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The Effect of Sertreline Versus Nortriptyline on Quality of Life and Depression After Stroke:A Randomized Double-Blind Controlled Study

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ABSTRACT

Background & Objective: Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants are utilized for treatment of post stroke depression, reduced quality of life and poor compliance. This study compared the effects of sertraline and nortriptyline on the quality of life and depression in post-stroke patients.

Materials & Methods: This randomized double-blind trial was conducted on 56 stroke patients admitted to Valiasr Hospital in Zanjan, Iran, 2016. Patients were randomly allocated in two groups by simple randomization and received sertraline in one group, nortriptyline in the other and nobody received placebo. Patients were screened for depression using BDI (II) questionnaire and those without depression were entered into study. During follow-up, patients completed a quality of life questionnaire named Nottingham Health Profile (NHP). Data were analysed using repeated measure and Bonferroni tests in SPSS 22. P<0.05 was considered statistically significant.

Results: The mean age of patients in sertraline and nortriptyline groups were 61.7 and 63.6, respectively (P=0.194). No significant differences were observed for sex, marital status and education between two groups. The mean score of total quality of life and its dimensions decreased significantly during 6 months for both groups (P=0.001). The effect of sertraline in these reductions was not different from nortriptyline (P=0.60). The proportions of moderate or severe depression were 17.9% and 37.0% in sertraline and nortriptyline groups, respectively (P=0.24).

Conclusion: Both sertraline and nortriptyline improved all aspects of quality of life and their effect on prevention of depression was similar. Therefore, the administration of sertraline or nortriptyline could be beneficial in post-stroke patients.

Keywords: Sertraline, Nortriptyline, Stroke, Depression, Quality of life

Introduction

Brain stroke is a syndrome characterized by the onset of a neurological disorder for at least 24 hours. This syndrome is a reflection of central nervous system involvement and is the result of a cerebrovascular disorder. Stroke consists of two types of ischemic and hemorrhagic. The ischemic type is more common and occurs due to local thrombosis of the cerebrovascular or embolization following thrombosis in distant places such as cardiovascular system (1). This syndrome is associated with a high mortality and is known to be the third leading cause of death (2). In Iran, after heart disease and cancers, brain stroke is the third leading cause of death in people over 45 years of age (2, 3). Brain stroke is more common in men, increases with age, and about two-thirds of cases occur in people over age of 65.

Factors that increase the risk of stroke include hypertension, hypercholesterolemia, smoking, alcohol and contraceptive pills (3). During the last decades, anti-hypertensive treatment has reduced the incidence of cerebrovascular accidents. Several factors affect the prognosis of patients after a brain stroke, and the most important of these factors is the severity of the neurological disorder caused by stroke (4). Age of patient, cause of stroke, and comorbidity also affect on prognosis. In general, less than 80% of patients with brain stroke survive for at least one month and the proportion of a 10-year survival after stroke is 35% (5).

Psychological problems are also common during the post-stroke period which can be directly related to central nervous system disease and damage or in the event of a loss of efficacy and severe damage to self-confidence and a person's sense of being healthy (5). Mood problems and especially depression are of the most common diseases which occurs in people with brain stroke (6). Depression occurs at varying degrees in these patients and in addition to causing a number of problems related to the nature of

the depression itself, it can lead to poor performance, poor quality of life, and reduced patient collaboration in the treatment and rehabilitation process **(7, 8)**. Lack of cooperation in the process of treatment and rehabilitation causes other problems, including death and exacerbation and stabilization of disabilities **(9)**.

Several studies have reported that fluoxetine, nortriptyline and sertraline compared with placebo were effective for treatment and prophylaxis of post-stroke depression and improvement of daily activities during follow-up time **(10-12)**. Recently, a protocol for a systematic review of sertraline RCTs for patients with post-stroke depression has been published, the results of which are not yet available **(13)**. This study was conducted to evaluate the effect of sertraline compared to nortriptyline on the quality of life and prophylaxis of depression in post-stroke patients.

