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Research Paper

Nano-curcumin Effects on Ischemic Stroke Clinical Outcomes and Interleukin-6 Levels: Pilot Randomized Clinical Trial

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ABSTRACT

Background: Accumulation of inflammatory factors in the stroke area results in brain tissue damage and a patient's disability. It has been demonstrated that curcumin has neuroprotective effects.

Objectives: This study aims to evaluate the effects of nano-curcumin, a more stable and soluble form than the common curcumin, on the National Institutes of Health Stroke scale (NIHSS) and modified Rankin scale (mRS) scores and interleukin-6 (IL-6) serum levels in ischemic stroke patients.

Materials & Methods: Forty ischemic stroke patients were randomly divided into two groups of nano-curcumin and control, with 20 patients in each group. The curcumin group received nano-curcumin with a dose of 80 mg/d for one month, and the control group received placebo. Neurological disabilities were assessed by NIHSS and mRS over three time points. IL-6 serum levels were evaluated over two time points. Infarct area volume was evaluated in two time points.

Results: NIHSS and mRS scores were significantly lower in the curcumin group than in the control group (P=0.038 and P<0.001, respectively). Serum levels of IL-6 were significantly lower in the curcumin group than in the controls (P<0.001). The cerebral infarct volume did not change significantly one week after the treatment with curcumin.

Conclusion: Nano-curcumin improves the stroke clinical symptoms in ischemic stroke patients, as indicated by the reduction of NIHSS and mRS, in addition to a decrease in serum levels of IL-6.

Keywords: Stroke, Curcumin, Interleukin-6

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Highlights

- Curcumin is a potential antioxidant and anti-inflammatory agent.
- The treatment with nano-curcumin can improve the National Institutes of Health Stroke scale (NIHSS) and modified Rankin scale (mRS) in patients with ischemic stroke.
- Nano-curcumin can decrease the interleukin-6 (IL-6) serum levels in ischemic stroke patients.

Introduction

Stroke is classified into two main types: Ischemic and hemorrhagic. Ischemic stroke can result from a thrombotic or embolic event that reduces blood flow to the brain. Penumbra refers to the poorly perfusion tissue around the ischemic core, where blood flow is low for electrical activity but enough to maintain ion channels. However, this region is exposed to various harmful metabolic processes, including excitotoxicity, oxidative stress and inflammatory response, which spread from the core to adjacent tissues, leading to the expansion of the ischemic core and subsequent clinical consequences [1].

Significant increases in interleukin-6 (IL-6) levels have been demonstrated in patients with stroke shortly following the ischemic event [2]. Elevated IL-6 levels in the early phase of ischemic stroke can be related to infarct size, neurological deterioration, and poor outcome [3]. On the other hand, IL-6 can induce the liberation of prostaglandin E2 (PGE2) in the brain [4]. PGE2 activates the hypothalamus, giving rise to an increase in body temperature [5]. Fever has been reported to be associated with poor outcomes following stroke [6].

Reactive oxygen species (ROS) serve a crucial role in human physiological processes. Nevertheless, ROS overproduction occurs in ischemic stroke, an important mediator of ischemic damage [7]. Anti-ROS treatments have been used in ischemic stroke [7]. Curcumin is an extract from the *Curcuma longa* (turmeric) root. Turmeric extract contains three curcuminoids: Curcumin, desmethoxycurcumin, and bisdemethoxycurcumin. Curcumin is turmeric's most active component [8]. It exerts a preventive effect on stroke by reducing oxidative stress and improving vascular endothelial function [9]. Curcumin is believed to be a potential antioxidant and anti-inflammatory agent [10]. It reduces lipid peroxidation and inhibits the expression of nuclear factor-κB (NF-κB) and tumor necrosis factor-alpha (TNF-α) [10].

Curcumin is lipophilic and can cross the blood-brain barrier [11, 12]. It reduces brain TNF-α and IL-6 levels in the animal model of stroke [13]. Jiang et al. [14] demonstrated that a single curcumin dose (1 and 2 mg/kg, IV) 30 minutes following focal cerebral ischemia in rats would reduce mortality, infarct volume, the brain's water content, and neurological deficits.

