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*Original Article*

# Effects of high-dose atorvastatin on prevention of contrast-induced nephropathy after cerebrovascular intervention

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**Abstract:** Objective: The aim of this study was to investigate the effects of different doses of atorvastatin on prevention of contrast-induced nephropathy after cerebrovascular intervention, examining possible mechanisms. Methods: A total of 100 patients with ischemic cerebrovascular disease that underwent cerebrovascular intervention were randomly divided into the control group and observation group. Patients in the control group orally received atorvastatin 20 mg, while the observation group received 40 mg each day starting 3 days before intervention. Incidence of contrast-induced nephropathy, adverse drug effects, serum creatinine, urea nitrogen, cystatin, lipid profiles, and liver function indicators were compared between the two groups. Inflammatory factors (high sensitivity C reactive protein and interleukin-6) and oxidative stress indicators (nitric oxide synthase and superoxide dismutase) were also compared. Results: Within 72 hours after intervention, the observation group had significantly lower incidence of contrast-induced nephropathy (P=0.008) and lower serum creatinine (P<0.001), urea nitrogen (P=0.025), and cystatin (P=0.001) levels than the control group. No significant differences were detected in blood lipid profiles and liver function indicators throughout the study. The observation group showed significantly lower high-sensitivity C reactive protein and interleukin-6 levels and significantly higher nitric oxide synthase and superoxide dismutase levels than controls after intervention. No adverse effects occurred in either group. Conclusion: Application of atorvastatin at 40 mg/day can significantly improve post-interventional renal function and reduce incidence of contrast-induced nephropathy.

**Keywords:** Atorvastatin, cerebrovascular intervention, contrast-induced nephropathy, inflammatory factor, oxidative stress

## Introduction

Contrast-induced nephropathy (CIN) refers to an increase in absolute value of serum creatinine greater than 44.2 μmol/L within 72 hours after interventional therapy or greater than 25% increase in serum creatinine on a pre-interventional basis, without other influencing factors. In recent years, with wide application of digital subtraction angiography, contrast agents have become the most commonly used drugs in vascular interventional therapy. Incidence of CIN has increased year by year. Studies have reported that incidence of CIN is about 1.2-1.6% and the mortality rate is about 3.8-6.4% [1, 2]. CIN not only adds to the economic burden of patients, but also poses a great threat to their physical and mental health. Studies have shown that oxidative stress and inflammatory response play an important role in the development of CIN [3, 4]. Abnormal blood lipids can easily cause damage to vascular endothelial cell function, making the response to contrast agents more acute and more likely to cause CIN [5]. Meola et al. reported that statins have a role in prevention of CIN, with atorvastatin as one of the most commonly used statins [6]. In addition to lowering blood lipids, atorvastatin has anti-oxidation and anti-inflammation effects, as well as the ability to improve vascular endothelial cell function and blood hemodynamics. As a result, it is currently widely used in the treatment of acute coronary syndrome [7]. It has been demonstrated that the use of atorvastatin before or during coronary intervention can significantly improve renal

function and reduce incidence of CIN [8]. In addition, most studies on coronary intervention divided atorvastatin calcium (Lipitor) into 40 mg/day high - and 20 mg/day low-dose groups, according to characteristics of the domestic population and ARMYDA-ACS study protocols [9]. Studies have shown that incidence of CIN, after coronary intervention, was significantly lower in the high-dose atorvastatin calcium (40 mg/day) group than in the low-dose (20 mg/day) group [10, 11]. Compared with coronary intervention, cerebrovascular intervention has a different protocol regarding operative procedures and contrast agents. However, very few studies have focused on the effects of atorvastatin in cerebrovascular intervention patients. To this end, the current study selected 100 patients with ischemic cerebrovascular disease that underwent cerebrovascular intervention, investigating the effects of different doses of atorvastatin on CIN and aiming to provide experimental basis for clinical management of this condition.

## Materials and methods

### *Patients*

Informed consent was obtained for all enrolled patients in this study, which was approved by the Ethics Committee of The People's Hospital of Linyi. This study examined 100 admitted patients with ischemic cerebrovascular disease undergoing cerebrovascular intervention from January 2015 to December 2017. Patients were divided into the observation group and control group using a random number table, with each group containing 50 patients. Patients in the observation group received oral atorvastatin at 40 mg/day, starting 3 days before intervention and each day throughout the study. The control group received 20 mg/day, starting 3 days before intervention and each day throughout the study. Both groups underwent atorvastatin treatment for 4 weeks.

