Original Article

Does Resveratrol Enhance Recovery from Acute Ischemic Stroke? A Randomized, Double-blinded, Placebo-controlled Trial

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Abstract

Introduction: Animal studies indicated the protective effect of resveratrol against cerebral ischemic damages, but it has not been researched well in human ischemic stroke. In the present study, the effect of resveratrol on recovery outcomes after acute ischemic stroke was investigated among patients with ischemic stroke who were not eligible for taking recombinant tissue plasminogen activator as an accepted intervention for stroke condition. **Materials and Methods:** In this double-blind clinical trial, 100 patients with ischemic stroke who suffered from the territory of the middle cerebral artery were randomly allocated to either resveratrol or placebo group. In the intervention group, resveratrol was administered orally at a dose of 500 ± 10 mg daily in three 170 mg divided doses, whereas the placebo group was treated with lactose, both for 30 consequent days. Systolic and diastolic blood pressures and the National Institute of Health Stroke Scale (NIHSS) were measured at the stroke onset and during discharges. Besides, the Barthel index and Modified Rankin Scale (MRS) were performed 3 months after the intervention. **Results:** Resveratrol had no significant effects on NIHSS ($P = 0.97$), systolic ($P = 0.17$), and diastolic blood pressure ($P = 0.42$) compared with placebo. There were no significant differences in the Barthel index ($P = 0.84$) and MRS ($P = 1.00$) between the two groups 3 months after treatment. **Conclusion:** Resveratrol did not improve functional recovery measured by the NIHSS, MRS, and Barthel index in patients with acute ischemic stroke. In addition, it had no significant effect on blood pressure.

Keywords: *Antioxidants, ischemic stroke, neuroprotective agents, resveratrol, stroke rehabilitation*

Introduction

Stroke, as the second cause of death and the major cause of disability in the world,[1] is a "rapid development of focal neurological deficits" resulted from impaired blood flow to the brain either by occlusion or rupture of blood vessels in ischemic or hemorrhagic stroke, respectively.[2] Approximately 80% of strokes are ischemic.[3] The brain's response to ischemic injury leads to the releasing of proinflammatory cytokines and chemokines and the production of damage-associated molecular patterns by glial cells and neurons. These consequences lead to molecular cascades that accelerate neuronal death.[4] Cytokines as inflammatory mediators cause secondary damage to the ischemic brain tissues.[5,6] Prevention of these secondary damages resulted in molecular and physiological cascades, which remains one of the major problems in the management of ischemic strokes. Using recombinant tissue plasminogen activator (r-TPA) agents, facilitating oxygenation, and antihypertensives and antipyretics drugs are widely accepted and used in clinical situations.[7]

Nutritional management of stroke has been proposed, and dietary polyphenols have been associated with a lower risk of ischemic stroke.[8] Polyphenols may prevent pathological molecular cascades at different levels in the early and late stages of the stroke.[9] Resveratrol (3,5,4-trihydroxystilbene) is a polyphenolic phytoalexin that has anti-inflammatory, anti-apoptotic, antioxidative, antidiabetic, antiviral, and cardioprotective properties.[10] Resveratrol can also increase cerebral blood flow, so it may have a protective effect on neurogenic conditions such as stroke, Alzheimer's disease, and vascular dementia, which are related to the brain–blood flow problems.[11]

Previous investigations confirmed the neuroprotective effects of resveratrol in

How to cite this article: Sariaslani P, Asgharzadeh S, Mohammadi H, Ghanbari A, Hezarkhani LA, Shahbazi F, *et al*. Does resveratrol enhance recovery from acute ischemic stroke? A randomized, double-blinded, placebo-controlled trial. J Rep Pharma Sci 2022;11:192-8.