As curcumin is lipophilic, the oral curcumin absorption is very low. However, nano-curcumin is encapsulated in the hydrophobic part of curcumin nano-micelles. These spherical nano-micelles are 10 nm in size and increase the water curcumin solubility, and their bioavailability after oral use is significantly higher than that of a simple powder form of common curcumin [15].

Previous findings have demonstrated curcumin's anti-inflammatory effects. Given this substance's low absorption and rapid metabolism, we decided to investigate the improvement of ischemic stroke symptoms after treatment with nano-curcumin, which is more stable and soluble than curcumin.

Materials and Methods

This study is a double-blind, randomized clinical trial pilot study on ischemic stroke patients hospitalized at Neurology Ward, Poursina Hospital, Guilan University of Medical Sciences, Rasht City, Iran. Forty acute ischemic stroke patients confirmed by computed tomography (CT) scan of the brain with symptoms no more than a week were included in the study. Informed consent was obtained from these subjects.

With blocks of four, using a randomization process, the patients were allocated to nano-curcumin and control groups, with 20 subjects in each group. In addition to routine antiplatelet, anti-lipid and antihypertensive medications, which were given to both groups for possible stroke prophylaxis, the curcumin group received an 80-mg curcumin capsule in the form of nano-micelles (Sina Curcumin®, Nano Sina Elixir Co., Iran) daily for

1 month. The controls received a placebo of curcumin (capsule containing polysorbate 80 produced by Nano Sina Elixir Co., Iran) for 1 month. The patients and their evaluator were blind to the treatment or placebo.

Patients were followed for one month, and the National Institutes of Health Stroke Scale (NIHSS) [16, 17] and modified Rankin scale (mRS) [18] were used for the assessment of the neurological deficits of the patients. These questionnaires were completed at three time points: baseline (before the treatment, starting point for assessing the variables), one week and one month after the treatment.

A blood sample was collected from the patients in three stages. IL-6 serum levels were assessed at the baseline and one month after the treatment using an ELISA kit in the two groups.

The prothrombin time (PT), partial thromboplastin time (PTT), clotting time (CT), and bleeding time (BT) were assessed in the two groups at the baseline and after one week.

The volume of the infarct area was also evaluated using brain CT scans one day and one week after the stroke. A brain CT scan was also performed if the patient's symptoms worsened with a suspicion of hemorrhagic stroke.

The study's inclusion and exclusion criteria are tabulated in Table 1.

Table 1. Inclusion and exclusion criteria about the study

Criteria	Data Study
Inclusion criteria	The involved arteries (anterior cerebral arteries, superior and inferior branches of deep middle cerebral arteries, thalamus, and basal nuclei of the brain) and the involved side of the brain
	Hospitalized in the Neurology Ward of Poursina Hospital in Rasht
	Their stroke was confirmed by a neurologist using a brain CT scan
	NIHSS ≤20
	mRS ≤4
	Stroke within at most a week following the symptom onset
Exclusion criteria	Intolerance to continue taking the medication for any reason
	Patients not showing up for follow-up
	Death of the patient
	Hemorrhagic infarct area
	CVST
	Posterior circulation stroke
	Hemorrhagic ischemic area
	Internal capsule ischemia (involvement of deep arteries) and the trunk of the middle cerebral artery
	History of gallstones
	Bile duct obstruction
	Increased stomach acid or active peptic ulcer
	treatment with NSAIDs and reserpine
	Treatment with anticoagulants and thrombolytic in the previous 24 hours and warfarin in the previous week

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Abbreviations: NIHSS: National Institutes of Health Stroke scale; mRS: Modified Rankin scale; CVST: Cerebral venous sinus thrombosis; NSAIDs: Non-steroidal anti-inflammatory drugs.

A per-protocol approach was used in data analysis. The data were analyzed using SPSS statistical software, version 22. Quantitative variables in the two groups were examined by an independent t-test when the data were normally distributed and by the Mann-Whitney U test in case of a non-normal distribution. Qualitative variables in the two groups were compared using the chi-square test. A repeated measure analysis of variance (ANOVA) was used to compare the results at different follow-up times.

