Hypertension

Efficacy of Antihypertensive Therapy in the Acute Stage of Cerebral Infarction – A Prospective, Randomized Control Trial

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Background: This study investigated whether patients in the acute stage of cerebral infarction (ACI) might benefit from single-drug antihypertensive therapy (AT) without the use of preset target levels.

Methods: A total of 320 ACI patients were randomly divided into an AT group and a control group (group C) (160 patients in each group). The AT group received single antihypertensive drug treatment after the first 48 hours of onset with 5 mg of amlodipine besylate or 150 mg of irbesartan once a day. The primary end-point event was mortality on the 14th day and in the 6th month after onset, significant dependent-survival status (SDS, Barthel Index ≤ 60), mortality/disability ratio (modified Rankin Scale ≥ 3), and recurrence rate of cardio-cerebral vascular events (RR-CVE).

Results: The National Institutes of Health Stroke Scale (NIHSS) score was 8.39 ± 3.21 vs. 8.16 ± 3.27 in the AT and C groups on entry to the study. On day 14, there were no significant differences in mortality (2.5% vs. 3.1%, p = 0.9994), SDS (50.0% vs. 49.0%, p = 0.864), and mortality/disability ratio (61.3% vs. 66.3%, p = 0.352) between the two groups, however the RR-CVE in the AT group was lower than in group C (4.4% vs. 11.9%, p = 0.014). In month 6, there were no significant differences in mortality rate between the two groups (3.1% vs. 3.8%, p = 0.767), however the SDS (23.4% vs. 34.4%, p = 0.033), mortality/disability ratio (32.1% vs. 45.0%, p = 0.018), and RR-CVE in group AT were lower than in group C (10.7% vs. 19.4%, p = 0.030).

Conclusions: Appropriate AT for patients with ACI does not worsen the disease condition and may improve the prognosis for the patients with moderate or mild stroke severity.

Key Words: Acute cerebral infarction • Antihypertensive therapy • Prognosis • Randomized control trial

INTRODUCTION

Cerebral infarction (CI) is characterized by a high incidence, high disability, high recurrence rate, and high mortality rate. The overall prognosis is poor and is of global concern. A large number of clinical trials have demonstrated that antihypertensive therapy (AT) can reduce the risk of stroke recurrence, however, whether it is beneficial to start AT in the acute stage of CI (ACI) is still uncertain. About 70% of ACI patients exhibit an increase in blood pressure, however the blood pressure in some patients spontaneously decreases within 24 hours of CI. The mechanism remains unclear.1-3 The traditional view is that increasing blood pressure in ACI benefits cerebral blood perfusion in the ischemic region and the opening of collateral circulation; therefore, active AT might be harmful. During the first 24 hours after the onset of stroke, the general consensus is that medications...
should be withheld unless the SBP is > 220 mmHg or the diastolic blood pressure is > 120 mmHg. However, a blood pressure range has not yet been scientifically determined after the first 24 hours after the onset of stroke.

An arterial blood pressure range likely exists that is optimal during acute ischemic stroke on an individual basis, however this range has yet to be determined. Multiple studies have investigated various blood pressure parameters during admission for acute ischemic stroke and clinical outcomes, and elevated in-hospital blood pressure during acute ischemic stroke has been associated with worse clinical outcomes in a more linear fashion. Persistent post-CI hypertension may increase the risk of cerebral edema and intracranial hemorrhage, as well as increasing the risk of recurrent cardio-cerebral vascular events (RR-CVE). Therefore, appropriate AT could improve functional outcomes and reduce stroke recurrence and mortality. Many clinical studies have also shown a significant correlation between increasing blood pressure in ACI and the prognosis. Disability and mortality rates in patients with high blood pressure are also high, and significant hypertension in patients with ACI has been reported to indicate a poor prognosis. In recent years, some studies have also found a U-shaped relationship between blood pressure in ACI and the prognosis, i.e., the prognosis would be poor if or not the blood pressure was too high or too low.