Received: 09 Jul 2021
Accepted: 18 Jun 2022
Published: 23 Dec 2022

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Access this article online

Website: www.jrpsjournal.com

DOI:10.4103/jrptps.JRPTPS_95_21

Quick Response Code:

animal stroke models.[12] Animal studies have confirmed the neuroprotective effect of resveratrol against ischemic stroke and reported decreased infarct volume and improved neurological functions from resveratrol.[13,14] Animal studies also revealed a molecular and signaling mechanism that may play a role in the protective effect of resveratrol.[13-17] Treatment with resveratrol before and after the rodent stroke model reduced the infarct volume and fluid content of the brain via increasing SIRT1/PGC1a/mitochondrial anti-oxidative enzymes, pAkt/pCREB/Bcl-2 and activation of p38, and inhibiting effects on increased pERK1/2.[18] In a rat model of asphyxial cardiac arrest, pre-treatment with 10, 50, and 100 mg/kg dosages of resveratrol significantly enhanced ATP synthesis efficiency in hippocampal mitochondria and protected the neurons of this region.[19] Also, resveratrol upregulates brain-derived neurotrophic factor via SIRT1 activation.[20] Reduced brain damage and improved cognitive functions have been reported after treatment with 30 mg/kg resveratrol in ischemic mice model.[21] Combination of resveratrol with valproate and rosuvastatin could reduce infarct volume and neurologic defects from stroke in mice ischemic stroke models.[22,23]

Studies of resveratrol effect on brain function among healthy populations reported inconsistent results. In a study, resveratrol supplement therapy for 26 weeks improved word retrieval, amplified the functional connectivity of the hippocampus, improved glucose metabolism, and significantly reduced HbA1C levels in healthy older overweight adults.[24] Another study failed to demonstrate a positive effect of resveratrol on verbal memory and hippocampus functional activity among healthy elderly adults who received resveratrol (200 mg/day) for 26 weeks.[25] Resveratrol intake for 90 days at a dose of 1000 mg/day significantly improves psychomotor speed but had no significant effect on verbal memory, verbal learning, and task switching compared with placebo and a group of participants who take 300 mg/day resveratrol.[26] Another study indicated that 26 weeks of resveratrol (200 mg/day) intake among people with mild cognitive impairments reduced glycated hemoglobin A1c and improved hippocampus volume and functional connectivity but did not improve memory performance compared with placebo.[27]

Despite strong evidence obtained from animal studies, few clinical trial studies have investigated the neuroprotective and treatment effect of resveratrol in human ischemic stroke. Synergic effect of resveratrol (2.5 mg/kg, maximum 250 mg) and r-TPA was investigated in timely early (first 120 min) and delayed r-tPA treatment (120–240 min after the stroke onset) groups. Results indicated that treatment with resveratrol along with r-tPA in the delayed group significantly improved NIHSS and plasma matrix metalloproteinase (MMP)-2 and MMP-9 concentration levels after 24 h.[28] Besides, treatment with resveratrol (e.g., 100 or 200 mg) for 1 year significantly decreased secondary stroke recurrence risk factors including systolic and diastolic blood pressures, body mass index, blood sugar, and low-density lipoprotein cholesterol in patients with ischemic stroke within the previous year.[29] Experimental and clinical evidence suggests that polyphenol consumption is associated with lower risk of stroke events. In addition, polyphenols can enlarge the therapeutic window for acute stroke patients.[30]

Although the protective effects of resveratrol on neurodegenerative conditions and animal model of ischemic stroke have been reported, few studies have focussed on the possible effects of resveratrol on human ischemic stroke recovery. In addition, many patients are not eligible for taking r-TPA because of the 4-h narrow therapeutic windows or contraindications which severely limit its clinical efficacy. Efficacious intervention for this group of ischemic patients is an important problem. Therefore, the present study aimed to evaluate the effects of resveratrol administration during the acute phase of ischemic stroke on neurological defects among patients who did not receive rTPA.