Results

As shown in Table 2, half of the patients were men, and half were women in the curcumin group. In the control group, 60% of the patients were women and 40% were men. Also, the Mean±SD of the age of the patients participating in the present study was 73.45±9.87 and 67.35±11 years in the curcumin group and the controls, respectively. In terms of the location of the stroke, most of the infarcts in both the curcumin and control groups were in the right superior and inferior middle cerebral arteries (MCA) (n=6, 30%). No significant differences in the stroke location were seen between the two curcumin groups (P=0.990) (Table 2).

The comparison of the NIHSS scores between the two groups showed no significant difference at the baseline and one week after the treatment (P>0.05), while a significant difference was seen between the two groups one month after the treatment. The NIHSS scores after one month in the curcumin group were significantly lower than those in the control group (5.75±2 vs 7.45±1.95, P=0.038) (Figure 1).

The comparison of the mRS scores indicated no significant differences between the two groups at the baseline and one week following the treatment. However, one month after the treatment, mRS scores in the curcumin group were significantly low compared with those in the control group (1.95±0.99 vs 3.15±0.74, P<0.001) (Figure 2).

The comparison of the volume of the infarct at the baseline (43.10±15.61 vs 37±12.51) and one week after the treatment (44.25±16.83 vs 42.90±13.17) showed no significant difference between the curcumin and the control groups (P>0.05) (Table 3).

One month after the treatment, evaluation of IL-6 serum levels demonstrated no significant differences between the two groups (P=0.486). There was a significant difference in IL-6 serum levels at the baseline and one month after the treatment in the curcumin group (P<0.001). Nonetheless, no significant difference was seen among the controls (P=0.504) (Table 3).

As shown in Table 4, the results of comparing changes in the variables at the baseline and one week after the treatment, as well as at the baseline and one month after the treatment, illustrated a significant difference between the two groups. The changes in the curcumin group were significantly greater than those in the control group (P<0.05) (Table 4).

Table 2. Demographic and radiologic data in the curcumin and the control groups

Variables		No. (%)/Mean±SD		P
		Curcumin	Control	
Sex	Male	10(50)	12(50)	0.525*
	Female	10(50)	8(40)	
Age	-	73.45±9.87	67.35±11	0.070**
Arterial territories of infarct	Left superior MCA	5(25)	5(25)	0.990*
	Left inferior MCA	3(15)	3(15)	
	Right superior MCA	6(30)	6(30)	
	Right inferior MCA	6(30)	6(30)	

MCA: Middle cerebral artery.

*Chi-square test, **Independent t-test.

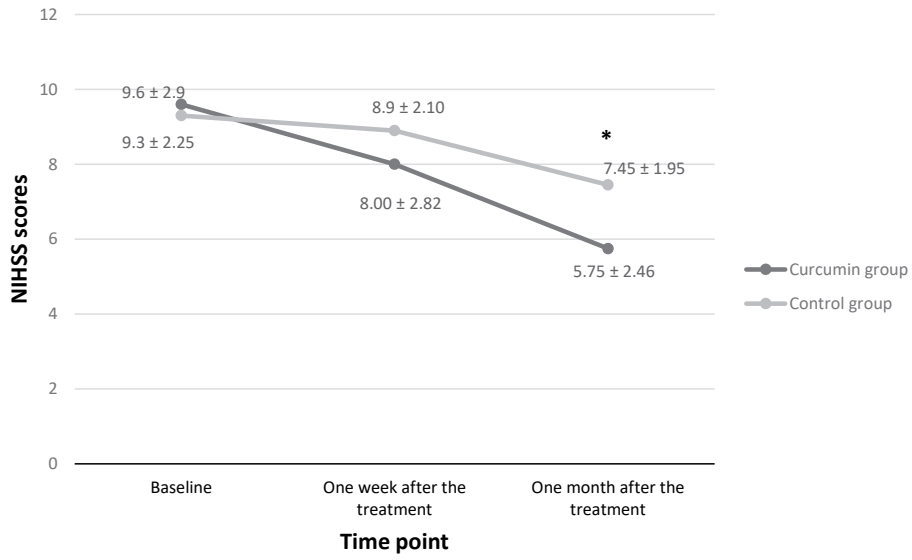

Figure 1. Comparing NIHSS scores (Mean±SD) between the curcumin and control groups in three time points

NIHSS: National Institutes of Health Stroke scale.