Blood pressure management in ACI is an important part of stroke treatment. The management of arterial hypertension in patients not undergoing reperfusion strategies remains challenging. There is still insufficient evidence about how to manage blood pressure in ACI, and findings on whether AT should be performed in patients with ACI, AT targets, and when CI patients with hypertension can resume their original antihypertensive treatment have been inconsistent. Until more definitive data are available, the benefit of treating arterial hypertension in the setting of acute ischemic stroke is unclear. It also remains unclear what the risk-benefit ratio is for lowering or raising the blood pressure during acute ischemic stroke. Larger trials with well-defined criteria are needed. Many of the previous studies have had limitations and inconsistencies, including whether to start AT immediately after the onset of stroke, whether to start AT immediately in patients with pain, vomiting and other secondary increased blood pressure without lifting, whether to establish a fixed target blood pressure, and whether AT should include powerful and multi-drug combinations through intravenous administration. These factors increased the number of exacerbations. In addition, patients with cerebral hemorrhage were included in some studies. Furthermore, the endpoints did not include indicators such as RR-CVE. These effects may have neutralized the benefits of AT, with harmful results due to inappropriate blood pressure reduction. This study used a prospective, randomized control method, based on avoiding predetermined AT targets. We aimed to determine whether or not appropriate and reasonable AT for ACI patients would aggravate the disease condition and improve their long-term prognosis.

**METHODS/DESIGN**

**Trial design and patients**

This was a randomized, prospective, controlled single-center clinical trial. The patients in the treatment and control groups were distributed in a 1:1 ratio. A unified research team was established for all patients enrolled in the study. The intervention implementer, efficacy evaluator, and data analyst were all included in the unified team, and the efficacy evaluator and patients were blinded (Figure 1).

**Figure 1. Flow diagram of Trial profile. Group AT, the antihypertensive therapy group; group C, the control group.**
The inclusion criteria were: ACI within 48 hours of onset; systolic blood pressure (SBP) on admission ≥ 160 mmHg (1 mmHg = 0.133 kPa) or diastolic blood pressure (DBP) ≥ 95 mmHg; and CI diagnosed using the “Treatment guidelines of Acute ischemic stroke in China (2014)” and confirmed by brain computed tomography (CT) and/or magnetic resonance imaging (MRI). The exclusion criteria were: hemorrhagic CI; watershed CI; SBP ≥ 220 mmHg or DBP ≥ 120 mmHg; SBP < 160 mmHg and DBP < 95 mmHg; thrombolytic therapy; consciousness disorder, cognitive dysfunction, or mental illness before onset; concurrent acute myocardial infarction, severe left ventricular failure, respiratory failure, aortic dissection, acute renal failure, acute pulmonary edema, or hypertensive encephalopathy; or uncontrollable intracranial hypertension, pain, nausea and vomiting, urinary retention, restlessness, sleep disorders, stress, or anxiety.

ACI patients hospitalized in the Department of Neurology of our hospital from July 1, 2013 to June 30, 2016 were included and randomly assigned to AT and control (C) groups. The hospital’s Institutional Review Board approved the trial (Institutional Review Board approval identifier: 2013001), and all patients or their representatives provided written informed consent before enrollment.

Procedures

Group AT received single antihypertensive drug treatment after the first 48 hours of onset with 5 mg of amlodipine besylate (Dispersible Tablets, Heilongjiang Aolida Ned Pharmaceutical Co., Ltd., China) or 150 mg of irbesartan (Zhuhai Rundu Pharma Co., Ltd., China) once a day. Any antihypertensive drugs taken before onset were discontinued, and the original AT program was adopted after the first 48 hours of onset. No specific AT target was set. Group C was not given any antihypertensive drugs. One week after onset, both groups received conventional AT, with a target SBP of < 140 mmHg and DBP < 90 mmHg. Both groups were routinely given antiplatelet drugs, statins, neuroprotection, rehabilitation, and symptomatic support; patients with coronary heart disease, diabetes, and other diseases received appropriate drugs.

Efficacy indexes

The primary efficacy indexes were as follows: day 14 (D14) and month 6 (M6) mortality, significant dependent-survival status (SDS) (Barthel Index, BI ≤ 60), mortality/disability (modified Rankin scale score, MRS ≥ 3), and RR-CVE (including myocardial infarction, cardiac arrest, transient ischemic attack, recurrent CI, and post-infarction hemorrhage). The secondary efficacy indexes were as follows: National Institutes of Health Stroke Scale (NIHSS) score on D3, D7, and D14 after onset; and morning blood pressure on D3, D4, D5, D6, and D7 after onset. Cardiovascular events were diagnosed according to guidelines. All evaluations were performed by another doctor blinded to the treatment of each patient. All endpoints were independently adjudicated.