Materials and Methods

Design and setting

This is a randomized double-blind controlled trial study with parallel groups and a 1:1 allocation ratio that was conducted on stroke patients admitted to Valiasr Hospital of Zanjan University of Medical Sciences in 2016.

Participants

This study was conducted on patients with brain stroke admitted to the Brain and Neural department of Zanjan Valiasr Hospital in 2016, Iran. Inclusion criteria were: 1) patients with first brain stroke, 2) aged between 50–70 years old, and 3) patients without aphasia. Exclusion criteria were: 1) drug users, 2) diagnosis of depression at study entry or history of antidepressant use, 3) history of renal, hepatic and CNS disorders, and 4) patients with contraindication of TCA use such as CVD, glaucoma and prostate hypertrophy.

Sample size was calculated given an alpha error of 0.05 and a statistical power of 90% and a possible 20% attrition rate (10% in each group). Using data from a similar study **(14)**, we assumed that S_1= S_2=10 and the difference of quality of life between two groups was 20 scores. Based on the information above, sample size for each group was estimated to be 27 by the following formula and with 10% attrition rate in each group, 30 patients were considered for each group.

$$n = \frac{\left[Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right]^2 \left[S_1^{\,2} + S_2^{\,2}\right]}{(\mu_1 - \mu_2)^2}$$

Sixty patients assessed for eligibility at the time of study but four of them were excluded; two did not meeting the inclusion criteria, one declined to participate and one died. Fifty six patients were randomly allocated in two groups by simple randomization. Randomization sequence was created using a random numbers table by a statistician. Odd and even numbers were taken to assign treatments A (sertraline) and B (nortriptyline), respectively, to the patients by an independent nurse. Patients in the intervention group received 50 mg/day sertraline and patients in the other group were received 25 mg/day nortriptyline. During follow-up, one patient was died in the nortriptyline group (Fig 1). In this study, patients and outcomes assessors were kept blinded after assignment to interventions.

Outcome assessment

The primary objective of this study was to compare quality of life and its dimensions between two groups that have received sertraline and nortriptyline, respectively. The secondary objective was to estimate the proportion of depression in two groups at the end of study.

During the first two weeks after stroke, all patients were screened for depression using BDI (II) questionnaire by a psychiatrist and those without depression were entered into the study. At study entry and during follow-up at the second and sixth month, all patients in both groups completed the quality of life questionnaire. At the end of study, patients were re-examined for depression using BDI (II) questionnaire. During follow-up, patients were asked to attend the neurology clinic and complete the questionaires.

The quality of life of patients was evaluated by a standardized questionnaire named Nottingham Health Profile (NHP). This scale contains two parts. The first part has 38 questions in 6 subareas including energy level (EL): 3, pain (P): 8, emotional reaction (ER): 9, sleep (S): 5, social isolation (SI): 5, physical abilities (PA): 8 and each question answered as "Yes" or "No". There is a weighted value for each question and the sum of all weighted values in a given subarea adds up to 100. A lower score indicates a better quality of life. The second part of NHP contains 7 questions on affected life areas. In this study, only the first part of NHP was used.

The second questionnaire used in this study, was BDI (II) and consisted of 21 questions about how the subject has been feeling in the last week. Each question had a 4-point scale ranging from 0 to 3 based on severity. The standard cut-off for total score was as follows: normal (0-14), mild (15-31), moderate (32-47) and severe depression (48-63).

Ethical Considerations

This study was registered in the Iranian Registry of Clinical Trials (IRCT) with a code number of IRCT2016111530912N1. The study was also approved by the Ethical Committee of the Zanjan University of Medical Sciences and informed consent has been obtained from all subjects.