Materials and Methods

Participants

In this placebo-controlled double-blinded randomized clinical trial (IRCT2016061328430N1), 100 ischemic stroke patients were enrolled during 7 months from 11 September 2017 to 9 April 2018. Ischemic stroke occurred in the territory of the middle cerebral artery (MCA). The subjects were recruited from Imam Reza University Hospital in Kermanshah, western Iran. Ischemic stroke patients aged between 45 and 90 years old and those in acute stage, symptoms of whom lasted more than 24 h, were eligible. For controlling the effect of time after stroke on the second evolution, participants who discharged 5 ± 2 days after hospitalization were included in the study. Pregnant participants, those who received rTPA, had intracranial hemorrhage, had a history of previous cerebrovascular attack (CVA), and had an allergy to resveratrol were excluded [Figure 1]. These patients were not eligible to take rTPA because of contraindications or narrow therapeutic time windows. The study was approved by the Ethics Committee of Kermanshah University of Medical Sciences (KUMS) (Ethic Number: IR.KUMS.REC.1395.647). All procedures were in accordance with the Helsinki Declaration and guidelines. Detailed written informed consent was obtained from all participants or their caregivers (or legal guardian).

Patients were randomly allocated to the placebo and intervention groups using a permuted block randomization method performed by a statistician who was blinded to patients and intervention. Both groups received routine stroke treatments. Identical resveratrol (e.g., contained 170 mg resveratrol) and placebo (e.g., lactose) capsules were prepared, packaged, and labeled appropriately. Participants

