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Haemodialysis improves uraemic patients' cognition: a pilot study

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Abstract

Uraemia is a state of elevated plasma urea well related to a low cognitive profile. Although renal transplantation has been proved to improve cognition in these patients, little is known about how haemodialysis act on this scenario. Here we aimed to conduct a pilot study to fathom the presence and magnitude of a possible benefit of haemodialysis in cognition. Our main instrument was the Montreal Cognitive Assessment (MoCA) test, a tool designed to allow for a sensitive score for cognitive impairment. Although preliminary, our data were significant (p=0.012) to suggest that haemodialysis might be an important tool for cognitive improvement of end-stage kidney disease patients, tough not sufficient for a full cognitive recovery.

Introduction

Uraemia or uraemic syndrome is a state caused by elevated plasma urea, usually accompanied by other nitrogen compounds elevation, molecules commonly excreted through the kidneys. It's a more limited term than azotaemia, since uraemia generally refers to high plasmatic urea causing a certain degree of symptomatology due to kidney dysfunction, while azotaemia is a laboratorial indication of elevated plasma urea that can also imply pre- and post-renal defects, such as reduced renal blood flow and obstruction of urine flow, respectively [1]. Although we intent to use the narrow definition, both terms indicate the same organic contingency for our purposes, one in which the cognition might be impaired due to nitrogen compounds' neurotoxicity.

It is estimated that between 30 and 70% of chronic kidney disease patients have some degree of cognitive issues [2]; however, the precise relation between uraemia and cognitive impairment is still unknown. Asymmetric dimethylarginine and guanidine-related compounds are proposed neurotoxins involved in cognitive deterioration due to renal failure and uraemic encephalopathy. The CNS might also be damaged during renal failure by secondary hyperparathyroidism, which affects cytosolic calcium levels within synaptosomes, GABA content in the brain, and noradrenaline and acetylcholine metabolism [3,4]. The relationship between uraemia and cognitive decline is strengthened by the already described cognitive improvement in dialytic patients after renal transplantation [5,6]. The literature is well served of studies comparing cognition and CNS parameters of patients undergoing dialysis and healthy baseline parameters [3]. Nonetheless, to the best of our knowledge, no study has evaluated cognitive performance before and after haemodialysis starts in the same group of patients.

The Montreal Cognitive Assessment (MoCA) test was our tool for analysing cognitive performance. It consists of 30 questions that must be solved using drawing, careful listening, and intellectual and simple mathematical skills; each question accounts for one point, being thus the maximum score 30. MoCA is a relatively new test which is being increasingly used for cognitive impairment assessment, due to its high sensitivity and test-retest reliability [7] and concordance with standard neuropsychological tests [8].

The Geriatric Depression Scale with 15 questions (GDS-15) is a yes-no questionnaire that provides a quick alternative to the psychiatric interview when screening for depression, especially in older people. A work comparing GDS-15 to the Beck's Depression Inventory (BDI) – an already validated tool for depression assessment – in the context of haemodialytic patients has shown that GDS-15 has a high predictive accuracy versus the BDI and even a psychiatric interview, which is the gold-standard [9]. The cut-off value with best diagnostic accuracy in this study was a score of 5, the same value we used in this study (see Methods).

Methods

Patients

Patients were randomly chosen from the Hospital de Clínicas de Porto Alegre (HCPA) end-stage uraemia outpatient ambulatory's list and explained the purposes of the study. Including criteria were 1) having end-stage chronic kidney disease (that is, having a glomerular filtration ratio (GFR) equal or lower to 15 ml/min/1.73m^2) and 2) having plans to start dialysis within one year. The sole exclusion criterion was having any neurological or any psychiatric disorder

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other than depression. All patients explicitly agreed in participating at the study after being thoroughly explained about it, according to the Declaration of Helsinki and the HCPA Ethical Committee. A total of 17 patients were enrolled.

Regarding the experiment's control, we designed the study so that the patients are their own controls, since a separate group would be inevitably biased: healthy participants matching age and school years would always tend to score better, and participants with chronic kidney disease with no dialysis plan would tend to score worse in the second testing, due to disease progress in the meantime, thus biasing the results. Besides, comparing the patients to themselves has the advantage of giving a better view of the treatment's pure effect instead of mixing in the analysis the patients' different sociocultural backgrounds.

Cognitive testing

For cognitive testing, we used the Montreal Cognitive Assessment test (MoCA test) in its Brazilian version (MoCA-BR) made in 2007 by Bertolucci, Sarmento and Wajman [10] and validated in 2013 by Memória and colleagues [11]. MoCA-BR shows a sensibility of 81% and a specificity of 77% for mild cognitive impairment, [8] thus being more suited as a screening test than the Mini-Mental State Examination (MMSE), the most commonly used tool, which has the same sensitivity, but a much lower specificity (81% and 65%, respectively) determined for a population with similar characteristics than ours [12]. All tests were applied by the authors, having all received the same training by a neurogeriatrician (the last author). We used MoCA test results as a non-parametric variable, since all but one patient scored under the commonly used cut-off value of 23 points at the first evaluation.

Depressive symptomatology

To control for a possible confounder, we made a quick screening for depression using the Geriatric Depression Scale in its 15-question format (GDS-15), validated to Brazilian Portuguese [13]. We chose to use GDS-15 for depression screening due to the high sensibility and sensitivity of this scale (up to 87% and 82%, respectively) [10] and the little time it takes to be applied (less than five minutes). Patients scoring more than 5 points are considered to be of high risk for depression, and those scoring 5 or less to be of low risk.