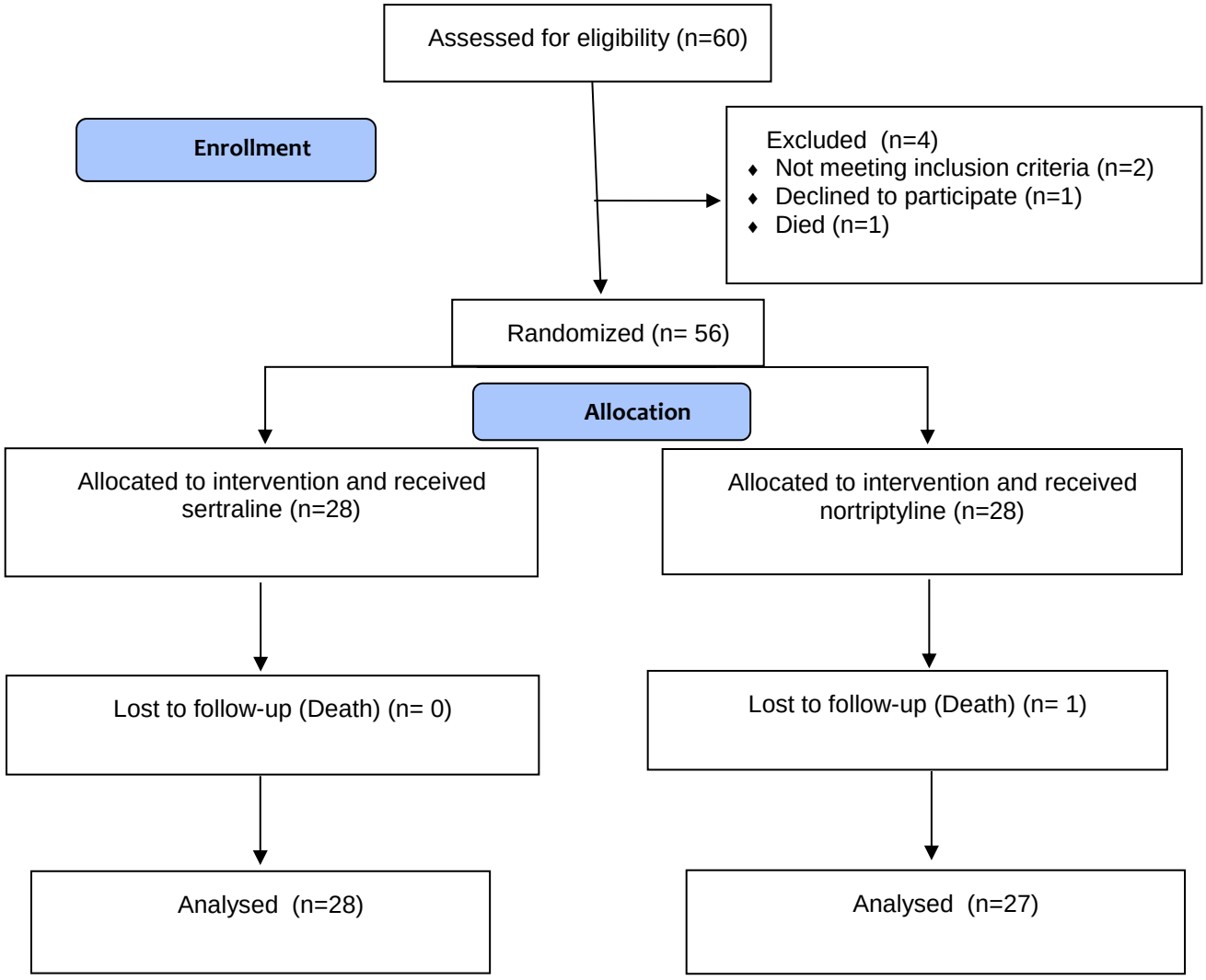

Figure 1. Flow diagram of patients

Statistical analysis

Values were expressed as number (percentage), and mean ± standard deviation, as appropriate. Baseline characteristics and depression were compared between treatment groups using chi-square, Fisher exact test and independent T test. Treatment effects on quality of life were analysed using a general linear model for repeated measures procedure, with time as within-subjects and between-subjects factors. Pairwise comparisons were performed by Bonferroni test. Data were analysed using the Statistical Package IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA). P-values less than 0.05 were considered as being statistically significant.