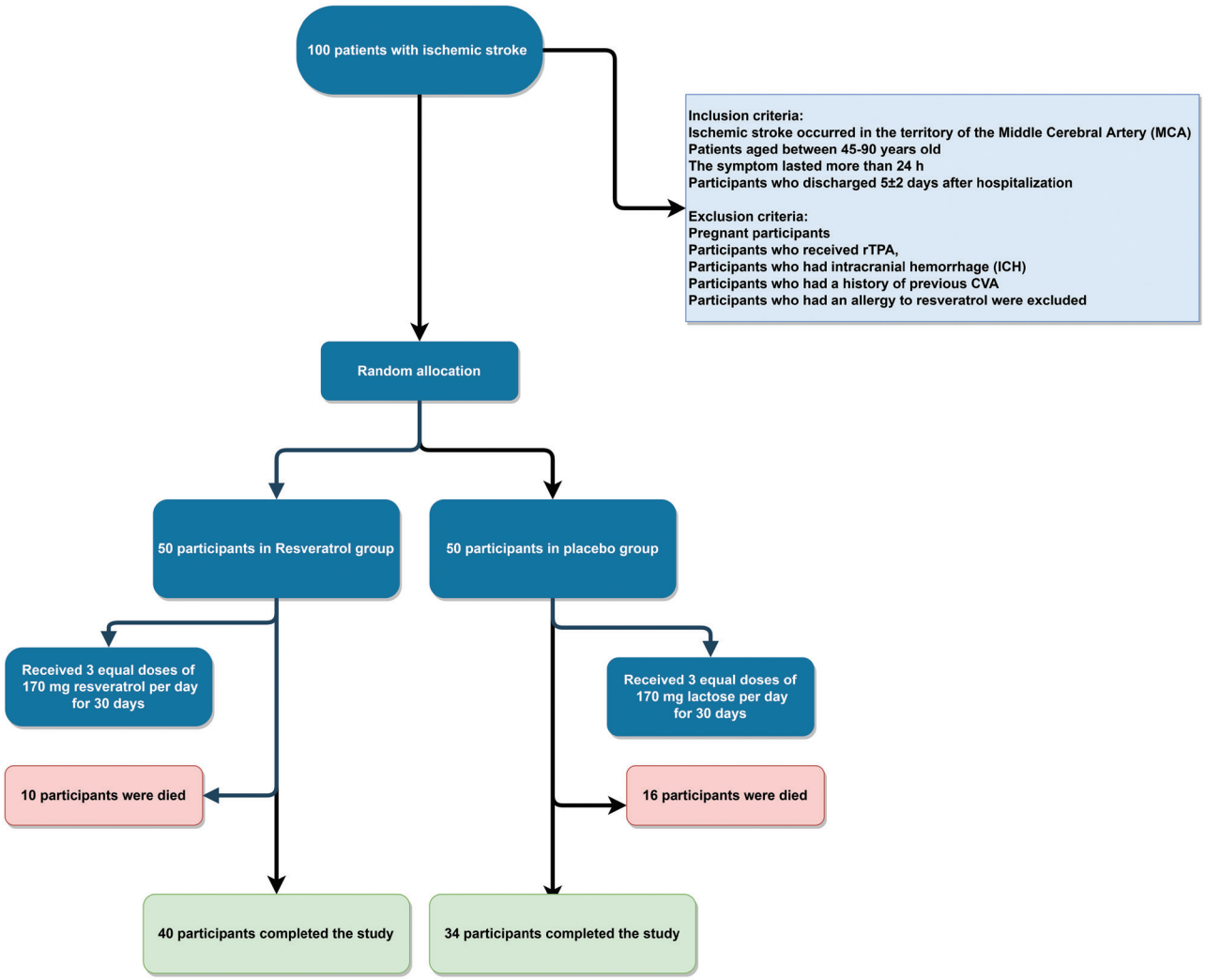

Figure 1: Flowchart of the study

and their caregivers, clinicians, data collectors, and data analysts were blinded to the drugs and group allocation.

Intervention

Patients were randomly allocated to receive identical resveratrol or placebo capsules (three capsules per day) during the first 24 h after ischemic stroke attack and continued for 30 days. Resveratrol powder was prepared from Nano-Kimia Company (Iran). The purity of the product was measured by the infrared spectrum in the Pharmacy School's Laboratory of KUMS. Then, placebo and resveratrol capsules (contained 170 mg resveratrol or lactose) were prepared. Resveratrol and placebo capsule contained lactose as a filler. The drugs and placebo are similar in taste and shape. All participants were followed up for any gastrointestinal side effects of lactose such as diarrhea. The dose of 500 ± 10 mg/day was considered on the basis of previous studies.[28,31,32] As the bioavailability of the agent does not increase with higher doses,[32,33] to improve serum levels, patients received 500 ± 10 mg in three equal doses of approximately 170 mg/per day. The safety, pharmacokinetics, and pharmacodynamics aspects of resveratrol had been investigated in previous studies.[32,34]

Evaluations

Patients were evaluated by the National Institute of Health Stroke Scale (NIHSS) on the first day of hospitalization before treatment onset and at the time of discharge. NIHSS has widely been used to evaluate the severity of acute ischemic stroke.[35] In addition, Barthel index and Modified Rankin Scale (MRS) were completed for all participants 3 months after CVA. MRS is the most commonly used index for outcome measures in stroke.[36] The Barthel index is another common outcome measure in stroke trials that used to measure performance activities of daily living.[37] Blood pressure was also measured over the first day and at the time of discharges. All evaluations were performed by a clinician who was blinded to treatment and placebo groups. Patients were also evaluated for possible adverse drug reactions during the study. A checklist of possible adverse drug reactions was prepared based on a previous study.[38] The checklist was completed daily for each participant

during hospitalization by a blind investigator. Then, the family of participants was trained for reporting any adverse effect mentioned in the checklist for 1 month. In addition, adverse drug reactions were followed and checked by the main investigator in interaction with main caregiver. Complications were evaluated based on the common terminology criteria for adverse events.[38]

Statistical analysis

Data were analyzed using multivariate analysis of covariance (MANCOVA) for investigation of the changes observed in NIHSS and blood pressures after treatment compared with baseline values. Participants were divided into ≥65 and >65 years old. Then the age group and gender were considered as covariates in all analyses. In addition, the Barthel index and MRS were analyzed between groups by MANOVA. All analysis was performed by Statistical Package for Social Sciences (SPSS) software version 26. The analysis was performed by a statistician who was blinded to the study groups and medication.