Estimation of sample size

According to one of our pilot studies, the mortality/disability rate on the 14th-day after onset (set as the index endpoint) was 42% in group C and 25% in group AT. Based on \( \alpha = 0.05 \) and \( \beta = 0.1 \), \( f(\alpha, \beta) = 10.5 \), \( n = \frac{(42\% - 25\%)}{(42\% - 25\%)} \times 10.5 = 156.6 \); hence, the sample size of each group was set as 160 patients.

Randomization and masking

We enrolled and randomly allocated eligible patients in a 1:1 ratio to group AT or group C according to their hospitalization time points. We used a random number table to generate the allocation sequence, and sealed, opaque, sequentially-numbered and coded envelopes. The allocations were blinded to the patients and efficacy evaluators.

Statistical analysis

SPSS 13.0 software was used for the analysis. Numerical data were described using mean ± s, and the tests were two-sided, with test level \( \alpha = 0.05 \). Normal distribution of the numerical data was determined with the single-sample K-S test; the homogeneity of variance was determined with the Levene test. Numerical data with a normal distribution were then submitted to an independent sample t-test; otherwise, a rank test was used. Comparisons of two data classes were performed using the \( \chi^2 \) test, and comparisons of survival ratio were performed using Kaplan-Meier estimates.
RESULTS

Baseline information

Figure 1 shows the screening, enrollment, and follow-up profile of the trial. No patients crossed over or were incorrectly randomized. Of 1,253 ACI patients hospitalized between July 1, 2013, and June 30, 2016, 320 (25.5%) were enrolled. All patients were followed up for 6 months. BI and MRS scores of some patients were obtained by telephone follow-up. Per-protocol population analysis was used. Table 1 shows the baseline characteristics of groups AT and C.

In group AT, all 160 patients were followed up on D14, but one was lost at the M6 follow-up. Group AT comprised 109 males and 51 females, aged 64.82 \pm 9.74 years, with a disease duration of 20.43 \pm 13.13 hours. Eighty-seven had a history of hypertension, 23 had diabetes, 25 had coronary heart disease, 61 had a history of smoking, and 23 had a history of alcohol abuse. Blood pressure on admission was 183.58 \pm 16.82/104.48 \pm 6.92 mmHg and the NIHSS score was 8.39 \pm 3.21 (2-17) points. Seventy-one patients received amlodipine and 89 received irbesartan.

In group C, all 160 patients were followed up, and no patient was lost. There were 102 males and 58 females, aged 66.60 \pm 9.94 years, with a disease duration of 20.83 \pm 12.85 hours. Ninety-one had a history of hypertension, 17 had diabetes, 36 had coronary heart disease, 49 had a history of smoking, and 27 had a history of alcohol abuse. Blood pressure on admission was 182.54 \pm 15.35/103.79 \pm 6.63 mmHg; and the NIHSS score was 8.16 \pm 3.27 (2-17) points. Sixty-three received amlodipine and 97 received irbesartan.

Table 1 shows the baseline characteristics of groups AT and C.

Mortality comparison between the two groups

As of D14, four patients in group AT had died, including two with respiratory failure, one with post-Cl hemorrhage and cerebral herniation, and one with cardiac arrest. Five patients in group C died, including one with respiratory failure, two with post-Cl hemorrhage and cerebral herniation, one with myocardial infarction, and one with cardiac arrest. From D14 to M6, one patient in group AT died of myocardial infarction, and one in group C died of cerebral hemorrhage plus cerebral herniation. There were no statistically significant differences in mortality at D14 and M6 the two groups (Table 2).

Blood pressure comparison between the two groups

The blood pressure in the two groups began to decrease after treatment.
crease on D3 after onset; the pressure in group AT decreased faster, and a difference between the two groups began to appear on D3 (p < 0.05). On D7, the pressure in group AT was close to normal, while that in group C was higher than normal (Table 3).