Results

Characteristics of stroke patients treated with sertraline (n=28) and nortriptyline (n=27) are shown in Table 1. The mean age of the patients in sertraline and nortriptyline groups were 61.68±5.43 and 63.56±5.13, respectively (P=0.194). No significant differences were observed for other variables between two groups.

Table 1. Characteristics of stroke patients in two treatment groups

Variables	Sertraline (n=28)	Nortriptyline (n=27)	P
Sex, n (%)			
Male	14 (50.00)	15 (55.60)	0.680*
Female	14 (50.00)	12 (44.60)	

Variables	Sertraline (n=28)	Nortriptyline (n=27)	P
Marital status, n (%)			
Single	2 (7.10)	1 (3.70)	1.000**
Married	26 (92.90)	26 (96.30)	
Education, n (%)			
Diploma or lower	24 (85.70)	27 (100.00)	0.111**
Higher	4 (14.30)	0 (0.00)	
Stroke type, n (%)			
Ischemic	22 (78.60)	23 (85.20)	0.729**
Haemorrhagic	6 (21.40)	4 (14.80)	
Stroke side, n (%)			
Right	12 (49.20)	8 (29.60)	0.308*
Left	16 (57.10)	19 (70.40)	

*Chi-Square test, **Fisher's Exact test.

The score for all dimensions of quality of life were indicated in table 2. The mean scores for energy level, social isolation, pain, physical ability, sleep and emotional response decreased significantly during 6 months for both groups (P<0.001 for all dimensions, Table 2). However, the effect of sertraline was not different from nortriptyline for energy level (P=0.466), social isolation (P=0.877), pain (P=0.449), physical ability (P=0.801), sleep (P=0.241), and emotional response (P=0.721) (Table 2).

Table 2. Scores for the dimensions of quality of life by treatment and time

Quality of Life		Sertraline M±SE	Nortriptyline M±SE	P-Value
Energy Level (EL)	Study entry	49.51±5.91	68.50±6.27	0.466*
	Second month	42.54±6.44	45.66±7.23	
	Sixth month	35.77±5.53	30.76±6.74	
P-Value		<0.001**		
Social Isolation (SI)	Study entry	47.37±6.72	52.21±6.03	0.877*
	Second month	46.92±6.78	43.94±5.81	
	Sixth month	34.23±6.53	36.13±6.35	
P-Value		<0.001**		
Pain (P)	Study entry	34.03±5.24	41.62±5.88	0.449*
	Second month	19.37±4.32	22.35±4.68	
	Sixth month	10.47±2.97	13.03±4.01	
P-Value		<0.001**		
Physical Ability (PA)	Study entry	73.47±5.82	71.92±5.23	0.801*
	Second month	67.31±6.33	64.50±5.49	
	Sixth month	53.63±7.35	52.01±5.41	
P-Value		<0.001**		
Sleep (S)	Study entry	44.43±7.24	56.70±6.43	0.241*
	Second month	31.75±5.95	33.25±5.71	

Quality of Life		Sertraline	Nortriptyline	P-Value
		M±SE	M±SE	
	Sixth month	18.43±3.95	30.41±6.06	
P-Value		<0.001**		
Emotional Response (ER)	Study entry	44.99±7.19	52.52±6.46	0.721*
	Second month	36.10±5.79	36.48±5.70	
	Sixth month	24.17±5.08	24.49±5.38	
P-Value		<0.001**		

M±SE=Mean± Standard Error, *Repeated Measures between-subjects, **Repeated Measures within-subjects (Sphericity/Huynh-Feldt)

The mean score of quality of life at study entry was 293.8 and decreased to 244.0 and 176.7 at the second and the six month, respectively, in the sertraline group and the mean score of quality of life at study entry was 343.5 and declined to 246.2 and 186.8 at the second and the six month, respectively, in the nortriptyline group (Figure 2, P<0.001). The effect of sertraline was not different from nortriptyline on the total score of quality of life (F=0.277, df=1, P=0.601) and the partial eta-squared was 0.005. The interaction between treatment group and time was also not significant (F=1.954, df=2, P=0.147).