Results

In the present study, the effect of resveratrol on recovery outcomes after ischemic stroke was compared with that of placebo. One hundred patients with ischemic stroke with a mean age of 70.62 ± 12.51 years (age ranged from 45 to 90 years) were recruited and randomly allocated to the resveratrol or placebo group. The two groups were matched for age, sex, diabetes, and hypertension distribution. According to the results, the number of patients with the diagnosis of hyperlipidemia was significantly higher in the placebo group than that in the resveratrol group ($P = 0.02$) [Table 1]. Of 100 participants, 52 had ischemic events in deep branches of MCA, 23 in the stem, 17 in the superior division, and 8 in the inferior division of MCA. In 61 participants, the left hemisphere suffered and 39 participants had right MCA ischemia. Nine participants from the placebo and five participants from the resveratrol group were taking Piracetam and Citicoline. The neuroprotective effects of both Piracetam and Citicoline have been reported.[39,40] Two participants in the placebo group had a history of atrial fibrillation but none in the resveratrol group. Five participants, including two in the placebo and three in the resveratrol groups, report a history of the coronary artery bypass graft. Also, five participants (one in the placebo group and four in the resveratrol group) reported a history of chronic heart failure. Three participants in each group reported a history of ischemic heart disease.

Changes in NIHSS, systolic blood pressure, and diastolic blood pressure at the time of discharge were compared between resveratrol and placebo groups by MANCOVA using gender, age groups, and baseline NIHSS and blood pressure as covariates. Although there was a tendency for reduction of NIHSS, systolic blood pressure, and diastolic blood pressure in the resveratrol group when compared with the placebo group [Figures 2 and 3], there was not a significant difference between the groups at the time of discharge, while adjusting for baseline NIHSS and blood pressures, gender, and age group [Table 2].

There was no significant difference in MRS and Barthel index between groups 3 months after the intervention, while adjusting for gender and age group [Table 3].

In general, out of the 100 patients, 26 died. In the placebo group, there were 16 participants (32.0%) and in the intervention group 10 participants (20.0%) died. Although death in the placebo group was more than that in the intervention group, this difference was not statistically significant ($P = 0.17$). The number of hemorrhagic transformations in both the groups was the same for one grade. In the intervention group, there was a case of gastrointestinal (GI) bleeding, and in the control group,

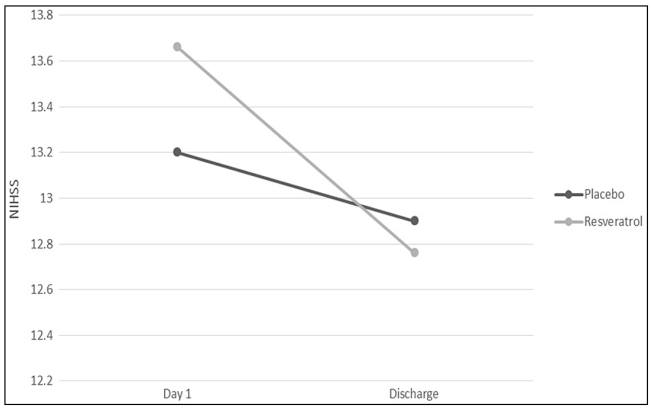

Figure 2: Plot over time for National Institutes of Health Stroke Scale (NIHSS) in resveratrol and placebo groups

