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Original Research Article

The Effect of Solifenacin on Cognitive Function following Stroke

Jin-Woo Park

Department of Physical Medicine and Rehabilitation, Dongguk University Ilsan Hospital, Goyang-si, Republic of Korea

Key Words

Stroke · Cognitive symptoms · Anticholinergics · Solifenacin · Muscarinic receptors

Abstract

Background/Aims: Our aim was to investigate the effect of solifenacin (an anticholinergic) on cognitive function after stroke. ***Methods:*** We retrospectively reviewed 66 stroke cases who were prescribed solifenacin for more than 2 months. A control group was generated matching the patients both for sex and age. The interval changes in the Mini-Mental State Examination (MMSE) score and Clinical Dementia Rating Sum of Boxes (CDR-SB) score after solifenacin administration were compared to those of the control group. ***Results:*** The baseline MMSE score of the control group was 15.9 ± 9.2 and that of the solifenacin group was 14.3 ± 7.8. After using solifenacin for an average of 76.9 days, there was a change in the MMSE score of 1.9 ± 5.2. During similar periods, there was a change in the MMSE score of 2.9 ± 3.7 in the control group (not using solifenacin). However, there was no significant difference between the two groups. Similarly, there was no significant difference in the CDR-SB score between the two groups. ***Conclusion:*** Solifenacin treatment did not affect the short-term cognitive performance in stroke patients. This information might be useful when prescribing anticholinergics to stroke patients.

Introduction

Neurogenic bladder after stroke, especially bladder storage problems, is frequent [1], and the disruption of the neuromicturition pathways might result in bladder hyperreflexia and urgency incontinence [2]. Anticholinergics have been used to improve detrusor overactivity and increase bladder capacity after stroke [3].

Jin-Woo Park, MD, PhD
Department of Physical Medicine and Rehabilitation
Dongguk University Ilsan Hospital, 27 Dongguk-ro
Goyang-si 410-773 (Republic of Korea)
E-Mail jinwoo.park.md@gmail.com

The central nervous system of older patients is very sensitive to adverse anticholinergic effects due to the significant decrease in cholinergic neurons or receptors in their brains, the reduction in the hepatic metabolism and renal excretion of medications as well as the increase in the blood-brain barrier permeability [4]. Many studies have found an association between the anticholinergic activity of medications and cognitive impairment or dementia [5, 6]. On the other hand, stroke is independently related to cognitive dysfunction. The prevalence of dementia in individuals with a history of stroke is about 30%, and the incidence of dementia is increased after stroke [7].

Do anticholinergics really worsen cognitive dysfunction after stroke? Currently, there is little known about this subject, but the answer may depend on the selectivity for muscarinic receptors or the permeability of the blood-brain barrier. In this study, we investigated whether solifenacin (an anticholinergic which has a high affinity for the muscarinic M3 receptor) has a negative effect on cognitive function after stroke.

Methods

Subjects

This was a retrospective case-control study. Medical charts were retrospectively reviewed for all individuals with a diagnosis of stroke who were admitted for rehabilitation to the university hospital from January 2010 to December 2011. A total of 72 consecutive patients were thus identified who were on a 2-month treatment course with solifenacin (5 or 10 mg) to control for abnormal urinary frequency or urgency symptoms. Six patients were excluded because data for evaluating their cognitive function [using the Mini-Mental State Examination (MMSE) or Clinical Dementia Rating Sum of Boxes (CDR-SB)] were not available, and therefore, 66 patients were included in this study. 66 age- and sex-matched stroke patients, who had not been prescribed anticholinergics during the same periods, were also selected as a control group for the comparison of changes in cognitive function. This study was approved by our Institutional Review Board.

Outcome Measures

In our rehabilitation setting, cognitive function tests are routinely performed by a trained physician during a patient's admission period; therefore, these data could be collected via a chart review of all patients selected for the study (from January 2010 to December 2011). Cognitive function was determined using the MMSE [8] and the CDR-SB [9].

