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Effect of low-dose aspirin on serum uric acid levels in Chinese individuals over 60: subanalysis of a multicentre randomized clinical trial

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Abstract. – OBJECTIVE: Uric acid is considered a biomarker for cardiovascular risk. Only a few studies have investigated the effect of aspirin on serum uric acid (SUA) levels with contradictory results. The present study evaluated the effect of aspirin on SUA levels in Chinese individuals over 60 years of age.

PATIENTS AND METHODS: Subjects over 60 with coronary artery disease or multiple cardiovascular risk factors were enrolled in a multicentre randomized clinical trial. Eligible subjects were randomized to receive 50 mg or 100 mg aspirin daily. Levels of arachidonic acid-induced platelet aggregation performed by light transmission aggregometry (LTA-AA) and SUA were measured at randomization and two weeks thereafter. In this subanalysis, subjects without aspirin use prior to enrolment were chosen.

RESULTS: A total of 446 subjects were analysed, of which 151 subjects took 50 mg aspirin, and 295 took 100 mg aspirin. Hyperuricaemia was present in 23.3% (104/446) of subjects at baseline. LTA-AA levels were significantly reduced in subjects after taking aspirin for two weeks (both 50 mg and 100 mg, $p < 0.001$). SUA levels were decreased after aspirin administration (311 μmol/L *vs.* 302 μmol/L, $p < 0.001$). Further analysis showed SUA levels were unchanged in normouricaemic subjects (284 μmol/L *vs.* 280 μmol/L, $p > 0.05$), while slightly decreased in hyperuricaemic subjects (429 μmol/L *vs.* 392 μmol/L, $p < 0.001$).

CONCLUSIONS: Our study showed that both 50 mg and 100 mg aspirin significantly inhibited platelet aggregation. Aspirin treatment for two weeks showed no hyperuricaemic effect in people over 60. SUA levels were unchanged after taking aspirin in normouricaemic subjects but decreased in hyperuricaemic subjects. This trial was registered at www. chictr.org.cn as ChiCTR1800018517.

Key Words:
Aspirin, Uric acid, Cardiovascular disease, Salicylic acid, Platelet reactivity.

Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity worldwide[1]. Aspirin is a widely used antiplatelet agent used to prevent thromboembolic events[2]. Several studies[3-5] reported that serum uric acid (SUA) levels were increased under low-dose aspirin treatment, whereas no hyperuricaemic effect was observed in other investigations[6,7].

Hyperuricaemia is regarded as an emerging risk factor for CVD[8]. However, existing evidence was based on small sample sizes with contradictory results. The effect of low-dose aspirin on SUA has not been well demonstrated, especially in Asian populations. The aim of this study was to evaluate the effect of low-dose aspirin on SUA levels in Chinese individuals over 60 years of age.

Patients and Methods

Study Design and Subjects

The design and results, concerning other data of this trial have been described in detail in the Chinese Circulation Journal[9]. Our study was a prospective, randomized, open-label, parallel controlled, multicentre pragmatic clinical trial. Subjects were recruited from 18 participating centres in China between Sep 2016 and Dec 2016. Eligible subjects were at least 60 years old and had coronary artery disease or multiple cardiovascular risk factors.

Inclusion criteria for the primary prevention of CVD were as follows: (1) at least one disease, including hypertension, dyslipidaemia and diabetes mellitus; and (2) at least two conditions, including a family history of premature CVD, obesity and active smoking[10]. Inclusion criteria for the secondary prevention of CVD were as follows:

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(1) stable coronary artery disease (CAD); and (2) more than one year after percutaneous coronary intervention. Exclusion criteria were as follows: (1) history of severe three-vessel or left main CAD; (2) severe hepatic and renal dysfunction, haematologic diseases, cancer or aspirin allergy; and (3) additional antiplatelet agents, anticoagulants or nonsteroidal anti-inflammatory drugs.

The study was designed as a noninferiority trial. The sample size was 1194 subjects (398 per group), which was calculated considering an 8% difference in arachidonic acid-induced platelet aggregation performed by light transmission aggregometry (LTA-AA) between the groups, with a 1-sided significance level (α) of 0.025, a power (1-β) of 0.80 and a drop-out rate of 20%.

Stratified block randomization was conducted by generating the random allocation sequence in SAS 9.3 (SAS Institute, Cary, NC, USA). The enrolled subjects were randomized 1:1:1 to receive enteric-coated sustained-release aspirin tablets (50 mg or 100 mg once daily) or enteric-coated aspirin tablets (100 mg once daily). Enteric-coated aspirin tablets were used as the positive control. Blood samples were obtained from all subjects at randomization and two weeks thereafter. The primary outcome parameter was LTA-AA after taking aspirin for two weeks, performed as previously described[11]. The adverse events included bleeding and gastrointestinal symptoms during the 28-day follow-up period. The levels of biochemical parameters were measured using standard methods. A total of 100 subjects violated the study protocol, and another 77 chose to withdraw from the study. The remaining 1017 subjects completed the study and were included in the per protocol set.