Inclusion criteria: Patients meeting the diagnostic criteria for ischemic cerebrovascular disease published by the American Heart Association/American Stroke Association in 2014, with indications for cerebrovascular intervention [12, 13]; Patients with normal pre-interventional serum creatinine (SCr) levels (less than 100 μmol/L by automatic biochemistry analyzer); Patients showing good compliance and cooperation.

Exclusion criteria: Patients with severe cardiovascular or cerebrovascular diseases and hepatic or renal comorbidities, such as dysfunction; Patients with malignant tumors, coagulopathy, autoimmune diseases, or mental illnesses; Patients allergic to contrast agents or atorvastatin; Patients receiving contrast agents or nephrotoxic drugs within 1 month before intervention; Patients with a history of kidney transplantation, nephrectomy, hemodialysis, acute renal failure, urinary tract infections, or obstruction; Patients with fevers or infectious diseases; Patients with contraindications for cerebrovascular interventions, such as brain herniation, brainstem failure, unstable vital signs, and skin or soft tissue infections at the puncture site.

### *Intervention*

Five hundred milliliters of normal saline (Shanghai Baxter Medical Products Co., Ltd., China) was slowly infused intravenously 12 hours before cerebrovascular intervention. A single dose of 100 mg of aspirin was also orally administered (Bayer Health Care, Germany). The operation area was sterilized and draped. All instruments were rinsed with heparin saline. The catheter and sheath were flushed to evacuate the remaining air before entering the blood vessels. Iopamiro 370 contrast agent (Shanghai Bracco Sine Pharmaceutical Co., Ltd., China) was withdrawn into a syringe. It was then connected to the high-pressure connecting tube. Local anesthesia was performed with 2% lidocaine (Shandong Hualu Pharmaceutical Co., Ltd., China). The femoral artery was punctured (puncture package purchased from B. Braun Medical Co., Ltd., Germany) using the Seldinger technique. This was followed by heparinization immediately after successful sheathing. The loach guidewire (Terumo Co., Ltd., Japan) and Pigtail catheter (Terumo Co., Ltd., Japan) were fed into the distal end of the ascending aorta through the femoral artery, external iliac artery, common iliac artery, abdominal aorta, and thoracic aorta. After the guidewire was withdrawn, the catheter was flushed with heparin saline. It was then connected with the syringe containing the contrast agent. The visual field was adjusted under fluoroscopy and aortic arch angiography was performed at a left anterior oblique angle of 30 degrees. Carotid and vertebral artery angiographies were performed after delivering the cath-

**Table 1.** Comparison of basic data

| Items | Observation group (n=50) | Control group (n=50) | $t/\chi^2$ | P |
|---|---|---|---|---|
| Male/Female | 27/23 | 30/20 | 0.367 | 0.545 |
| Age (year) | 57.6±6.3 | 58.4±5.9 | 0.655 | 0.514 |
| BMI (kg/m$^2$) | 24.3±0.7 | 24.1±0.6 | 1.534 | 0.128 |
| Dose of contrast agent (mL) | 125.6±20.1 | 130.2±16.4 | 1.254 | 0.213 |
| Operation time (min) | 145.8±35.6 | 151.2±31.9 | 0.799 | 0.426 |
| Hyperlipidemia (n/%) | 18 (36.0%) | 20 (40.0%) | 0.170 | 0.680 |
| Hypertension (n/%) | 26 (52.0%) | 22 (44.0%) | 0.641 | 0.423 |
| Diabetes (n/%) | 12 (24.0%) | 14 (28.0%) | 0.208 | 0.648 |

Note: BMI: body mass index.

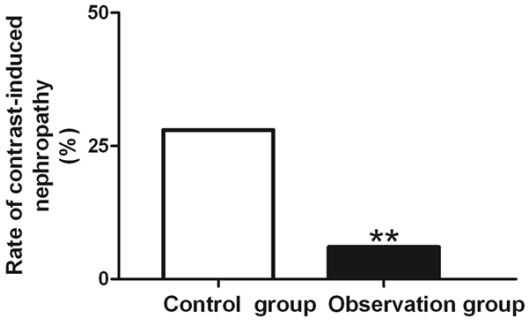


**Figure 1.** Comparison of incidence of contrast-induced nephropathy. Compared with the control group, **P<0.01.

eter along the guidewire to the proximal end of the carotid artery and to the vertebral artery opening in the subclavian artery. Appropriate stents were placed during the operation, according to patient cerebrovascular conditions.