Statistics

All the patients' data was kept in a Microsoft Excel data bank (Microsoft Inc, v15.0). Statistical analyses were made using SPSS (IBM, v18.0) with the help of a statistician from HCPA. For the comparison between paired, non-parametric samples (MoCA and GDS-15 scores before and during haemodialysis), Wilcoxon signed-ranks test was performed. For comparison between independent, non-parametric samples, Mann-Whitney U test was performed.

Results

Altogether, only 10 out of 17 patients started haemodialysis in 1.5 years, further reducing the sample size; of the 7 patients that did not enter the treatment, two were transplanted before dialysis began, and the other five decided to postpone it while clinical treatments could still be made. Median age of the patients that entered haemodialysis at the first testing was of 60.5 years, ranging from 33 to 66 years (SD=13.3). Median school years of patients that entered haemodialysis was of 7.5 years, ranging from 1 to 12 years (SD=4.12); all the patients received one extra point in their MoCA test final scores as an adaptation for low study years, as described in the score. Since the patients were compared with themselves, adjustment for age was not necessary.

MoCA test

The MoCA test results of the ten patients that did enter dialysis was of 17.5 ± 4.2 and 19.5 ± 3.5 (median ± SD) before treatment start and during treatment, respectively (p=0.081, Wilcoxon test). The calculated power of the association was of 25% considering a steady difference of 2.0 points, which allowed us to calculate the sample size for 80% power to be of 24 patients (48 measurements). Since approximately 40% of the originally tested patients did not enter haemodialysis at all during study time, we could conclude that a reasonable initial sample size for this study should be of at least 34 subjects (40% over 24); in the study that will be made from the information obtained in this pilot, this calculation will be considered. The MoCA score of the patients that did not enter haemodialysis resulted in a median of 18.0 ± 4.3, not being significantly different from the ones that did enter dialysis later (p=0.601, Mann-Whitney U test); this lack of difference helps to assure that no selection bias occurred.

We also performed an analysis excluding the only patient who was permanently (pre-and post dialysis) screened with major depression through GDS. This patient differed from the others in that the difference between his test during dialysis to the one before dialysis was of -5, while the median of the other patients was of 3.5 with a 3.3 SD. The new medians of before and during treatment testing were of 17.0 ± 4.1 and 20.0 ± 3.5, respectively, and the Wilcoxon test then yielded a significant p-value of 0.012.

GDS-15 results

The GDS-15 values did not change significantly from testing before to during haemodialysis (p>0.05, Wilcoxon test), being 4 ± 2.7 and 3 ± 2.7, respectively. Three patients had scores higher than 5 before dialysis and three during dialysis. There was also no difference between the GDS-15 scores of patients that entered haemodialysis and those that did not (p>0.05, Mann-Whitney test).

Due to low sample size, it was not possible to calculate whether GDS-15 values correlated in any way with the MoCA test results; however, in a scattering plot (data not shown), a simple visual analysis seems to show no correlation. This question will be better addressed in the study that will result from the learnings obtained in this pilot.

Discussion

Even though this is a pilot study, our data suggests that haemodialysis might be an important tool for cognitive improvement in patients with end-stage kidney disease. Although this might seem quite an intuitive statement, current data in the literature doesn't support it, mostly because the available studies paired their data to healthy patterns and do not measure cognitive parameters before dialysis is initiated as a treatment to match this information with the cognitive evaluation after dialysis [3]. However, their negative results while associating dialysis and cognition might have a meaning if merged with our findings. If both data are right, we might conclude that haemodialysis is a favourable resource for cognitive progress in patients with end-stage kidney disease, but not enough for a full cognitive recovery, since a measurable impairment still exists.

Regarding possible limitations in our methodology, we would like to address four reasonable ones. First, for technical reasons, we didn't have a precise assessment of the uraemic state of each patient at the time of each evaluation. Our parameter was their classification

as pre-dialytic patients, performed by specialists based on laboratorial and clinical judgement at the outpatient ambulatory. Second, for logistic limitations of small and medium range travelling, we were not able to immediately evaluate the patients after they began the dialytic treatment, in a way that we do not have a fixed time span from the beginning of dialysis and the second cognitive assessment. Yet, all follow-ups ranged from one to six months after the onset of the treatment and it did not seem to interfere in our results. Third, our sample is a quite small one, which limited the significance and power of our results: based on these results, we have calculated a sample of 34 individuals as a minimum point and presume to be able to reach this value in a foreseeable future in order to present a still stronger result. Finally, we didn't have a control group, which would give us a more accurate indication that our results didn't come from any interference or are part from the natural history of disease; since the main causes of chronic kidney disease, namely diabetes and hypertension, can cause *per se* some cognitive decline [14]. We may speculate that the effect of haemodialysis onto cognition could be even stronger.

As for the study's strengths, we would like to highlight the use of a sensitive clinical scale for cognitive outcomes, which possibly mimics reliably the patient's and the patient's family and friends experience with the cognitive decline – even though there are more sensitive methods to measure cognitive outcomes, their specificity to clinically significant findings tends to be lower, thus serving more as academic than practical means. We would observe as well the broad inclusion criteria, which suit a pilot study's objective of determining the general profile of a condition to better investigate it later.

Conclusion

Despite the small number of participants, this study preliminarily indicates that haemodialysis is an effective therapy for the cognitive decline caused by chronic kidney disease's uraemic syndrome, at least in non-depressed patients. Currently, we are starting a larger, more controlled study to test the validity of our results, and hope to soon be able shed a brighter light in the subject.

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