Comparison of neurological deficit scores
There was no significant differences in NIHSS score between the two groups on D3, D7, and D14 (p > 0.05, Table 4).

Comparison of SDS
Based on a criterion of BI ≤ 60 points, there was no significant difference in D14-SDS between the two groups (p > 0.05), however group AT showed a lower M6-SDS than group C (p < 0.05, Table 4).

Comparison of mortality/disability ratio
Based on the criterion of MRS ≥ 3 points, there was no significant difference in D14-mortality/disability ratio between the two groups (p > 0.05), however group AT showed a lower M6-mortality/disability ratio than group C (p < 0.05, Table 4).

Comparison of RR-CVE
The D14- and M6-RR-CVE in group AT were both lower than those in group C (p < 0.05, Table 4). The Kaplan-Meier curve showed that the RR-CVE-free rate of the patients in group AT was better than that in group C within 6 months (log-rank test: $\chi^2 = 3.970$, p = 0.046, Figure 2).

Comparison of survival ratio
The cumulative 6-month survival rate of the patients in group AT was comparable to that in group C (96.9%, 155/160 vs. 96.3%, 154/160); log-rank test: $\chi^2 = 0.096$, p = 0.756 (Figure 3). The 6-month event-free survival rate of the patients in group AT was comparable to that in group C (87.5%, 140/160 vs. 88.0%, 128/160); log-rank test: $\chi^2 = 3.086$, p = 0.079.

Table 2. Mortality comparison between the two groups

<table>
<thead>
<tr>
<th></th>
<th>AT (n = 160)</th>
<th>C (n = 160)</th>
<th>OR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>D14</td>
<td>4/160</td>
<td>5/160</td>
<td>0.795 (0.210, 3.016)</td>
<td>0.9994</td>
</tr>
<tr>
<td>M6</td>
<td>5/159</td>
<td>6/160</td>
<td>0.833 (0.249, 2.788)</td>
<td>0.767</td>
</tr>
</tbody>
</table>

AT, antihypertensive therapy; C, control; OR, odds ratio.

Table 3. Blood pressure comparison between the two groups

<table>
<thead>
<tr>
<th></th>
<th>AT (n = 160)</th>
<th>C (n = 160)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission</td>
<td>183.58 ± 16.82</td>
<td>182.54 ± 15.35</td>
<td>0.573</td>
<td>0.567</td>
</tr>
<tr>
<td>D3</td>
<td>171.85 ± 18.02</td>
<td>177.63 ± 13.17</td>
<td>-3.261</td>
<td>0.001</td>
</tr>
<tr>
<td>D4</td>
<td>165.33 ± 18.80</td>
<td>172.88 ± 15.67</td>
<td>-3.878</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>D5</td>
<td>153.16 ± 17.65</td>
<td>167.04 ± 18.43</td>
<td>-6.817</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>D6</td>
<td>141.76 ± 13.25</td>
<td>165.31 ± 18.15</td>
<td>-13.131</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>D7</td>
<td>140.22 ± 13.83</td>
<td>164.24 ± 18.92</td>
<td>-12.816</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 4. Comparison of NIHSS, SDS, mortality/morbidity ratio and RR-CVE between the two groups