*Observational indices*

Incidence of CIN was compared between the two groups. Diagnostic criteria for CIN: Within 72 hours after cerebrovascular intervention, the absolute value of SCr was greater than 44.2 μmol/L or greater than 25% increase on a pre-interventional basis, excluding kidney damage caused by other factors. Renal function indicators, blood lipid profile, liver function indicators, inflammatory factor levels, and oxidative stress levels were compared between the two groups, before and after intervention. Under fasting conditions, 5 mL of venous blood was drawn from the cubital veins of all patients, before and 72 hours after intervention. SCr, blood urea nitrogen (BUN), and Cystatin (Cys-C) values, as well as lipid profile triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), along with liver function indicators (aspartate transaminase (AST) and alanine aminotransferase (ALT)), were measured with 7600 automatic biochemistry analyzers (Hitachi, Japan) in all patients. Enzyme-linked immunosorbent assay (ELISA) was performed to detect high sensitivity C reactive protein (hsCRP), interleukin-6 (IL-6), nitric oxide synthase (NOS), and superoxide dismutase (SOD) levels in all patients. The procedure was carried out in strict accordance with manufacturer instructions (purchased from R&D Systems, USA). Incidence rates of adverse drug effects were compared between the two groups, including abnormal liver function, cerebrovascular events, and rhabdomyolysis.

*Statistical analysis*

Data was analyzed with SPSS 20.0 statistical package. Quantitative values are expressed as mean ± standard deviation ($\bar{x}$ ± sd) and differences between groups were evaluated using independent t-tests. Paired t-tests were used for comparisons of indicators before and after surgery. Enumeration data are expressed as number/percentage (n/%) and differences between groups were compared using $\chi^2$ tests. *P*-values less than 0.05 indicate statistical significance.

## Results

*Comparison of basic data*

There were no significant differences in age, gender, contrast dose, brain intervention time, and comorbidities between the observation group and control group (all P>0.05; **Table 1**).

*Comparison of incidence of CIN*

Within 72 hours after cerebrovascular intervention, there were 3 cases (6.0%) with CIN in the observation group and 14 cases (28.0%) in the control group. The difference was statistically significant (P=0.003; **Figure 1**).

**Table 2.** Comparison of renal function indicators (SCr, BUN, and Cys-C)

| Items | Observation group (n=50) | Control group (n=50) | $t/\chi^2$ | P |
|---|---|---|---|---|
| SCr (μmol/L) | | | | |
| Before intervention | 77.6±15.6 | 79.2±17.4 | 0.484 | 0.629 |
| 72 h after intervention | 80.5±19.1 | 97.4±20.2 | 4.299 | <0.001 |
| Differences | 2.9±0.8 | 18.2±1.1 | 79.540 | <0.001 |
| BUN (mmol/L) | | | | |
| Before intervention | 6.5±1.7 | 6.7±1.5 | 0.624 | 0.534 |
| 72 h after intervention | 7.0±1.9 | 7.8±1.6 | 2.277 | 0.025 |
| Differences | 0.5±0.1 | 1.1±0.3 | 13.420 | <0.001 |
| Cys-C (mg/L) | | | | |
| Before intervention | 0.8±0.3 | 0.7±0.2 | 1.961 | 0.053 |
| 72 h after intervention | 1.0±0.4 | 1.2±0.5 | 2.828 | 0.006 |
| Differences | 0.2±0.1 | 0.5±0.2 | 9.487 | <0.001 |

Note: SCr: serum creatinine; BUN: blood urea nitrogen; Cys-C: cystatin C.