Table 1: Age and sex distribution in resveratrol and placebo groups

Variables	Resveratrol *n*=40	Placebo *n*=34	Statistical value	*P*-value
Age, M (SD)	71.86 (11.79)	89.38 (13.20)	0.99*	0.32
Male, *n* (%)	24 (60)	25 (69)	0.04**	0.84
Hypertension, *n* (%)	27 (67)	31 (86)	0.65	0.41
Diabetes, *n* (%)	10 (25)	14 (38)	0.87	0.34
Hyperlipidemia, *n* (%)	9 (22)	19 (52)	4.96	0.02

*t-test
**χ^2

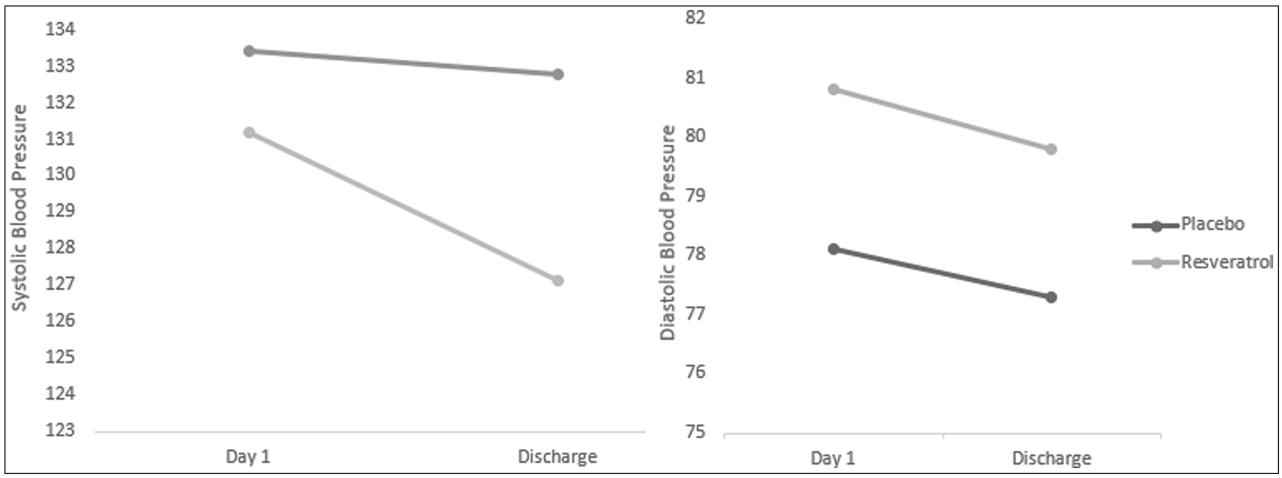

Figure 3: Plot over time for systolic and diastolic blood pressures in resveratrol and placebo groups

Table 2: Multivariate analysis of covariance (MANCOVA) for NIHSS and blood pressure at the time of discharge

Variables, M (SD)	Phase	Placebo	Resveratrol	*P*-value	Effect size
NIHSS	Day 1	13.20 (7.51)	13.66 (6.70)	0.97	0.00
	Discharge	12.90 (9.70)	12.76 (8.58)		
Systolic blood pressure	Day 1	133.40 (20.83)	132.80 (22.36)	0.17	0.02
	Discharge	131.16 (15.73)	127.12 (14.77)		
Diastolic blood pressure	Day 1	78.10 (7.27)	77.30 (5.82)	0.42	0.007
	Discharge	80.80 (10.12)	79.80 (10.34)		

Table 3: Comparison of MRS and Barthel index between resveratrol and placebo groups 3 months after the intervention by MANOVA

Variables, M (SD)	Placebo	Resveratrol	*P*-value
MRS	3.38 (2.26)	3.38 (1.97)	>0.99
Barthel index	49.20 (43.47)	50.90 (40.91)	0.84

there was a case of GI bleeding and one case of bronchial hemorrhage. Other complications were not reported during the study.

