The Usefulness and Clinical Characteristics of Antidepressant Use for Stroke Patients with Rehabilitation Program: An Exploratory Analysis

Kyung Ho Lee[1], Geun-Young Park[2], Won-Myong Bahk[3], Soo-Jung Lee[3], Chi-Un Pae[3,4]

Departments of [1]Dermatology, [2]Rehabilitation Medicine, and [3]Psychiatry, College of Medicine, The Catholic University of Korea, [4]Cell Death Disease Research Center, College of Medicine, The Catholic University of Korea, Seoul, Korea

Objective: There has been a lack of data regarding the usefulness and clinical characteristic between patients-treated with and without antidepressants (Pw/Pwo ADs).
Methods: One hundred and eighty inpatients were recruited and observed for a 6-month. The depressive, cognitive, daily activity, and motor symptoms were evaluated at baseline and tracked at month 6, with the use of rating scales including Beck Depression Inventory (BDI), Mini Mental State Examination (MMSE), Global Deterioration Scale (GDS), modified Rankin Scale (MRS), modified Barthel Index (MBI), and Berg Balance Scale (BBS).
Results: Among 178 patients, 84 (47.2%) were treated with ADs. PwAD had numerically or significantly higher depressive cognitive, and motor symptoms along with daily activity impairment (8.3 point higher in BDI score, $p < 0.001$; 3.6 point lower in MMSE, $p = 0.003$; 0.8 point higher in GDS score, $p =$ nonsignificant; 8.2 point lower in BBS score, $p = 0.053$, and 0.4 point higher in MBI score, $p =$ nonsignificant) than PwoAD. Psychiatric consultation was also significantly higher in PwAD than in PwoAD ($p < 0.001$). The numbers need to treat for good clinical outcomes between PwAD and PwoAD were 5.8, 6.0, and 7.5, respectively, by MRS, MBI, and BBS scores.
Conclusion: Our findings suggest the potential utility of AD treatment and different clinical parameters between patients-treated with and without ADs. Adequately-powered and well-controlled further studies are mandatory to confirm and fully elaborate such association.

KEY WORDS: Stroke; Depression; Activities; Motor; Antidepressant; Cognitive function.

INTRODUCTION

The beneficial effects of antidepressants (AD) on diverse clinical outcomes including functional recovery for patients with stoke have been proposed and well-accepted in clinical practice [1].

Indeed, a number of evidence has clearly shown a potential role of AD treatment in the clinical recovery and reduction of final disability of strokes, even in the non-depressed patients. In addition previous data provides preliminary evidence of promising role of AD in physical recovery and motor function regardless of the presence of depression [2,3], despite of opposing results [4]. The mainstay of potential effect of AD on rehabilitation in patients with stroke may be originated from their action mechanism in relation with the regulation of neuro-inflamation, cerebral blood flow, cortical excitation/inhibition, neutotrophic factors, neuronal cell growth leading to neuronal regeneration [1]. However, currently existing evidence is still in a dearth of supporting the use of ADs for prevention of post-stroke depression (PSD) or improvement of motor recovery as proposed by recent treatment guidelines and meta-analysis [5,6].

Few studies have investigated the usefulness of antidepressant and different clinical characteristics between patients-treated with antidepressant (AD) (PwAD) and without AD (PwoAD), especially in rehabilitation program after the first stoke. Therefore, this study investigated

the clinical utility of AD treatment at 6-month after rehabilitation treatment and distinctive clinical characteristics between PwAD and PwoAD in a naturalistic setting.

METHODS

The observation period was 6-month and collected data included socio-demographics as well as self- and clinician-rated scales for the evaluation of depressive, cognitive, daily activity, and motor symptoms at baseline and 6-month. All baseline data were achieved while patients hospitalized and followed up thereafter based on case report form. Rehabilitation process was composed of a complex program of universal activities that were performed five times per week for the first month. The presence of co-morbid conditions was determined following an assessment of patient medication and/or clinical history by the treating physicians. The present study was conducted in compliance with the Declaration of Helsinki and other ethical principles regarding human experimentation. The study protocol was approved by the Institutional Review Board (IRB) of Bucheon St. Mary's Hospital in Bucheon, Korea (IRB no: HC13RISI0015).