**Table 3.** Comparison of blood lipid levels (TG, TC, LDL-C, and HDL-C)

| Items | Observation group (n=50) | Control group (n=50) | $t/\chi^2$ | P |
|---|---|---|---|---|
| TG (mmol/L) | | | | |
| Before intervention | 1.7±0.4 | 1.8±0.3 | 1.414 | 0.161 |
| After intervention | 1.2±0.3 | 1.4±0.2 | 1.961 | 0.053 |
| Differences | 0.5±0.3 | 0.4±0.2 | 1.961 | 0.053 |
| TC (mmol/L) | | | | |
| Before intervention | 4.6±1.2 | 4.7±1.3 | 0.400 | 0.690 |
| After intervention | 3.4±1.0 | 3.3±1.1 | 0.476 | 0.635 |
| Differences | 1.2±0.5 | 1.4±0.6 | 1.811 | 0.073 |
| LDL-C (mmol/L) | | | | |
| Before intervention | 2.3±0.9 | 2.4±0.8 | 0.587 | 0.558 |
| After intervention | 1.6±0.7 | 1.8±0.6 | 1.534 | 0.128 |
| Differences | 0.7±0.4 | 0.6±0.3 | 1.414 | 0.161 |
| HDL-C (mmol/L) | | | | |
| Before intervention | 1.3±0.5 | 1.2±0.4 | 1.104 | 0.272 |
| After intervention | 0.8±0.4 | 0.7±0.3 | 1.400 | 0.165 |
| Differences | 0.5±0.3 | 0.6±0.3 | 1.667 | 0.098 |

Note: TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

*Comparison of renal function indicators*

There were no significant differences in pre-interventional SCr, BUN, and Cys-C levels between the two groups (all P>0.05). In the control group, the post-interventional levels of SCr, BUN, and Cys-C were significantly higher than those before intervention (all P<0.001). No significant differences were found between pre-interventional and post-interventional levels of SCr (P=0.408), BUN (P=0.169), and Cys-C (P=0.082) in the observation group. After intervention, SCr (P<0.001), BUN (P=0.025), and Cys-C (P=0.006) levels were significantly decreased in the observation group, compared to the control group. See **Table 2**.

*Comparison of blood lipid levels*

There were no significant differences between pre-interventional and post-interventional blood lipid levels in either group (all P>0.05). No significant differences in blood lipid levels were detected between the two groups, before or after intervention (all P>0.05). See **Table 3**.

*Comparison of liver function indicators*

There were no significant differences in liver function indicators (AST and ALT) between the two groups (all P>0.05; **Table 4**).

*Comparison of inflammatory factors*

There were no significant differences in pre-interventional levels of hsCRP and IL-6 between the two groups (all P>0.05). Post-interventional hsCRP and IL-6 levels decreased in both groups, compared with pre-interventional levels (all P<0.001). After intervention, levels of hsCRP and IL-6 in the observation group were significantly lower than those in the control group (all P<0.001). See **Table 5**, **Figure 2**.

*Comparison of oxidative stress indicators*

There were no significant differences in pre-interventional NOS and SOD levels between the two groups (all P>0.05). Post-interventional NOS and SOD levels in both groups were lower than those before intervention, respectively (all P<0.001). Post-interventional NOS and SOD levels in the observation group were higher

**Table 4.** Comparison of liver function indicators (AST and ALT)

| Items | Observation group (n=50) | Control group (n=50) | $t/\chi^2$ | P |
|---|---|---|---|---|
| AST (U/L) | | | | |
| Before intervention | 50.4±7.4 | 51.8±6.1 | 1.032 | 0.305 |
| 72 h after intervention | 61.2±8.7 | 62.8±9.5 | 0.878 | 0.382 |
| Differences | 10.8±3.5 | 11.0±3.8 | 0.274 | 0.785 |
| ALT (U/L) | | | | |
| Before intervention | 42.4±5.8 | 43.7±6.2 | 1.083 | 0.282 |
| 72 h after intervention | 59.2±6.9 | 61.6±7.2 | 1.702 | 0.092 |
| Differences | 16.8±3.6 | 17.9±4.3 | 1.387 | 0.169 |

Note: AST: aspartate transaminase; ALT: alanine aminotransferase.

**Table 5.** Comparison of inflammatory factors (hsCRP and IL-6)

| Items | Observation group (n=50) | Control group (n=50) | $t/\chi^2$ | P |
|---|---|---|---|---|
| hsCRP (mg/L) | | | | |
| Before intervention | 18.0±4.3 | 17.8±4.1 | 0.238 | 0.812 |
| 72 h after intervention | 10.7±2.7 | 13.8±3.5 | 4.959 | <0.001 |
| Differences | 7.3±1.6 | 4.0±1.2 | 11.670 | <0.001 |
| IL-6 (ng/L) | | | | |
| Before intervention | 122.4±40.1 | 125.9±36.2 | 0.458 | 0.648 |
| 72 h after intervention | 83.5±20.8 | 97.6±21.7 | 3.633 | <0.001 |
| Differences | 38.9±7.6 | 28.3±6.9 | 7.302 | <0.001 |

Note: hsCRP: high sensitivity C reactive protein; IL-6: interleukin-6.

