tool to identify low adherence to the drug therapy.

Table 4: Comparison between the surveys used to evaluate pharmacotherapy adherence.

BMQ Domain	MMAS-4			p-value*
	High adherence (n=99)	Medium adherence (n=67)	Low adherence (n=30)	
Regimen	2	2	3	<0.0001
Beliefs	0	0	0	0.393
Recall	1	1	2	<0.0001

*Krusky-Wallis. Data expressed as median

DISCUSSION

The present study showed predominance of the male gender, matching the national literature and dialysis census of 2013 from the Brazilian Nephrology Society[4,13-14]. This may be related to the fact that SAH, which is one of the major causes of chronic kidney failure, and consequently to SRT, has almost three times more prevalence in men than in women[15].

The majority of the study population were characterized by incomplete elementary school, household income less than two Brazilian minimum wages and dialysis time between one and five years, being comparable to the population described by the national literature[13-14]. Education and household income are low in the major part of the study population, which may affect the acquisition of medicines to control the disease[16], indicating a low-economic class population[14]. A little more than 50 % of the study population are aged between 25 and 56 years old, being considered an economically active population but are retired due to the disease.

The most prevalent comorbidity associated to dialytic chronic renal failure was SAH[6,16,17]. A study performed by Terra et al. (2010)[6] pointed out an incidence of 96.3 % of dialytic patients showing hypertension as a comorbidity associated to chronic dialytic renal failure.

Regarding the most commonly used medicines by patients in dialysis, as shown in a study conducted by Castro et al. (2009)[18], anti-hypertensive agents and phosphate binders are the most common, as presented by the current study. Post-dialysis drugs, such as recombinant human erythropoietin and iron hidroxyde saccharate are considered high-cost medicines, and patients need to pick them up at the City Health Department.

No influence of sociodemographic data upon adherence and the use of five or more medicines in his/her routine was found. The same result was seen by Sgnaolin & Figueiredo (2012)[8] in relation to the pharmacotherapy adherence and the use of five or more medicines. Gender does not have influence upon polypharmacy as described by Lucchetti et al. (2010)[19], matching our results.

Both comorbidities and TCI were influenced by the presence of polypharmacy in these patients. It is expected that patients with higher comorbidity numbers would have a higher amount of prescribed medicines (polypharmacy), and consequent higher TCI values. This index has a considerable value since 66.6 % of the study population presented polypharmacy, which is completely related to a high TCI value in these patients. In addition, no correlation was observed between TCI and the patient's adherence profile. Comparatively, Accurcio et al. found that more complex therapies are associated to less treatment adherence in the elderly[10]. On the other hand, in dialysis patients, despite polypharmacy, frailty, malnutrition, religiosity and resilience are more associated with adherence, showing the psichological status influence over adherence[24,25]. Thus, more studies are required to evaluate the degree of this influence.

Studies in patients with chronic dialytic renal diseases evaluating TCI were not found, however, a study conducted by Acurcio et al. (2009)[18] yielded in an elderly population, TCI values ranging from one to 24, requiring peculiar care since this is a fragile population. However, in the dialytic patients from the current study, TCI values showed a higher variation interval (two to 34), hence, dialytic patients have a higher therapeutic complexity, requiring even more specialized care.

Since the number of comorbidities shows a direct influence upon the presence of polypharmacy, it was expected to find the same for dialysis treatment time, although this relationship was not established and no data was found in the literature to corroborate the current study.

Even though these patients show a high index of polypharmacy, pointing towards kidney toxicity[19], the prescription of these medicines is not irrational. Because the patients are under end-stage chronic kidney disease conditions, these drugs are indicated for palliative purposes, especially to control blood pressure. As there are no chances of kidney regeneration, these drugs are not contra-indicated. Studies[20] indicate potential renal injury through long-term drug therapy, but CKD patients are not mentioned in the literature, corroborating the authors' inference described above. Thus, the evaluation of which medicine to be used should be based on the properties of the drug, such as protein-binding potential, molecular size and physical-chemical properties[19-20].

In the present study, according to MMAS-4, 50.5 % of the patients in dialysis showed high adherence, matching the literature where 55.4 % of the patients showed non-adherence via MMAS-4[8], linking such occurrence to the large amount of medicines, favouring no compliance or forgetfulness. Nevertheless, using BMQ, 80.6 % of the patients showed probable non-adherence, similar to the literature, although data in chronic dialytic renal disease patients was not found, but according to a study performed by Mantovani et al. (2015)[21] in hypertensive patients, 59.0 % of the patients showed probable low adherence and the usage of this instrument showed higher specificity and sensibility. In

the current study, MMAS-4 classified the patients as showing high adherence, however BMQ analysis evidenced that most patients presented low adherence. The contradiction between the results obtained by both tests is notorious. However, it can be evidenced that only for patients labelled as low adherent by MMAS-4, a relationship was obtained by BMQ. When comparing MMAS-4 and BMQ, it could be seen that MMAS-4 evaluates "regimen" and "recall" of patients due to significative p-values (<0.05).

Finally, there is no instrument judged as a "gold standard" to evaluate pharmacotherapy adherence. On one hand BMQ shows better specificity and sensibility, allowing understanding of the points in which patients show difficulties to continue with the therapy, since it provides subsidies through three dimensions (beliefs, regimen and recall)[23], on the other hand, MMAS-4 is portrayed as a highly simple and practical test to be used in the daily practice.

CONCLUSION

As expected for dialytic patients, a high level of polypharmacy and TCI was observed. Polypharmacy was influenced by the number of comorbidities and TCI and showed correlation with adherence measured by BMQ. No relation between polypharmacy and MMAS-4 was shown. Additionally, the adherence profile being poorly correlated with the variables analyzed seems to correlate with psychological variables. Meanwhile, more studies are required to evaluate this association. Finally, differences in results between the two adherence tests were observed, with agreement to poor adherence. Thus, it is suggested that the data related to poor adherence are reliable and useful to determine the need for intervention in this population.

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Conflict of interests

Authors have no conflict of interest to declare.

Contributors

NVG, KBA, AOB, CS - Design and/or data analysis and interpretation; NVG, KBA, TRS, AOB, CS - Article writing or critical review of intellectual content; AOB, CS - Final approval; NVG, KBA, TRS, CS - Be responsible for all aspects of the work in ensuring the accuracy and integrity of any part of the work.

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