RESEARCH ARTICLE

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The preventive effects of different doses of atorvastatin on contrast-induced acute kidney injury after CT perfusion

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Abstract

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Background: Contrast-induced acute kidney injury (CI-AKI) is a severe complication among patients receiving intravascular contrast media. The purpose of this study was to investigate the preventive effects of pretreatment of atorvastatin at intensive doses on CI-AKI after computed tomography (CT) perfusion.

Methods: The levels of serum creatinine (SCR), blood urea nitrogen (BUN), Cystatin C (CysC), estimated glomerular filtration rate (eGFR), high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6) in patients were compared between the observation group receiving 40 mg/kg atorvastatin and the control group receiving 20 mg/ kg atorvastatin before and 72 h after CT examination. In addition, the incidence of CI-AKI was recorded.

Results: Compared with the control group, the incidence of renal injury in the observation group was significantly reduced, from 8% to 2% ($\chi^2 = 6.62$, p = 0.010). In addition, there was no notable difference in the levels of Scr, BUN, CysC, hs-CRP, and IL-6 before CT examination between two groups (p > 0.05). The levels of SCR, BUN, CysC, hs-CRP, and IL-6 were increased, while the levels of eGFR were decreased in the control group at 72 h after CT examination (p < 0.05). At 72 h after CT enhancement, the levels of BUN, CysC, and hs-CRP were prominently increased in the observation group (p < 0.05), while SCR, eGFR, and IL-6 did not change (p > 0.05). Compared with the control group, the levels of SCR, BUN, CysC, eGFR, hs-CRP, and IL-6 in the observation group were significantly decreased at 72 h after CT examination (p < 0.05). Conclusion: Intensive dose of atorvastatin pretreatment can prevent CI-AKI undergoing CT perfusion through lowering inflammation as well as renal function indexes SCR, CysC, BUN, and eGFR.

KEYWORDS

acute kidney injury, atorvastatin, computed tomography, incidence, perfusion

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1 | INTRODUCTION

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Contrast-induced acute kidney injury (CI-AKI) is the third leading hospital-acquired health problem, which results in increased morbidity, mortality, and cost. CI-AKI is characterized by progressive decline in kidney function within a few days of contrast medium administration.¹ Under normal circumstances, as long as the kidney function is normal, the contrast agent can be discharged from the body within 6-8 h,² and the probability of occurrence of CI-AKI is very low. Moreover, if the patient has chronic kidney disease, the probability of AKI after treated with contrast agent will be greatly increased.³ Once CI-AKI occurs, the most effective treatment is hemodialysis, but hemodialysis is expensive, which will greatly increase the economic burden of patients and reduce the quality of life of patients. Therefore, it is very important to prevent the occurrence of CI-AKI. In recent years, because of environmental pollution, more and more people begin to suffer from various known or even unknown diseases, so the application of computed tomography (CT) becomes higher and higher.⁴ However, CT enhancement examination requires intravenous injection of contrast agent, which is mainly metabolized by the kidney.⁵ The rise in the variety of contrast-related procedures (contrast CT) has resulted in the increased number of CI-AKI.⁶

Atorvastatin is one of the most commonly prescribed statins, which is used for the prevention and treatment of cardiovascular diseases (CVDs). Atorvastatin at intensive doses was already shown to be effective in preventing CI-AKI in patients undergoing coronary intervention.⁷ However, there are few studies on this subject in China and more in foreign countries, mainly through clinical trials to compare the effects of different doses of atorvastatin in CI-AKI. Therefore, the purpose of this study was to explore the preventive effect of enhanced dose and conventional dose of atorvastatin on CI-AKI after CT perfusion through comparing kidney damage-related and renal function-related biochemical indicators.

2 | MATERIALS AND METHODS

2.1 | Patients

A total of 300 patients with CT enhancement examination in our hospital from January 2018 to January 2019 were included in our study. Inclusion criteria: (1) patients who did not take statins within 2 weeks before CT enhancement examination. (2) there was no statistical significance in cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and other blood lipid indexes before CT enhancement examination in all patients. Exclusion criteria⁸: (1) patients who were allergic to iohexol contrast agent. (2) patients who had severe organ failure such as heart and liver. (3) patients who had severe cognitive dysfunction and cannot cooperate with the examination. (4) patients who had infectious diseases such as hepatitis B. (5) patients who had chronic renal failure of more than 4 stages. This study was approved by the Ethics Committee of our hospital. All patients signed the informed consent.