Discussion

Stroke as the main cause of disability is a major problem worldwide in healthcare systems.[1] Stroke prevention, use of neuroprotective dietary agents for reducing the functional and structural defects, and treatment for faster recovery after injury are strategies that are used for the management of stroke costs. The main objective of this study was to evaluate the effect of resveratrol during the acute phase of ischemic stroke on neurological defects, as measured by NIHSS, MRS, and Barthel index criteria among patients who are not eligible for receiving r-TPA. Results did not reveal significant differences in NIHSS and blood pressures between placebo and intervention groups at the time of discharge. In addition, treatment with resveratrol for 1 month had no significant effect on MRS and Barthel index 3 months after the intervention.

Although animal studies have confirmed the neuroprotective effect of resveratrol against ischemic stroke,[13-23] resveratrol administration with a different dose among elderly healthy adults resulted in inconsistent findings in both brain functional connectivity and cognitive domains.[24-26] Similar to the present study, Köbe *et al.*[27] did not report a significant effect of resveratrol on brain cognitive functions, but they found reduced glycated hemoglobin A1c and improved hippocampus volume and functional connectivity among people who received resveratrol compared with the placebo group. In contrast to Köbe *et al.*, in the present study, no serological and brain mapping investigation was performed. So, any probable structural and molecular effect of resveratrol that may lead to functional recovery in a time window larger than a month was not recorded.[22] In contrast to the present findings, resveratrol at a dose of 2.5 mg/kg (maximum 250 mg) significantly improved the NIHSS after 24 h among delayed r-tPA treatment (120–240 min after stroke onset), compared with timely treatment early (first 120 min).[28] In the present study, patients who received rTPA were not included. So, it was no synergic effect of rTPA and resveratrol. In addition, in the study by Chen *et al.*, the resveratrol was administered in 3 h time window but in the present study, the treatment was started 1 day after stroke onset. Protective effects of resveratrol may be more prominent in the first hours of acute ischemic stroke, and this delay may restrict the protective effect of resveratrol on brain tissue.

Results did not indicate a significant effect of resveratrol on systolic and diastolic blood pressures at the time of discharge. In contrast to the present finding, treatment with resveratrol (e.g., 100 or 200 mg) for 1 year significantly decreased secondary stroke recurrence risk factors including systolic and diastolic blood pressures, body mass index, blood sugar, and LDL cholesterol in patients with ischemic stroke within previous year.[29] Hypertension is a major risk factor for heart disease, atherosclerosis, and stroke. Blood pressures were only recorded at the time of discharge, and the non-significant effects of resveratrol in our study may be due to the lower duration of resveratrol therapy. Perhaps prolonged use of resveratrol has different results. In addition, although participants were randomly allocated to intervention and placebo groups, they did not control for any medication which may affect the blood pressure. Since the mean age of the patients was high, they probably use some medications that could affect the blood pressure. The result should be interpreted on the basis of this limitation.

Limitations

In the present study, the blood pressure was only recorded during hospitalization. The effect of intervention on neurological recovery was also measured for 3 months after intervention initiation. So, the long-term effect of resveratrol may be ignored and future studies should consider this limitation. Besides, the duration of the intervention is short, and the null result should be interpreted according to this limitation. Lack of any serological and brain mapping measurements is another limitation of the present study. In addition, two groups were not controlled for any medication which may affect the blood pressure. Negative results may also result from low sample size, diverse sample size, and unstandardized product. The ADRs may not be reported completely because of bias that follow-up with families may induce. Telenursing and telemedicine procedures can reduce such a limitation.

Conclusion

The results of this study showed that resveratrol was not effective in improving the criteria for NIHSS, MRS, Barthel index, and blood pressure in patients with ischemic stroke symptoms. Further studies with more sample size and earlier and long duration (e.g., 3 months) of treatment are needed to confirm these findings.

Financial support and sponsorship

This study supported by Kermanshah University of Medical Sciences (Grant number: 96345). Trials Registry Code: IRCT2016061328430N1.

Conflicts of interest

All authors have no conflicts of interest to declare.

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