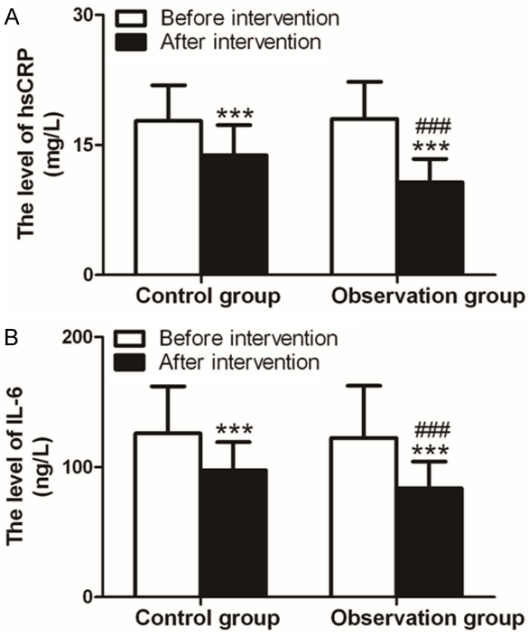


**Figure 2.** Comparison of inflammatory factors. hsCRP: high sensitivity C reactive protein; IL-6: interleukin-6. Compared with the same group pre-interventional, ***P<0.001; compared with the control group after intervention, ###P<0.001.

than those of the control group and differences were statistically significant (all P<0.001). See **Table 6**, **Figure 3**.

*Comparison of adverse drug effects*

No adverse drug effects, such as liver function damage, cerebrovascular events, and rhabdomyolysis, occurred in either group.

## Discussion

Cerebrovascular intervention is the first choice for treatment of ischemic cerebrovascular disease [14, 15]. Contrast agents have been widely used in cerebrovascular intervention, contributing to the diagnosis and treatment of diseases. With extensive development of cerebrovascular intervention, CIN is one of the most common complications in the clinical application of contrast agents. It is mainly characterized by non-oliguric renal failure. In severe patients, dialysis is often required [16, 17]. At present, the pathogenesis of CIN remains unclear. Occurrence of CIN has a negative impact on the prognosis of patients. Effective prevention CIN has been given more and more attention by scholars.

Atorvastatin is an HMG-CoA reductase inhibitor. In recent years, studies have shown that it can regulate inflammation processes to counteract the pathogenesis of CIN, showing certain preventive effects on occurrence of CIN [18]. Taking atorvastatin before PCI can effectively reduce incidence of post-interventional CIN and cardiovascular adverse events [19]. In the current study, patients underwent cerebrovascular intervention. The contrast agent was Iopamiro 370. The average distribution half-life of Iopamiro 370 is about 21 minutes and the average elimination half-life is about 2 hours. This study demonstrated that incidence of CIN (6.0%) was significantly lower in the observation group, taking 40 mg/day of atorvastatin, than in the control group, taking 20 mg/day (26.0%). Results indicate that high-dose atorv-

**Table 6.** Comparison of oxidative stress indicators (NOS and SOD)

| Items | Observation group (n=50) | Control group (n=50) | $t/\chi^2$ | P |
|---|---|---|---|---|
| NOS (U/mL) | | | | |
| Before intervention | 21.3±3.7 | 20.5±3.5 | 1.111 | 0.269 |
| 72 h after intervention | 17.2±3.2 | 14.4±2.9 | 4.585 | <0.001 |
| Differences | 4.1±1.1 | 6.1±1.4 | 7.943 | <0.001 |
| SOD (U/mL) | | | | |
| Before intervention | 127.1±30.2 | 125.7±26.8 | 0.245 | 0.807 |
| 72 h after intervention | 112.7±22.3 | 100.6±21.4 | 3.502 | <0.001 |
| Differences | 14.4±3.2 | 25.1±4.0 | 14.770 | <0.001 |

Note: NOS: nitric oxide synthase; SOD: superoxide dismutase.