The MMSE provides a quick evaluation of cognitive function and is often used to screen for dementia or monitor its progression. The MMSE tests orientation, registration, attention and calculation, recall, praxis and language, and is scored on a 30-point scale (30 being normal and 1 being severely impaired).

The CDR was initially developed as a staging instrument to test for Alzheimer's disease severity [10] and covers the following 6 categories or 'boxes': memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR global ratings are calculated using a complex algorithm and range from 0 (no dementia) to 3 (severe dementia) [11]. The CDR-SB scores are calculated by simply adding the box scores; therefore, they range from 0 to 18 (higher scores indicate more impairment). The CDR-SB has been proposed as a sole primary end point for disease-modifying trials on Alzheimer's disease [9].

Statistical Analysis

Statistical analyses were performed using SPSS version 12.0 (SPSS, Inc., Chicago, Ill., USA). Quantitative variables are expressed as means ± SD, and qualitative variables are

Table 1. General characteristics of the study participants

	Solifenacin group (n = 66)	Control group (n = 66)	p value
Mean age ± SD, years	69.3±11.5	69.3±11.5	NS
Minimum–maximum	49–86	49–86	
Gender			NS
Male	18	18	
Female	48	48	
Etiology			
Intracerebral hemorrhage			
Basal ganglia	26	24	
Thalamic	9	10	
Cerebellar	3	2	
Pontine	1	3	
Infarction			
Middle cerebral artery	18	18	
Striatocapsular	7	6	
Anterior cerebral artery	0	2	
Thalamic	2	1	
Mean duration of illness (stroke) ± SD, days	58.5±40.6	56.0±21.2	NS
Minimum–maximum	26–100	16–115	
Mean MMSE score ± SD (at baseline)	14.3±7.8	15.9±9.2	NS
Minimum–maximum	0–26	0–26	
Mean CDR-SB score ± SD (at baseline)	10.1±4.8	8.1±6.2	NS
Minimum–maximum	1.5–18	0–18	
Mean duration of solifenacin use ± SD, days	76.9±12.5		
Minimum–maximum	60–108		
Mean interval between baseline and follow-up ± SD, days	91.5±18.3	90.4±19.3	NS
Minimum–maximum	64–132	62–130	

NS = Not significant.

expressed as absolute values. Group comparisons of baseline demographics and clinical characteristics (sex, age, duration of illness, MMSE, CDR-SB) were performed using Student's t test for continuous variables and the χ^2 test for categorical variables to test for unbalancing between the groups. Changes in the MMSE and CDR-SB scores after more than 2 months of solifenacin treatment were compared between the two groups using Student's t test. The significance level was set at $p < 0.05$.

Results

The average age in both groups was 69.3 ± 11.5 years. There were 18 males and 48 females in each group. The general characteristics of the participants are shown in table 1. There were no significant differences between the groups with respect to demographic variables, duration of illness, baseline MMSE score, baseline CDR-SB score and interval between baseline and follow-up test. The average duration of solifenacin use was 76.9 ± 12.5 days.

There were changes in the MMSE score of 1.95 ± 5.22 in the solifenacin group and of 2.91 ± 3.65 in the control group. Neither was significantly different between the two groups. There were changes in the CDR-SB score of –1.16 ± 2.65 in the solifenacin group and of –1.00 ± 2.27 in the control group. Neither was significantly different between the two groups (fig. 1).