For comparison of clinical characteristics between PwAD and PwoAD, socio-demographics and various clinical variables as well as the Korean version of Beck Depression Inventory (BDI) [7-9], Mini-mental Status Examination (MMSE) [10], and Global Deterioration Scale (GDS) [11], were collected at baseline.

For comparison of clinical utility of AD including disability or dependence in the daily activities and functional balance (motor impairment), the modified Rankin Scale (MRS) [12], Modified Barthel Index (MBI) [13], and Berg Balance Scale (BBS) [14] were utilized and measured at baseline and 6-month. Good clinical outcomes were defined by three criteria (otherwise poor outcome); 1) a score of 1 or 2 on the MRS score at 6-month [12]; 2) $\geq$ 75 on MBI score [15]; or 3) $\geq$ 41 on BBS score at 6-month [14]. The number needed to treat (NNT) was also calculated based on the differences in proportions in accordance with such criteria between PwAD and PwoAD.

Statistical Analyses

For all descriptive statistics, continuous variables were presented as mean with standard deviations, and categorical variables were presented as number with percentage.

As for group differences in sociodemographics and rating scales at baseline, independent-*t* test or chi-square was used where appropriate.

As for group comparison of clinical utility of AD including physical disability or dependence in the daily activities and functional balance (motor impairment), the proportions of good outcome based on priori defined scores of MRS, MBI, and BBS at 6-month were compared by chi-square test between PwAD and PwoAD. The NNTs and odds ratio (OR) of PwAD group for good outcome were also calculated with 95% confidential intervals, based on proportional differences between the two group.

Regarding sample power, the present study would have a power of 0.725 to detect a medium effect of 0.3447. This corresponded to approximately 17% difference of the proportion in the MRS score at 6-month between PwAD and PwoAD.

All statistical analyses were conducted using the NCSS 2007® and PASS 2008® software packages (NCSS LLC, Kaysville, UT, USA). Statistical significance was two-tailed and set at $p < 0.05$.

RESULTS

Among 178 enrolled patients, 84 patients (47.2%) took AD, while 94 patients (52.8%) did not. Baseline sociodemographics and clinical parameters were categorized by PwAD and PwoAD which is presented in Table 1.

None of sociodemographics were significantly different between the two groups (Table 1). As for clinical characteristics, psychiatric consultation (54.3% vs. 15.1%, $p < 0.001$), moderate to severe depression (42.5% vs. 11.2%, $p < 0.001$), and presence of depression (70.3% vs. 33.7%, $p < 0.001$) were significantly higher in PwAD than in PwoAD (Table 1). Among baseline clinical rating scales, the BDI, MRS, and BBS scores were marginally or significantly higher in PwAD than in PwoAD (marginal significance in BBS score comparison), while MMSE and MBI scores were significantly lower in PwAD than in PwoAD (Table 1). However, the MBI score was not significantly different between the two groups (Table 1).

The proportion of good outcomes by MRS (17.2% difference favoring PwAD over PwoAD, $p = 0.068$) and MBI (22.4% difference favoring PwAD over PwoAD, $p = 0.056$) scores showed a trend of significant difference between the two groups not reaching statistical difference as

priori defined; however, the proportion of good outcome by BBS score was not significantly different between the two groups (Table 2).

The NNTs and ORs for good outcomes by MRS, MBI, and BBS scores in the PwAD were 5.8/2.4, 6/2, and 7.5/1.7, respectively, in comparison with those of PwoAD.