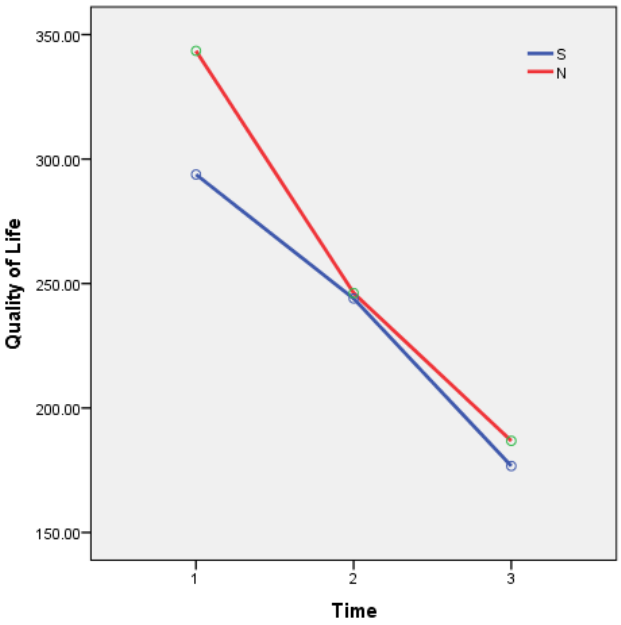

Figure 2. Quality of Life in Stroke Patients by treatment and time

Pairwise comparisons of the mean scores for total quality of life between study entry and second month, study entry and six month, second and six month with Bonferroni test were statistically significant (P<0.001 for all). Pairwise comparisons of the mean score of energy level in these occasions were statistically significant (P<0.001, P<0.001 and P=0.034, respectively). The mean score of social isolation between study entry and six month, second and six month were statistically different (P=0.007, P=0.001, respectively). However, the mean score of social isolation at study entry was not different from its mean score at the second month (P=0.574). Pairwise comparisons of the mean score of pain and emotional response between study entry and second month, study entry and six month, second and six month were statistically significant (P<0.001 for both in all occasions). The mean score of physical ability in these occasions were significantly different (P<0.033, P<0.001 and P<0.001, respectively). The mean score of sleep between study entry and second month, study entry and six month were significantly different (P<0.001 for both). However, the mean score of sleep at the second month was not different from its mean score at the six month (P=0.054).

At the end of study, 35.7% of patients in the sertraline group and 33.3% in the nortriptyline group

had no depression. The proportions of moderate or severe depression were 17.9% in the sertraline group and 37.0% in the nortriptyline group, respectively (P=0.24, Table 3). The mean score of depression in the sertraline group was 20.64±11.79 and in the nortriptyline group was 22.89±16.18 (P=0.56) at the end of study. The only adverse event was dry mouth that reported by two patients in the nortriptyline group.

Table 3. Proportion of depression by treatment at the end of study

Depression n (%)	Sertraline (n=28)	Nortriptyline (n=27)	P
Normal	10 (35.70)	9 (33.30)	
Mild	13 (46.40)	8 (29.60)	0.235**
Moderate/Severe	5 (17.90)	10 (37.00)	

**Chi-Square test

Discussion

This study was conducted on patients with the first episode of brain stroke who were between 50 and 70 years old. During the first two weeks after stroke, these patients were screened for depression using BDI (II) questionnaire by a psychiatrist and those without depression were randomized into two groups. Patients in these two groups were treated with sertraline and nortriptyline, respectively. During follow-up and at the end of study, quality of life and depression were assessed in the patients.

