Journal of the Neurological Sciences 385 (2018) 39–44

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Anti-cholinergic medications for bladder dysfunction worsen cognition in persons with multiple sclerosis

Sarah A. Morrow[a,*], Heather Rosehart[b], Alp Sener[c], Blayne Welk[d]

[a] Department of Clinical Neurological Sciences, Western University, London Health Sciences Center, LHSC-UH, 339 Windermere Rd, London N6A 5A5, ON, Canada
[b] Department of Clinical Neurological Sciences, London Health Sciences Center, London, ON, Canada
[c] Western University, London Health Sciences Center, London, ON, Canada
[d] Department of Epidemiology and Biostatistics, Western University, London Health Sciences Center, London, ON, Canada

ARTICLE INFO

Keywords:
Multiple sclerosis
Cognition
Anti-cholinergic
Bladder

ABSTRACT

Bladder dysfunction is common in persons with MS (PwMS), often due to detrusor muscle overactivity. Anticholinergic medications are considered the first line treatment for bladder dysfunction and are known to worsen cognition in healthy older adults and in persons with dementia. Yet, it is not known if these medications have the same effect on PwMS. Thus, the *Objective* of this prospective matched-cohort study was to determine if anticholinergic medications affect objective measures of cognition in PwMS. We recruited PwMS starting either oxybutynin or tolterodine (cases). Cases and controls were tested with the Brief International Cognitive Assessment for MS (BiCAMS) battery prior to starting anticholinergic medications and 12 weeks later. The primary outcome was change on the Symbol Digit Modalities Test (SDMT) between groups; secondary outcomes were changes on the other BiCAMS measures. Analysis of Covariance with baseline measures as covariates to assess the significance of between group differences was performed at 12 weeks. Forty eight PwMS starting anticholinergic medications and 21 matched PwMS controls were recruited. There was a significant difference ($p < 0.001$) in the change on the cognitive measures over 12 weeks between groups. The controls demonstrated improvement, consistent with practice effect, while the cases remained unchanged. This study demonstrates that anticholinergic medications may have a negative effect on cognition in PwMS; further confirmatory studies are needed.

1. Introduction

Bladder function is commonly affected in persons with MS (PwMS); the incidence of increased urinary urgency, frequency and/or incontinence reported in PwMS ranges from 64 to 88% and is most frequently associated with detrusor muscle over activity on urodynamic testing [1]. These symptoms are very distressing to PwMS and can have a negative effect on quality of life. Anticholinergic medications are commonly used in PwMS to treat bladder dysfunction. Contraction of bladder detrusor muscles is mediated by acetylcholine acting on muscarinic receptors [2]. Anticholinergic medications block the action of acetylcholine at muscarinic receptors to reduce the frequency and intensity of involuntary detrusor contractions, and alter the sensory properties of the urothelium. Anticholinergic medications cross the blood brain barrier and can act centrally on muscarinic receptors in the brain and thus can have an effect on cognitive function. Anticholinergic medications are known to worsen cognitive function in patients with dementia, including Alzheimer's disease (AD), Mild Cognitive Impairment (MCI), and dementia in Parkinson's disease [3–5]. Further, healthy older people taking anticholinergic medication often demonstrate a decline in cognitive ability, specifically information processing speed, attention and memory [6–10]. Studies have shown that anticholinergic medications may lead to an increased development of de novo dementia, and brain atrophy [11,12]. Cognitive impairment is a common symptom in PwMS, affecting 40–65% of patients [13]; it is unknown to what extent these medications will affect cognitive processes in PwMS. The objective of this study was to determine whether treatment with anticholinergic medications for bladder dysfunction, specifically oxybutynin and tolterodine, affects objective measures of cognitive function in PwMS.

2. Methods

This was a prospective matched-cohort study. We evaluated PwMS who were to be treated with either oxybutynin or tolterodine who presented with frequency, urgency or urgency incontinence suggestive

* Corresponding author.
E-mail address: Sarah.morrow@lhsc.on.ca (S.A. Morrow).

https://doi.org/10.1016/j.jns.2017.11.028
Received 28 July 2017; Received in revised form 26 October 2017; Accepted 21 November 2017
Available online 22 November 2017
0022-510X/

of overactive bladder symptoms. They completed a validated cognitive assessment at baseline (prior to starting the medication), and after 12 weeks of medication exposure. Matched controls were PwMS who were not starting an anticholinergic medication. They were also evaluated at study enrollment and then 12 weeks later.

2.1. Outcomes

Cases and controls were evaluated with the Brief International Cognitive Assessment for MS (BiCAMS) battery, a validated screening battery developed specifically for PwMS [14]. It is composed of Rao's oral version of the Symbol Digit Modalities Test (SDMT) [15,16], the Brief Visuospatial Memory Test – Revised, immediate recall measure (BVMTR-IR) [17] and the California Verbal Learning Test 2nd Edition, immediate recall measure (CVLT2-IR) [18].

The SDMT consists of the presentation of a standard letter sized paper (8.5 × 11 in.) that contains the numbers and symbols to be processed [19]. At the top of the page is a key where nine symbols are each paired with a single digit. The remainder of the page has a pseudo-randomized sequence of these symbols. In the oral version of the SDMT, adapted for the MS population by Rao [15], the subject responds orally with the digit associated with each of the symbols as quickly as possible, and is scored as the total number of correct responses in 90 s.

The CVLT2-IR assesses auditory/verbal memory, with five learning trials of the same 16 words. It is scored as the total number of words recalled, or learned, for each of the five trials [18]. The BVMTR-IR is a measure of visual/spatial memory with three recall trials of the same six figures, marked for accuracy of the figure drawn and their spatial location on the page. Similar to the CVLT2-IR, it is scored across the three learning trials [17].