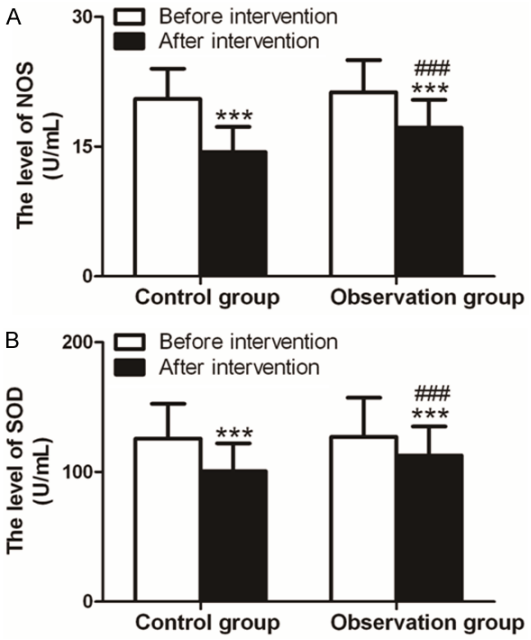


**Figure 3.** Comparison of oxidative stress indicators. NOS: nitric oxide synthase; SOD: superoxide dismutase. Compared with the same group pre-interventional, ***P<0.001; compared with the control group after intervention, ###P<0.001.

astatin, administered before surgery, can effectively reduce incidence of CIN after cerebrovascular intervention. Present results are in agreement with the results reported by Su et al. [20].

A sensitive indicator of early kidney injury, cystatin has good biological stability. It is unlikely to be affected by factors such as individual differences. Therefore, it can reflect glomerular filtration rates [21, 22]. SCr and BUN are widely used indicators for evaluation of glomerular dysfunction. This study showed that levels of SCr, BUN, and Cys-C in the observation group, at 72 hours after intervention, were not significantly different from those before intervention. However, they were significantly lower than those in the control group. This indicates that patients taking 40 mg/day of atorvastatin had less renal damage and better recovery of renal function than patients taking 20 mg/day, further indicating that 40 mg/day of atorvastatin can effectively prevent occurrence of CIN. Regarding adverse drug effects, results showed no liver function damage, cerebrovascular events, or rhabdomyolysis in either group, suggesting that the use of 40 mg/day of atorvastatin for prevention of CIN is safe and reliable.

Mechanisms of atorvastatin in the prevention and treatment of CIN remain unclear. It has been reported that dyslipidemia is one of the risk factors for CIN, which may be related to oxidative stress induced by dyslipidemia [23, 24]. Results of this study showed no significant differences in blood lipid levels between the two groups within 72 hours after cerebrovascular intervention, indicating that lipid-lowering effects of atorvastatin were not related to its preventive effects of CIN. Recent studies have revealed that inflammatory response and oxidative stress play important roles in the development of CIN [25, 26]. Statins have multiple therapeutic benefits, such as anti-inflammatory and anti-oxidative effects, as well as positive regulation of immune responses and renal circulation. Studies have shown that hsCRP, one of the indicators of inflammation *in vivo*, is an independent risk factor for CIN. It has the function of activating, complementing, and participating in apoptosis. An increase of hsCRP levels is related to occurrence of CIN [27]. IL-6 is a key cytokine in the inflammatory response network, playing an important role in inflammatory response. Studies have shown that elevated levels of IL-6 can lead to glomerulonephritis and other diseases [28]. The current study showed that hsCRP and IL-6 levels significantly decreased after intervention in both groups, with the observation group decreasing to a greater extent. This provides further support

that atorvastatin can significantly reduce the release of inflammatory mediators and inhibit inflammatory response, thereby reducing the toxic effects of contrast agents on the kidneys. This beneficial effect is likely presented in a dose-dependent manner. This is generally consistent with the reports of Fu et al. [29]. With respect to oxidative stress indicators, nitric oxide (NO) is involved in the regulation of inflammatory response *in vivo*, having the effect of scavenging oxygen free radicals. NO is mainly released by vascular endothelial cells, while NOS regulates the amount of NO released by the cells [30]. SOD is an antioxidant that acts as an oxygen free radical scavenger [31]. Results of this study demonstrated that post-interventional NOS and SOD levels significantly increased in both groups, with the observation group increasing more significantly. Results suggest that atorvastatin can significantly reduce occurrence of oxidative stress after cerebrovascular intervention by stimulating the release of antioxidants, reducing incidence of post-interventional CIN. This is in accord with the findings of Deng et al. and Ortega et al. [32, 33].

The current study had certain limitations, however. These include the small sample size, no long-term follow-up results, and merely a single-center study. In future studies, larger sample sizes are required. Present results should be confirmed by randomized controlled trials with long-term follow-ups.

In conclusion, taking atorvastatin at 40 mg/day is safe and effective in patients with cerebrovascular intervention. It can significantly reduce incidence of post-interventional CIN. Underlying mechanisms may be related to its anti-inflammatory and anti-oxidative effects.

## Disclosure of conflict of interest

None.

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