2.2 | Methods of examination

All patients were randomly divided into the observation group receiving intensive dose atorvastatin (150 patients per group) and the control group receiving conventional dose atorvastatin (150 patients per group). All patients needed to be fasted for more than 12 h before the examination to take the venous blood which was sent to determine the routine biochemical indicators.⁹ The levels of serum creatinine (SCR), blood urea nitrogen (BUN), Cystatin C (CysC), high sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6) were recorded, and the estimated glomerular filtration rate (eGFR) value was calculated. After 72 h of CT examination, the venous blood was taken again more than 12 h after fasting. The levels of SCR, BUN, CysC, hs-CRP, and IL-6 were determined and eGFR was calculated. In the observation group, the patients were treated with intensive dose (40 mg/kg) of atorvastatin.¹⁰ In the control group, the patients were treated with intensive dose (20 mg/kg) of atorvastatin.¹¹ The patients were given atorvastatin orally one day before CT examination, once a night for 4 consecutive days. The levels of SCR, BUN, CysC, eGFR, hs-CRP, and IL-6 before and 72 h after CT examination were compared between two groups. In addition, the incidence of CI-AKI was recorded.

2.3 | Evaluation criterion

- 1. Diagnostic criteria for CI-AKI $^{11-13}$: The level of SCR within 48– 72 h after injection of contrast agent was more than 25% higher than that of the original base, or the absolute value was more than 44.2 μ mol/L (0.5mg/dl), and other factors affecting renal function should be excluded.
- The level of eGFR was calculated by Cockcroft Gault formula^{14,15}: eGFR (male) = (140-age) × weight (kg) × 88.4 / [72×SCR (µmol/L)] eGFR (female) = (140-age) × weight (kg) × 88.4 / [72×SCR (µmol/L)] × 0.85
- 3. SCR: The levels of SCR were determined by enzyme colorimetry, and the normal value reference ranged from 59 to 104 μ mol/L.
- 4. BUN: The levels of BUN were determined by colorimetry, and the normal value reference ranged from 0 to 8.3 mmol/L.
- 5. CysC: The levels of CysC were determined by Immunoturbidimetry, and the normal value reference ranged from 0.47 to 1.09 mg/L.
- hs-CRP: The levels of hs-CRP were determined by Immunoturbidimetry, and the normal value reference ranged from 0 to 5 mg/L.

2.4 | Statistical analysis

Statistical analysis was made by software Statistical Product and Service Solutions (SPSS) version 20.0 (International Business Machines, corp.). Significant differences between the two groups were assessed by χ^2 test and t test. The counting data were expressed as percentage (%). The measurement data were expressed as means \pm standard deviation (SD). Differences were considered statistically significant when p < 0.05.

3 | RESULTS

3.1 | Baseline characteristics and the incidence of CI-AKI patients

A total of 300 patients with CT enhancement examination in our hospital was chosen in this study. The average age of patients was 65.0 years (range 36–85 years). 48.5% of examinations were performed in women.

After CT examination, the incidence of CI-AKI patients in the two groups was evaluated according to the diagnostic criteria. Compared with the control group, the incidence of CI-AKI in the observation group was significantly reduced from 8% to 2% ($\chi^2 = 6.62$, p = 0.010) (Table 1).

3.2 | Comparison of the levels of SCR in the two groups before and after CT examination

The levels of SCR in the two groups before and after CT examination are shown in Table 2. In the control group, the levels of SCR after CT examination were significantly higher than those before the examination (t = 12.702, p = 0.000). However, in the observation group, there was no notable difference in the levels of SCR after CT examination in comparison with those before the examination (t = 0.451, p = 0.653). Similarly, there was no significant difference in the levels of SCR between the two groups before CT examination (p > 0.05). After CT examination, the levels of SCR in the observation group were significantly lower than those in the control group (t = 10.218, p = 0.013).

3.3 | Comparison of the levels of BUN in the two groups before and after CT examination

Blood urea nitrogen levels in the two groups before and after CT examination are provided in Table 3. In the control group, the levels of BUN after CT examination were markedly increased compared to those before the examination (t = 9.558, p = 0.000). In addition, in

 TABLE 1
 Comparison of the incidence of CI-AKI between the two groups

Groups	n	The incidence of CI-AKI
Control group	150	12 (8%)
Observation group	150	3 (2%)
χ^2		6.62
p		0.010

the observation group, the levels of BUN after CT examination were also notably increased in comparison with those before the examination (t = 3.172, p = 0.031). However, no remarkable difference in the levels of BUN was found before the examination between the two groups (p > 0.05). After the examination, the levels of BUN in observation group were significantly decreased in comparison with the control group (t = 4.857, p = 0.012).