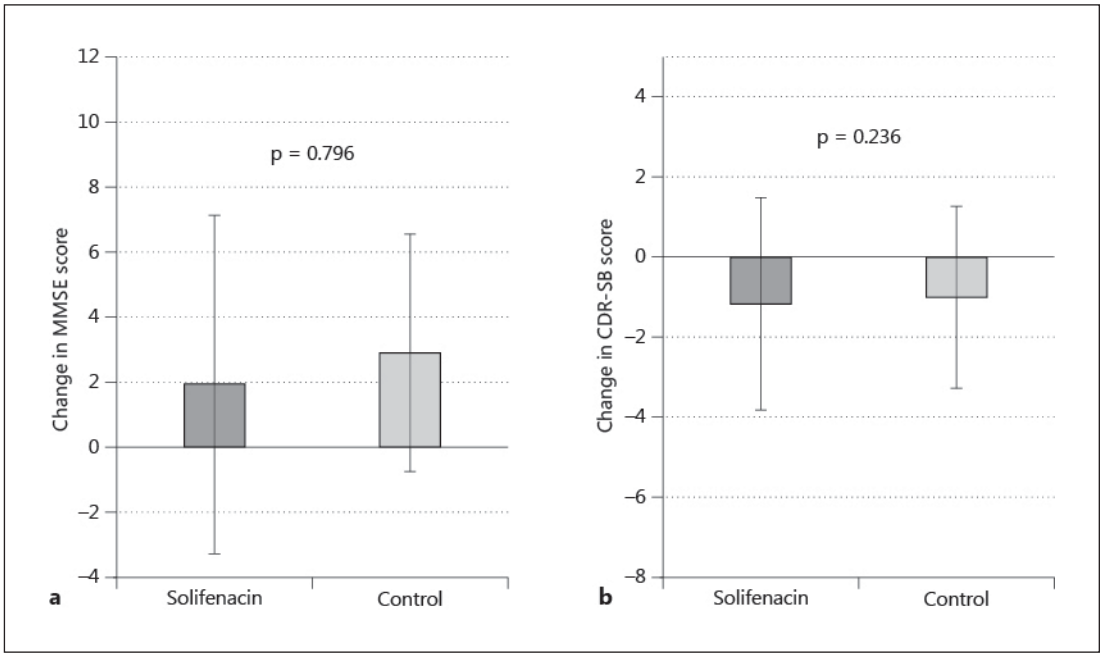

Fig. 1. Comparison between the solifenacin and control groups with respect to changes in the cognitive function tests. **a** MMSE. **b** CDR-SB. Boxes = Average scores; whiskers = standard deviations.

Discussion

This study showed that the use of solifenacin for 2 months does not affect the cognitive performance after stroke. There are two possible factors that may be responsible for this result: one is the muscarinic receptor selectivity and the other is the blood-brain barrier permeability.

Acetylcholine is the best-known neurotransmitter involved in micturition and is released from parasympathetic nerve endings. Five muscarinic receptor subtypes (M1–M5) have been identified by both molecular biological and pharmacological investigations [12], of which the muscarinic M2 and M3 receptor subtypes are located postsynaptically on the detrusor smooth muscle. Although the muscarinic M3 receptor is a minority in this tissue, it has been shown to play a predominant role in mediating detrusor smooth muscle contraction [13, 14]. The muscarinic M1 receptor subtype is considered to be involved in learning and memory processes in the central nervous system, and side effects in the central nervous system due to antimuscarinic agents are related to this M1 receptor [15]. Even though the blood-brain barrier permeability is increased after stroke [16], solifenacin has a higher affinity for the muscarinic M3 receptor than the M1 receptor [17, 18]; therefore, solifenacin might not increase cognitive dysfunction after stroke.

Cognitive dysfunction is a common sequela of stroke. The acute phase of cognitive impairment after stroke is related to its direct local effects as well as hypoperfusion [19] and functional deactivation (diaschisis) in nearby or remote areas of the brain [20]. The prognosis regarding the development of cognitive disorders after stroke is generally favorable and recovery is possible [21]. In this study, cognitive dysfunction was found in both groups, but the average MMSE and CDR-SB scores were improved at follow-up regardless of whether solifenacin was used or not.

This study was based on retrospective chart reviews, and the study group consisted of only a small number of patients. To compensate for these limitations, we used an age- and sex-matched control group; however, this still is not as effective as a prospective randomized control study. Another limitation may be the 2-month period of solifenacin treatment, which can be considered somewhat short.

Solifenacin treatment did not worsen the short-term cognitive performance in stroke patients. This information might be useful when prescribing anticholinergics to stroke patients. However, there should further be a large-size study in the future.

Disclosure Statement

There are no conflicts of interest.

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