<table>
<thead>
<tr>
<th></th>
<th>AT (n = 160)</th>
<th>C (n = 160)</th>
<th>t/χ^2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS on admission</td>
<td>8.39 ± 3.21</td>
<td>8.16 ± 3.27</td>
<td>0.655</td>
<td>0.513</td>
</tr>
<tr>
<td>D3-NIHSS</td>
<td>8.44 ± 3.56</td>
<td>8.55 ± 3.47</td>
<td>-0.286</td>
<td>0.775</td>
</tr>
<tr>
<td>D7-NIHSS</td>
<td>7.49 ± 4.23</td>
<td>6.76 ± 3.76</td>
<td>1.623</td>
<td>0.106</td>
</tr>
<tr>
<td>D14-NIHSS</td>
<td>6.12 ± 3.73</td>
<td>5.40 ± 3.49</td>
<td>1.746</td>
<td>0.082</td>
</tr>
<tr>
<td>D14-SDS</td>
<td>50.0% (78/156)</td>
<td>49.0% (76/155)</td>
<td>0.029</td>
<td>0.864</td>
</tr>
<tr>
<td>M6-SDS</td>
<td>23.4% (36/154)</td>
<td>34.4% (53/154)</td>
<td>4.567</td>
<td>0.033</td>
</tr>
<tr>
<td>D14-mortality/morbidity ratio</td>
<td>61.3% (98/160)</td>
<td>66.3% (106/160)</td>
<td>0.865</td>
<td>0.352</td>
</tr>
<tr>
<td>M6-mortality/morbidity ratio</td>
<td>32.1% (51/159)</td>
<td>45.0% (72/160)</td>
<td>5.623</td>
<td>0.018</td>
</tr>
<tr>
<td>D14-RR-CVE</td>
<td>4.4% (7/160)</td>
<td>11.9% (19/160)</td>
<td>6.028</td>
<td>0.014</td>
</tr>
<tr>
<td>M6-RR-CVE</td>
<td>10.7% (17/159)</td>
<td>19.4% (31/160)</td>
<td>4.704</td>
<td>0.030</td>
</tr>
</tbody>
</table>

AT, antihypertensive therapy; C, control; NIHSS, National Institutes of Health Stroke Scale; RR-CVE, recurrence rate of cardio-cerebral vascular events; SDS, significant dependent-survival status.
DISCUSSION

There still is no final consensus about whether AT for ACI exacerbates the condition of patients with stroke or whether it improves their short-term and long-term prognoses. Blood pressure in humans is influenced by many internal and external environmental factors, such as mood, noise, pain, or stressful events. The specific mechanism of an increase in blood pressure after stroke remains unclear, and a hypertensive status before onset is only one factor. Additional important factors that increase blood pressure post-stroke include stress, intracranial hypertension, hypoxia, pain, nausea and vomiting, urinary retention, restlessness, anxiety, noise, sleep disorders, and a “white coat effect”, meaning that the patient’s “high blood pressure” may not be true hypertension.2,17,25 In this study, we found that within the first 48 hours after stroke, even a combination of a variety of antihypertensive drugs had a limited effect on reducing the patient’s blood pressure. Moreover, once the blood pressure was reduced to a normal level, the patient usually exhibited worsening neurological deficits and progressive disease, which may have been related to a further reduction in cerebral blood flow in the ischemic area when the systemic blood pressure had decreased.10-12

After the first 48 hours, with either disease progression or appropriate treatment, these secondary blood pressure-increasing factors no longer existed. Therefore, even when no AT was given, the blood pressure exhibited a spontaneous decreasing trend, and the patients in this study showed these characteristic changes.1-3 Therefore, it would be more reasonable to determine whether AT should be performed after the first 48 hours, at which time the patient’s blood pressure might be close to the actual pre-stroke blood pressure, and this is why this study was designed to consider AT 48 hours after stroke onset.

In this study, blood pressure in the acute stage was significantly increased and then gradually decreased in both groups after admission. The blood pressure in the AT group was close to a normal level within 1 week, while that in group C was still higher than the normal level, similar to other reports.5,7-9 Increasing blood pressure in ACI may be beneficial for local cerebral ischemia. On one hand, the collateral circulation could determine the severity of ischemic brain damage, and rapidly opening the collateral circulation could rescue the ischemic penumbra. Therefore, maintaining a high mean arterial pressure would be the most direct and effective way of opening the collateral circulation.4,6,8,10 On the other hand, after CI, the vascular autoregulatory functions in the ischemic penumbra are lost, so the maintenance of blood flow in these areas would depend on cerebral perfusion pressure. However, cerebrovascular resistance and intracranial pressure increase after CI, requiring a relatively higher brain cerebral perfusion pressure to ensure blood flow. Therefore, a relatively higher mean arterial pressure may be required to maintain adequate cerebral perfusion pressure.
perfusion pressure. At this time, the body automatically increases blood pressure through neuroendocrine mechanisms, resulting in a rightward shift in the Bayliss curve to maintain normal cerebral perfusion. The situation in patients with combined cerebral large artery stenosis may be more obvious. Many studies have suggested that the increase in blood pressure in ACI can help to preserve brain tissues in the ischemic penumbra. Improper AT may result in poor opening of the collateral circulation and secondary perfusion reduction in the ischemic region, thus expanding the infarct volume and exacerbating the disease. However, persistent post-CI hypertension would exacerbate cerebral edema in the ischemic region, increase the risk of cerebral hemorrhage transformation from ischemia, and increase damage in the heart, brain, liver, or kidney, as well as significantly increase the risk of stroke recurrence. Blood pressure reduction in ACI has been shown to reduce the formation of cerebral edema, the incidence of cardiovascular events, and the risk of hemorrhagic transformation. However, if a single target blood pressure value is set, combined therapy with multiple antihypertensive drugs would be detrimental to cerebral perfusion in the ischemic region and opening of the collateral circulation.