Table 1. Clinical characteristics between antidepressant users and nonusers at baseline

Variable	Users (n = 84)	Nonusers (n = 94)	p value
Age	61.8 ± 11.7	60.4 ± 14.9	NS
Sex, female	41 (51.2)	35 (37.2)	NS
Education, ≥ middle school	79 (70.0)	91 (67.9)	NS
Number of stroke	1.2 ± 0.5	1.2 ± 0.4	NS
Onset of stroke	60.3 ± 13.4	58.1 ± 16.5	NS
Work status, employed	52 (63.4)	60 (64.5)	NS
Family history of stroke, yes	3 (3.6)	10 (10.8)	NS
SES, ≥ middle income	70 (84.3)	79 (84.0)	NS
Use of alcohol, yes	27 (32.1)	41 (44.1)	NS
Use of tobacco, yes	38 (45.2)	40 (42.6)	NS
Living status, married	70 (84.3)	79 (84.0)	NS
Comorbidity number	1.0 ± 0.8	1.0 ± 0.9	NS
Consultation to psychiatry	44 (54.3)	14 (15.1)	< 0.001
Severity of depression, moderate-severe	34 (42.5)	10 (11.2)	< 0.001
Presence of depression, yes	52 (70.3)	28 (33.7)	< 0.001
BDI	17.0 ± 12.9	8.7 ± 6.6	< 0.001
MMSE	18.5 ± 8.1	22.1 ± 6.3	0.003
GDS	4.0 ± 1.9	3.2 ± 1.8	0.003
MRS	4.1 ± 1.1	3.7 ± 1.2	0.02
MBI	37.7 ± 29.5	44.3 ± 31.1	NS
BBS	17.0 ± 18.7	25.2 ± 22.1	0.053

Values are presented as mean ± standard deviation or number (%). SES, socioeconomic status; BDI, Beck Depression Inventory; MMSE, Mini Mental State Examination; GDS, Global Deterioration Scale; MRS, modified Rankin Scale; MBI, Modified Barthel Index; BBS, Berg Balance Scale; NS, not significant.

DISCUSSION

Our study found several meaningful information in the use of ADs for patients with stroke. Interestingly, psychiatric consultation was significantly higher in PwAD than in PwoAD, indicating more active use of ADs for such patients when they were referred to psychiatrist during admission. In fact psychiatric consultation was approximately 3.5 times higher in PwAD than PwoAD in our study. There has been a growing evidence of ADs use by non-psychiatric health providers [16]. However, AD treatment has also many risk to develop undesirable adverse events, especially for comorbid medical illnesses such as stroke, which may limit active use of ADs by treating physician of rehabilitation program. Indeed treatment guidelines and large scale data analyses also suggest not to use ADs for stroke patients as blind or preventive way for better clinical outcomes concerning PSD, ADL, physical independence, and motor improvement [5,6].

In addition, AD treatment was more prevalent upon the existence and severity of PSD at baseline in the present study. We previously reported the association of PSD and diverse clinical outcomes of patients with stroke in relation with ADL, physical dependence, and motor function, where we found that PSD was one of critical factors in the success of rehabilitation of stroke patients [17,18]. In this context we have also found substantial practicability of AD treatment for patients with stroke in the present study, where beneficial effects was found favoring PwAD over PwoAD in ADL, physical independence, and motor function, which were assessed by measure of multiple rating scales, although they failed to reach clear and statistical differences between the two groups. When considering

Table 2. Proportion of clinical outcomes as priori defined at 6-month between AD users and nonusers

Parameters	Users	Nonusers	p value	NNT (95% CIs)	OR (95% CIs)
By MRS score	n = 43	n = 40			
Good	16 (37.2)	8 (20.0)			
Poor	27 (62.8)	32 (80.0)	0.068	5.8 (54.7−2.8)	2.37 (0.9−6.4)
By MBI score	n = 51	n = 59			
Good	24 (52.9)	18 (30.5)			
Poor	27 (47.1)	41 (69.5)	0.056	6.0 (66.8−2.9)	2.02 (0.9−4.4)
By BBS score	n = 36	n = 38			
Good	19 (52.8)	15 (39.5)			
Poor to acceptable	17 (47.2)	23 (60.5)	0.180	7.5 (10.8−2.8)	1.71 (0.7−4.3)