*P=0.038 Mann-Whitney U test=0.038.

The coagulation parameters were within normal limits in the two groups. The Mann-Whitney U test results indicated no significant difference between the curcumin group and the controls at the baseline and one week after the treatment in PT (P=0.98, P=0.56, respectively), PTT (P=0.18, P=0.49, respectively), CT (P=0.65, P=0.10, respectively) and BT (P=0.77, P=0.98, respectively) parameters.

Discussion

In this double-blind, randomized clinical trial pilot study, the effect of nano-curcumin (Sina Curcumin®, Nano Sina Elixir Co., Iran) was evaluated on clinical symptoms and IL-6 serum levels in ischemic stroke patients. Nano-curcumin in ischemic stroke patients in the acute phase of the disease significantly reduced NIHSS and mRS scores one month after the treatment compared to those of the controls.

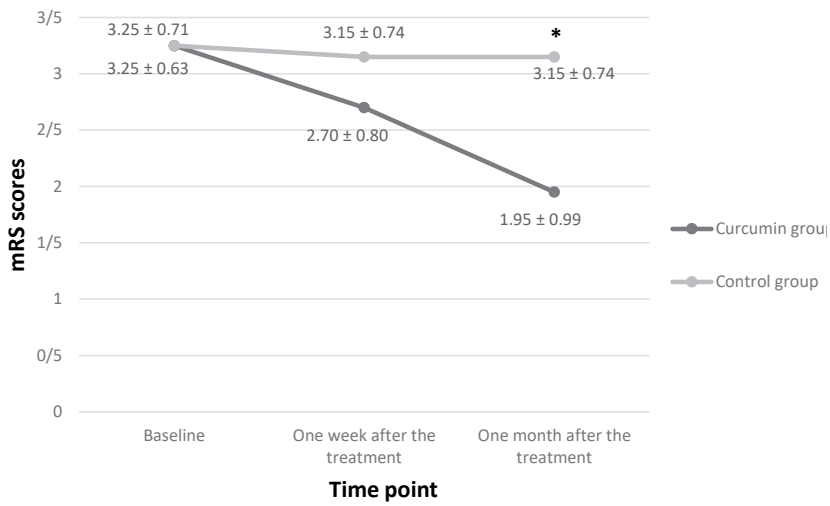

Figure 2. Comparing mRS scores between the curcumin and control groups within 3 time points

mRS: Modified Rankin scale.

*P<0.001 (Mann-Whitney U test).

Table 3. Comparing variables over 3 time points between the curcumin and control groups

Variables		Mean±SD		P
		Curcumin	Control	
Cerebral infarct volume	Baseline	43.1±15.61	37±12.51	0.181*
	One week after the treatment	44.25±16.83	42.9±13.17	0.947*
IL-6	Baseline	18.46±8.76	12.68±14.88	0.486**
	One month after the treatment	8.51±3.49	10.26±4.25	
	P***	<0.001	0.504	

IL-6: Interleukin-6.

*Independent samples t-test, **ANOVA, ***Wilcoxon test.

After one month, it was observed that nano-curcumin could reduce IL-6 serum levels in the patients compared with those in the controls. Abdolahi et al. [19] demonstrated the effect of nano-curcumin on reducing the IL-6 serum levels of subjects afflicted with migraine. In the Zhang et al. [20] investigation, the stroke models of rats received curcumin (25 mg/kg). IL-6 and TNF-α decreased significantly in the brain region after using curcumin. Zahedi et al. [21] studied the effect of Curcumin C3 Complex® on 62 patients with traumatic brain injury for 7 consecutive days. Compared with baseline, serum levels of IL-6 and TNF-α were significantly reduced in the treated patients. Dolati et al. [22] evaluated the nano-curcumin anti-inflammatory effect in 50 relapsing-remitting multiple sclerosis patients for 6 months. The results indicated significant down-regulation in the levels of expression of IL-6, TNF-α and other inflammatory factors. A clinical trial by Ringman et al. [23] indicated no significant difference in MMSE scores in the patients with Alzheimer's disease who were treated with two doses of 2 g/d and 4 g/d of curcumin C3 Complex® compared with those in the placebo group.