At the end of study, 35.7% of patients in the sertraline group and 33.3% in the nortriptyline group had no depression and the proportion of mild depression in the intervention group was 46.4% and in the other group was 29.6%. The proportion of moderate to severe depression in the sertraline group was 17.9% and in the nortriptyline group was 37.0% (P=0.24). This finding showed that the effect of sertraline and nortriptyline for prevention of depression in this study was similar. The result of our study was contradicted with the finding of Robinson et al. They compared nortriptyline and fluoxetine with placebo in the treatment of post-stroke depression and reported that nortriptyline had a significantly higher response rate than fluoxetine or placebo in treating poststroke depression **(10)**. However, this study was different from ours in several ways. One was the comparison of nortriptyline with fluoxetine, the second was the treatment of depressed people, and the third was that the dose of nortriptyline used for patients that was higher than our study, starting at 25 mg/day and increased to 100 mg/day. These can justify the difference between our results and theirs.

Some prospective studies have also looked at the natural history of depression after stroke. Ayis et al. in a study performed on patients from the South London Stroke Register between 1998 and 2013, reported that 15.51% of patients were free of depression symptoms when screened for depression symptoms at 3 months after stroke **(15)**. Hornsten et al. also stated that 57.2% of patients with a history of stroke were not depressed with taking antidepressants **(16)**. This proportion for our population in both groups, at the end of study, was 35% which could be due to the prevention effects of medication.

Consequences of stroke such as depending on others for daily activities and disruption of their social life have a negative impact on the quality of life (QoL) of patients. In this study, the effect of sertraline and nortriptyline on the quality of life was compared during six months. The results showed that the mean score of quality of life and its dimensions at the second, fourth and six month significantly declined for both groups (P<0.001) given that a lower score indicates a better quality of life. Therefore, both sertraline and nortriptyline played a significant role for improving all aspects of quality of life during follow-up. However, the effect of sertraline on total quality of life was not significantly different from nortriptyline (P=0.601) and the partial eta-squared was 0.005 that only 0.5% of quality of life variations are due to the effect of the intervention. Bilge et al., in a study showed that citalopram antidepressant therapy has been effective in improving the function and quality of life of these patients **(17)**. Mikami et al. reported patients who received fluoxetine or nortriptyline had significantly greater improvement and recovery from disability compared to patients who received placebo (p = 0.002). They also suggested that antidepressants may facilitate the neural mechanisms of recovery in patients with stroke **(11)**. Robinson et al. in a study compared nortriptyline and fluoxetine with placebo in the recovery from physical and cognitive impairments after stroke. They reported that nortriptyline had a significantly higher response rate than fluoxetine or placebo in improving anxiety symptoms, and in improving recovery of activities of daily living **(10)**. Mead et al. in a systematic review have concluded that the administration of specific inhibitors of serotonin increases the quality of life in stroke patients **(18)**.

Ghorashizadeh et al. conducted a study on stroke patients and compared the effect of sertraline with placebo on reducing disabilities. Those who received sertraline in comparison with controls had a lower level of depression and higher quality of life during a 9-month follow up **(14)**. In a recent meta-analysis, Feng et al. reported that sertraline is safe and effective in the treatment and prevention of poststroke depression **(12)**. The results of these two recent studies on the effect of sertraline on depression and quality of life are in accordance with ours. However, we evaluated the effect of sertraline in comparison with nortriptyline on depression and quality of life and observed that both sertraline and nortriptyline were effective.

One of limitations in our study was lack of a control group without treatment because quality of life in post-stroke patients without medication also improves over time. The small sample size in our study may have limited our statistical power to find a significant difference between two groups in terms of moderate to severe depression.

Conclusion

The results of this study indicate that, both sertraline and nortriptyline played a significant role for improving all aspects of quality of life during follow-up, however, the effect of sertraline on quality of life was not significantly different from nortriptyline. In addition, the effect of sertraline and nortriptyline for prevention of depression was similar. Therefore, in patients suffering from brain stroke, the administration of sertraline or nortriptyline could be beneficial and improve their recovery.

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Conflict of Interest

The authors declare that they have no conflict of interests.

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