3.4 | Comparison of the levels of CysC in the two groups before and after CT examination

The results of the levels of CysC in the two groups before and after CT examination are shown in Table 4. In the control group, the levels of CysC after CT examination were significantly higher than those before the examination (t = 29.987, p = 0.000). Besides, in the observation group, the levels of CysC after CT examination were also markedly increased compared to those before the examination (t = 9.487, p = 0.031). However, there was no significant difference in the levels of CysC before the examination between the two groups (p > 0.05). After the examination, the levels of CysC in observation group were prominently decreased in comparison with the control group (t = 5.678, p = 0.023).

3.5 | Comparison of the values of eGFR in the two groups before and after CT examination

The results of eGFR values in the two groups before and after CT examination were shown in Table 5. It was suggested that, the values of eGFR after CT examination in the control group were significantly decreased compared to those before the examination (t = 17.683, p = 0.000). Moreover, in the observation group, no significant difference was indicated in the values of eGFR after CT examination in comparison with those before the examination (t = 1.783, p = 0.681). Furthermore, no significant difference in the values of eGFR was found before the examination between the two groups (p > 0.05). After the examination, the values of eGFR in observation group were markedly increased in comparison with the control group (t = 4.987, p = 0.019).

3.6 | Comparison of the levels of hs-CRP in the two groups before and after CT examination

The results of hs-CRP levels in the two groups before and after CT examination are demonstrated in Table 6. In the control group, the levels of hs-CRP after CT examination were significantly increased compared with those before the examination (t = 28.732, p = 0.000). In the observation group, the levels of hs-CRP after CT examination were higher than those before the examination (t = 16.831, p = 0.000). There was no difference in the levels of hs-CRP before the examination between the two groups (p > 0.05). However,

4 of 6

Groups

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Groups

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Control group

Observation group

Control group

Observation group

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Groups	n	Before examination	After examination	t	p
Control group	150	80.90 ± 16.72	93.29 ± 21.98	12.702	0.000
Observation group	150	80.70 ± 14.79	80.79 ± 13.82	0.451	0.653
t		0.392	10.218		
p		0.781	0.013		

After

4.857

0.012

After

4.987

0.019

examination

68.31 ± 21.79

78.02 ± 20.38

examination

 6.23 ± 1.12

5.73 ± 0.98

t

9.558

3.172

t

17.683

1.783

р

р

0.000

0.081

0.000

0.031

Before

n

150

150

n

150

150

examination

 5.78 ± 1.32

 5.54 ± 1.38

0.387

0.798

Refore

0.273

0.829

examination

79.68 ± 25.43

77.54 ± 21.46

TABLE 2 Comparison of the levels of SCR in the two groups before and after CT examination (µmol/L)

TABLE 3 Comparison of the levels of BUN in the two groups before and after CT examination (mmol/L)

Groups	n	Before examination	After examination	t	р
Control group	150	0.95 ± 0.23	1.98 ± 0.34	29.987	0.000
Observation group	150	0.93 ± 0.25	1.04 ± 041	9.487	0.000
t		0.296	5.678		
р		0.832	0.023		

TABLE 4 Comparison of the levels of CysC in the two groups before and after CT examination (mg/L)

TABLE 5 Comparison of the values of EGFR in the two groups before and after CT examination (min $\times 1.73$ m²)

Groups	n	Before examination	After examination	t	р
Control group	150	4.67 ± 1.33	17.68 ± 3.20	28.732	0.000
Observation group	150	4.92 ± 1.38	8.94 ± 2.93	16.831	0.000
t		0.573	12.687		
р		0.832	0.000		

TABLE 6 Comparison of the levels of hs-CRP in the two groups before and after CT examination (mg/L)

after the examination, the levels of hs-CRP in observation group were prominently decreased in comparison with the control group (t = 12.687, p = 0.023).

Comparison of the levels of IL-6 in the two 3.7 | groups before and after CT examination

The results of the levels of IL-6 in the two groups before and after CT examination are shown in Table 7. In the control group, the

levels of IL-6 after CT examination were significantly increased than those before the examination (t = 9.892, p = 0.000). However, in the observation group, there was no marked difference in the values of IL-6 after CT examination in comparison with those before the examination (t = 1.832, p = 0.167). Furthermore, the levels of IL-6 before examination in observation group were not significantly changed when compared to those in control group (p > 0.05). After the examination, the levels of IL-6 in observation group were prominently lower than those in the control group (t = 4.018, p = 0.032).