NIHSS scores were evaluated in the present study at the baseline, one week after the treatment and one month later. The results showed that NIHSS scores decreased significantly over time in both groups, and the comparison showed no significant difference in NIHSS scores between the curcumin and control groups at the baseline and one week after the treatment. However, one month after the treatment, the NIHSS scores in the curcumin group were significantly lower than in the controls. This result means that the clinical symptoms improved in the curcumin group more than in the control group [24, 25].

Table 4. Comparing changes in variables over time between the curcumin and control groups

Variables	Mean±SD		P
	Curcumin	Control	
NIHSS changes at the baseline and one week later	1.27±1.6	0.4±0.68	0.002*
NIHSS changes at the baseline and one month later	0.81±3.85	1.85±0.48	>0.001*
mRS changes at the baseline and one week later	0.55±0.51	0.1±0.44	0.009*
mRS changes at the baseline and one month later	1.3±0.57	0.1±0.44	>0.001*
Cerebral infarct volume changes at the baseline and one week later	1.15±2.47	5.9±2.14	>0.001**
IL-6 changes at the baseline and one month later	9.94±9.47	2.41±15.48	>0.001*

Abbreviations: NIHSS: National Institutes of Health Stroke scale; mRS: Modified Rankin Scale; IL-6: Interleukin-6.

*Mann-Whitney U test, **Independent samples t-test.

Also, mRS scores were assessed at the baseline, one week following the treatment, and one month later. A comparison of mRS scores illustrated no significant difference between the two groups at the baseline and one week after the treatment. However, one month after the treatment, in the curcumin group, the mRS scores were significantly low compared with those in the controls. Also, an intragroup comparison of mRS scores showed that in the curcumin group, mRS scores decreased significantly over time, while no significant difference was observed in the control group. mRS is used to assess disability after a stroke. This outcome means that functional independence increased in the curcumin group more than in the control group [24, 26].

Using the CT scan, the cerebral infarct volume in the patients was compared at the baseline and one week after the treatment. The results indicated a significant increase in the cerebral infarct volume in the controls within one week, while this observed increase was not significant in the curcumin group. Preclinical studies suggested that decreased volume infarction may reflect curcumin's protective and anti-inflammatory effects against the damaged brain [27, 28].

Anti-inflammatory and neuroprotective effects of nano-curcumin have been shown in various preclinical and clinical studies. The nano-curcumin indicated a much higher aqueous diffusion than the free form, which leads to improved systemic availability. Also, nano-encapsulation of curcumin may improve circulation and retention of medicine in the body. This mechanism reduces and maintains the threshold level of curcumin [29]. This pilot study's findings demonstrated the nano-curcumin effect on improving NIHSS and mRS scores and reducing infarct volume and serum levels of IL-6.

Conclusion

In this pilot study, we examined the effect of nano-curcumin on stroke clinical symptoms and serum IL-6 levels in ischemic stroke patients. The present study showed nano-curcumin's protective and anti-inflammatory effects against the damaged brain. Future studies with a larger sample size should evaluate if nano-curcumin could be a promising treatment for improving stroke clinical symptoms in ischemic stroke patients.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Guilan University of Medical Sciences, Rasht, Iran (Code: IR.GUMS.REC.1398.222) and was registered by the Iranian Clinical Trials Registration System (IRCT) (Code: IRCT20091108002680N3).

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Authors contributions

All authors have contributed to this study and preparation of this article. All authors approved the final version of the article.

Conflict of interest

The authors declared no conflict of interest.

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