Therefore, this study was designed to use mono-drug therapy, without target blood pressure values or forced blood pressure reduction. Treatment was adjusted according to the actual situation to avoid aggravating ischemia. It has been found that excessive blood pressure reduction in the acute phase of ischemic stroke can cause leukoaraiosis, which is an important precursor to post-stroke dementia. Therefore, appropriate management of blood pressure after stroke may reduce the occurrence of post-stroke dementia. We aimed to investigate whether single antihypertensive drug therapy for patients with ACI after the first 48 hours of onset could still be beneficial, thus providing the basis for blood pressure management in ACI.

The FAST-MAG trial showed that first-time intravenous administration of magnesium sulfate after stroke would slightly decrease SBP, but that the prognosis was no different from that in the placebo group. The PROFESS study subgroup showed that AT with telmisartan within the first 48 hours of onset in 1,360 patients with mild acute ischemic stroke and mild hypertension could slightly decrease the blood pressure, and was safe, but no improved efficacy was shown. In the current study, we found no differences in neurological deficits, mortality, SDS, and mortality/disability ratio between the two groups on D14, and no differences in the cumulative survival and event-free survival at M6 in the two groups, confirming that appropriate AT in ACI would not worsen the disease, increase mortality, or decrease the cumulative survival and event-free survival. Furthermore, the M6-SDS and M6-mortality/disability ratio in the AT group were significantly reduced, and D14- and M6-RR-CVE were also significantly decreased, indicating that proper AT could benefit the long-term prognosis. Previous studies have noted that AT aggravated neurological damage. This may be because one protocol planned for the acute stage performed blood pressure reduction immediately after the onset of CI, while failing to relieve any secondary blood pressure-increasing factors such as urinary retention. In this case, powerful combined blood pressure reduction may have exceeded the body’s own compensatory ability under stress conditions, especially in the patients with large vessel stenosis. Thus, enhanced AT would be more prone to cause exacerbations, and the benefits of AT may be neutralized due to poor collateral circulation and secondary cerebral perfusion reduction in the ischemic area. Accordingly, patients with post-CI hypertension should not initially receive aggressive AT; instead, secondary blood pressure-increasing factors should be ruled out. For example, treating increased intracranial pressure, relieving hypoxia, controlling pain, stopping vomiting, emptying the bladder, providing appropriate sedation and psychological comfort, and moving the patient to a quieter ward may enable a spontaneous decline in blood pressure in some cases.

There are several limitations to this study. We only included patients with CI who started AT at least 48 hours after onset, and only a single oral antihypertensive agent was given. In addition, changes in the long-term endpoint were monitored instead of meeting a specific AT target.

The results of this study showed that single antihypertensive drug therapy or resumption of a pre-stroke antihypertensive program at least 48 hours after CI onset, as well as initiating a conventional blood pressure reduction protocol 1 week after onset could reduce blood pressure to a normal level. In addition, this prospective,
randomized control study showed that appropriate AT in ACI patients would not aggravate the disease and may improve the long-term prognosis. However, the mean NIHSS was around 8 in both groups, which indicated a moderate and mild condition of stroke. Therefore, the findings seem to be applicable to ACI patients with moderate and mild stroke severity. In addition, due to the small number of patients in this study, no placebo control was performed. Final verification will require a multicenter, large-sample, placebo-controlled, randomized double-blind study.

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CONFLICT OF INTEREST

All authors have no conflict of interest regarding this paper.

REFERENCES