TABLE 7 Comparison of the levels of IL-6 in the two groups before and after CT examination (ng/L)

Groups	n	Before examination	After examination	t	p
Control group	150	125.51 ± 18.08	149.63 ± 18.64	9.892	0.000
Observation group	150	126.73 ± 17.98	129.38 ± 16.97	1.832	0.167
t		0.873	4.018		
р		0728	0.032		

4 | DISCUSSION

With the continuous improvement of medical standards, CT enhancement examination is becoming common, and more and more diseases need to be confirmed by enhanced examination.⁴ Contrast agents have to be used for CT examination. For patients with renal insufficiency or impairment, the use of contrast agents can lead to acute renal impairment. Therefore, the incidence of CI-AKI has been greatly increased, which has attracted the attention of scholars around the world. Studies abroad have reported that atorvastatin have the effect of preventing AKI, but there are few reports in China.^{16,17} This study investigated the preventive effect of intensive dose of atorvastatin and conventional dose of atorvastatin on CI-AKI after CT perfusion and showed that the intensive dose of atorvastatin can significantly improve CI-AKI through reducing lipid, inflammation, and the incidence of CI-AKI patients.

Atorvastatin exerts various pharmacological efficacies such as lowering low-density lipoprotein cholesterol, anti-inflammation, antioxidative stress-related injuries, and anti-thrombosis.^{14,18,19} This study proves that, after CT examination, the incidence of CI-AKI in the control group is 8%, and that in the observation group is 2%. It is suggested that the use of intensive dose of atorvastatin can effectively reduce the incidence of AKI, which is consistent with the research results reported abroad.²⁰⁻²² Kidney function is assessed by determination of SCR, CysC, BUN and eGFR, which are used as indexes of renal function although they are affected by age, gender, muscle mass, liver disease, and diet.^{23,24} The levels of SCR, CysC, BUN, and eGFR can be used to evaluate the conditions and prognoses of AKI patients. It is believed that both SCR and BUN are determined by glomerular overpower, but they are not sensitive. Only when the kidney has a large area of necrosis and damage, they will change, and their specificity is also low, and they are susceptible to inflammation, diet and other factors.^{25,26} CysC is more sensitive and accurate than SCR and BUN, and it can be used as one of the diagnostic criteria for early renal function damage.^{22,27,28} eGFR is more accurate, stable, and comprehensive than CysC, SCR, and BUN in the evaluation of renal function, and it is the most commonly used evaluation index of renal function.^{29,30} The values of eGFR were significantly decreased in the control group, but were almost no change in the observation group, indicating that the intensive dose of atorvastatin has a certain protective effect on renal function as indicated as the changes of the levels of SCR, CysC, BUN, and eGFR.

In addition, in the control group, the levels of hs-CRP and IL-6 are significant increased 72 h after CT examination. In the observation group, the level of hs-CRP after the CT examination is significantly higher than that before the examination, but the level of IL-6 is not significantly changed in comparison with that before the examination. A previous study pointed out that hs-CRP is an important index of systemic inflammatory responses.³¹ IL-6, a multifunctional, plays a key role As a relatively representative proinflammatory cytokine, IL-6 also plays an important role in the development of inflammatory response and is involved in patho AMI.³² Our results showed that the levels of hs-CRP and IL-6 in the observation group are markedly lower than those in the control group, indicating that the intensive dose of atorvastatin has a certain anti-inflammatory effect on CI-AKI patients.

In conclusion, before CT enhancement, treatment with intensive dose of atorvastatin can effectively prevent the occurrence of CI-AKI in lowering inflammation as well as indexes of renal function (SCR, CysC, BUN, and eGFR).

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Guarantor of integrity of the entire study: Shi-Xin Yan, Man Gao. Study concepts: Shi-Xin Yan, Man Gao. Study design: Shi-Xin Yan, Man Gao. Definition of intellectual content: Literature research: Song Jin. Clinical studies: Shi-Xin Yan, Tian-Hao Yang, Chao Tian. Data acquisition: Shi-Xin Yan, Tian-Hao Yang, Chao Tian. Data analysis: Man Gao, Tian-Hao Yang, Chao Tian. Statistical analysis: Man Gao. Tian-Hao Yang, Chao Tian. Manuscript preparation: Shi-Xin Yan, Man Gao. Manuscript editing: Shi-Xin Yan, Man Gao. Manuscript review: Shi-Xin Yan, Man Gao, Song Jin.

CONSENT FOR PUBLICATION

Informed consent was obtained from all individual participants included in the study.

DATA AVAILABILITY STATEMENT

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

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