Values are presented as number (%); Definition of good clinical outcome, 1 or 2 on modified Rankin Scale (MRS) score, ≥ 75 on modified Barthel Index (MBI) score, and ≥ 41 on Berg Balance Scale (BBS) score at 6-month, respectively.
AD, antidepressant; NNT, number needed to treat; OR, odds ratio; CI, confidence interval.

statistical but intuitive concept measure, NNTs for PwAD on good clinical outcomes on ADL, physical independence, and motor function, the least was 7.5 indicating substantial clinical utility of AD treatment for patients with stroke in the present study. Four to six of NNTs are usually considered "somewhat treatable" [19]. It is well-known that NNT represents an absolute effect measure that has been used to assess beneficial and harmful effects of medical interventions, in which single-digit of ≤ 9 appears acceptable intervention under certain conditions, such as less clinically urgent situations [19,20]. The usefulness of ADs in physical recovery and motor function regardless of the presence of depression has been proposed in rigorous controlled clinical trials [2,3]. Indeed numerous data exist favoring the AD effects on regulation of neural excitation and inhibitory modulation (modulation of cortical γ-aminobutyric acid, etc.), augmentation/facilitation of cerebral blood flow (cerebral blood flow autoregulation, etc.), activation of neurotrophic growth factors (activation of brain-derived neurotrophic factor, etc.) and neurogenesis (hippocampal regeneration, etc.), all of which are positive on physical recovery and motor functions; such results were also supported and replicated by a number of clinical studies.

Our study has strength for the use of highly validated ADL measures such as MRS in routine practice [15] as well as exclusion of comorbid psychiatric disorders other than depression. Our study has also clear pitfalls. Since the definitions of clinical endpoint in stroke patients are still in debate, it has been proposed that optimal use of clinical outcome should be based on a mixture of different rating scales and other related clinical factors; we used different rating scale to compensate each other [15].

A larger sample size would allow to draw more conclusive remark for detecting smaller differences between PwAD and PwoAD; for instance, to detect significant difference for good outcomes based on MRS and BBS scores, we should have included at least 220 and 450 samples, respectively [21,22]. Other covert multiple factors influencing ADL and motor functions should be also considered in interpretation of our study findings since we performed merely a naturalistic observation but not the well-controlled study design [23]. A short follow-up period and substantial loss of follow-up proportion should be another critical limitation. A cohort design cannot determine any causal relationship between certain clinical factors and disease outcomes. Therefore, our findings should be taken as preliminary and exploratory information for further elaboration.

Our study has shown a substantial differences in clinical characteristic in choice of AD treatment for patients with stroke in routine practice. The AD treatment was found to be beneficial in improvement of ADL and physical independence for patients with stroke. An adequately-powered and well-controlled clinical trials and observation studies will facilitate to find more clear determinants in the use of AD for patients with stroke.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Chi-Un Pae, Geun-Young Park, Protocol development: Kyung Ho Lee, Chi-Un Pae, Draft writing: Kyung Ho Lee, Chi-Un Pae, Intellectual comments and critics on the content: Won-Myong Bahk, Soo-Jung Lee, Data acquisition: Kyung Ho Lee, Chi-Un Pae, Geun-Young Park, Data analysis: Kyung Ho Lee, Chi-Un Pae.

■ ORCID

Kyung Ho Lee   https://orcid.org/0000-0003-1473-2125
Geun-Young Park   https://orcid.org/0000-0003-0084-2403
Won-Myong Bahk   https://orcid.org/0000-0002-0156-2510
Soo-Jung Lee   https://orcid.org/0000-0002-1299-5266
Chi-Un Pae   https://orcid.org/0000-0003-1632-4248

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