Processing speed is the most frequently affected cognitive domain in PwMS, occurring in 52% of individuals [20]. Further, the SDMT is known to be the most sensitive and reliable measure of processing speed in PwMS [21]. Thus the primary outcome was change on the SDMT in cases compared to controls. Change on the BVMTR-IR and CVLT2-IR, between groups served as secondary outcomes.

Due to the potential confounding nature of mood symptoms and fatigue, the Hospital Anxiety and Depression Scale (HADS) [22], and the Fatigue Severity Scale (FSS) [23] were also administered. The HADS is a self-reported scale that detects both anxiety (HADS-A) and depressive (HADS-D) symptoms. The HADS is composed of 14 questions, each scored from 0 (no symptoms) to 3 (severe symptoms) and composite scores for the HADS-A and HADS-D are calculated individually. The FSS, a measure of generalized fatigue, is composed of nine questions which are scored from 0 (no symptoms) to 7 (severe symptoms). The final score ranges from 0.0 to 7.0.

2.2. Subjects

Subjects, or “cases”, were PwMS, 18–59 years of age, who were offered treatment with either oxybutynin or tolterodine for clinical symptoms of overactive bladder (urinary urgency or urge incontinence). Bladder scans were not done; treatment was based on clinical judgement. In order to be included in the study, cases were not on another anticholinergic medication, had not used oxybutynin or tolterodine in the past, had not received corticosteroids or had a relapse in the last thirty days and all other medications were stable over the last three months. Further, if there was a history of a medical condition, such as a psychiatric disorder, learning disability, or dementia, which could affect the cognitive assessment, the subject was excluded. Similarly, if the subject had a diagnosis of severe depression that was currently not treated, or scored 13 or higher on the Beck Depression Inventory, Fast Screen (BDIFS), he/she was not included. Cases were recruited from the London MS Clinic in London (ON) Canada.

Two weeks after initiation of the treatment, the study coordinator contacted the subject to review compliance and adverse effects. At the 12 week follow up visit, medication updates and adverse effects were reviewed.

2.3. Intervention

Cases started either tolterodine or oxybutynin for the treatment of bothersome overactive bladder symptoms as per the discretion of the treating clinician. Cases were started on either tolterodine 1 mg BID or oxybutynin 2.5 mg BID, and increased to the full dose (tolterodine 2 mg BID or oxybutynin 5 mg BID) after 2 weeks, as tolerated.

2.4. Controls

Controls, or PwMS not being treated with either oxybutynin or tolterodine, were also recruited from the London MS clinic. Controls had to meet the same inclusion criteria as the cases (other than treatment with oxybutynin or tolterodine) and were matched on age (± 5 years) and baseline SDMT scores (± 3.0 points).

2.5. Statistical analysis

Little data was available at the time of the design of this study to calculate an appropriate sample size as it is unclear what is considered a meaningful (negative) effect from a medication. After recruiting for almost 4 years, which was limited due to the new pharmacologic treatment available, recruitment for the study was closed.

To compare cases and controls on baseline characteristics, *t*-tests and chi-square analysis were used, as appropriate. To compare longitudinal changes on cognitive tests across groups over 12 weeks, Analysis of Covariance (ANCOVA) was used, with baseline scores employed as covariates and the test scores at 12 weeks designated as the dependent variable. Where significant linear relationships were found between the outcomes and potential covariates (i.e. gender), these variables would be included in these models.

3. Results

From December 2012 to June 2016, 55 potential cases were approached and signed consent to participate in the study. Of those, seven did not complete Visit 1 or did not start an anticholinergic medication; thus there were 48 cases (Fig. 1). Additionally, 21 controls were recruited to the study. The two groups were well matched on age (cases 48.2 ± 8.3 years vs. controls 49.1 ± 11.2, $p = 0.682$) and baseline SDMT (cases 44.4 ± 15.6 vs. controls 46.1 ± 14.8, $p = 0.674$).

The cases group were predominantly women (32, 66.7%) and had achieved a mean years of education of 13.3 ± 2.1 years. On average, the cases had been diagnosed with MS 11.8 ± 9.8 years ago and 17 (35.4%) were on a disease modifying therapy at the time of this study. The median Expanded Disability Status Scale (EDSS) was 3.5 (range 1.5–7.5), with few in the severe range (EDSS 0.0–3.0: 21 (43.8%); EDSS 3.5–5.5: 18 (37.5%); EDSS ≥ 6.0: 9 (18.8%)); 25 had RRMS, 20 SPMS and 3 PPMS. The two groups had similar demographics and disease characteristics with no significant differences (Table 1).

In the cases group, 31 (64.6%) were impaired on the SDMT. The mean score on the CVLT2-IR in the cases group was 43.7 ± 13.1, and 23 (47.9%) were impaired. On the BVMT2-IR, the mean score in the cases group was 20.2 ± 9.1, and 22 (45.8%) were impaired. Finally, the mean HADS-A score was 7.6 ± 4.0, the mean HADS-D score was 5.8 ± 3.8, and the mean FSS score was 4.8 ± 1.4 in the cases group. These were not significantly different from the control group (Table 2).

Of the 48 cases that completed Visit 1, 16 did not complete the study. The most common reason was that the anticholinergic medication was stopped (n = 6) due to lack of efficacy or never started (n = 3) prior to Visit 2. Only three subjects stopped the medication prior to visit 2 due to adverse events. Additionally, two controls, after signing consent, withdrew consent and thus did not complete Visit 2 (Fig. 1). When