This trial was registered with the Chinese Clinical Trial Registry (registration No: ChiCTR1800018517). The protocol was approved by the local Ethics Committee of each participating centre and complied with the principles of the Declaration of Helsinki. Before recruitment, written informed consent was obtained from each subject.

Subanalysis

For the current analysis, subjects without aspirin use prior to enrolment were chosen. Subjects who were taking urate-lowering agents, losartan, irbesartan, fenofibrate or thiazide diuretics were further excluded (Figure 1). The present subanalysis was not pre-specified, and no additional medical intervention was conducted among subjects with hyperuricaemia during the follow-up period. Hyperuricaemia was defined as baseline SUA levels >7 mg/dL (420 μmol/L) in men or > 6 mg/dL (360 μmol/L) in women[12].

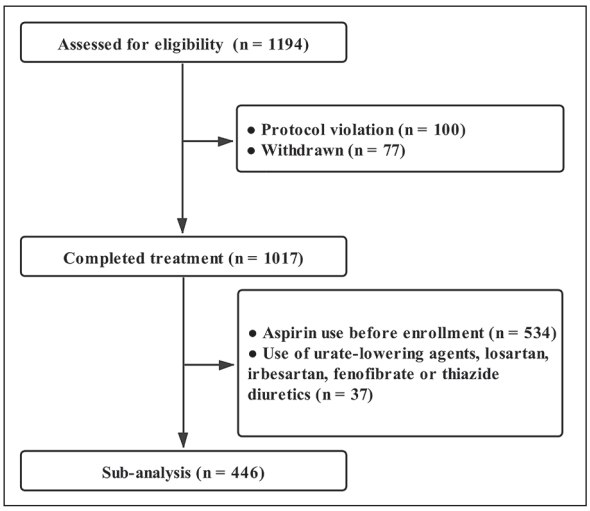

Figure 1. Flow chart of subjects included in this subanalysis of our multicentre randomized clinical trial.

Statistical Analysis

Normally distributed continuous variables are presented as the mean ± SD and were analysed with paired or unpaired Student's *t*-test. Non-normally distributed continuous variables are presented as medians with interquartile ranges (IQRs) and were evaluated by the Wilcoxon signed-rank test or Mann-Whitney U test. Categorical variables are expressed as the frequency and were determined by the χ^2-test or Fisher's exact test as appropriate. $p < 0.05$ was considered as statistically significant. Statistical analyses were performed using SPSS version 20.0 software (IBM, Armonk, NY, USA).

Results

Baseline Characteristics of the Subjects

A total of 446 subjects were enrolled in this subanalysis, of which 104 had elevated SUA levels; 151 subjects received 50 mg aspirin daily, and 295 subjects received 100 mg aspirin daily. The clinical characteristics of the subjects are summarized in Table I.

Effect of Low-Dose Aspirin on Platelet Aggregation

As shown in Table II, the inhibitory effects

Table I. Baseline characteristics of the subjects.

Clinical features	Overall (n = 446)	50 mg aspirin (n = 151)	100 mg aspirin (n = 295)	*p*-value
Age, yrs	65.00 (62.00-69.00)	64.00 (62.00-69.00)	65.00 (62.00-69.00)	0.605
Males, n (%)	156 (35.0%)	43 (28.5%)	113 (38.3%)	0.046*
Weight, kg	65.00 (60.00-70.00)	63.00 (58.00-70.00)	65.00 (60.00-70.00)	0.016*
BMI, kg/m^2	24.02 (22.65-26.03)	23.66 (22.35-25.71)	24.17 (22.77-26.25)	0.109
Active smoking, n (%)	49 (11.0%)	15 (9.9%)	34 (11.5%)	0.636
Family history of premature CVD, n (%)	12 (2.7%)	6 (4.0%)	6 (2.0%)	0.374
Hypertension, n (%)	292 (65.5%)	93 (61.6%)	199 (67.5%)	0.247
Dyslipidemia, n (%)	236 (52.9%)	90 (59.6%)	146 (49.5%)	0.046*
Diabetes mellitus, n (%)	101 (22.6%)	31 (20.5%)	70 (23.7%)	0.475
Coronary heart disease, n (%)	31 (7.0%)	10 (6.6%)	21 (7.1%)	1.000
Prior vascular disease†, n (%)	17 (3.8%)	5 (3.3%)	12 (4.1%)	0.799
Previous PCI, n (%)	4 (0.9%)	0 (0%)	4 (1.4%)	0.365
ACEIs, n (%)	28 (6.3%)	7 (4.6%)	21 (7.1%)	0.410
ARBs, n (%)	49 (11.0%)	18 (11.9%)	31 (10.5%)	0.749
Beta blockers, n (%)	14 (3.1%)	5 (3.3%)	9 (3.1%)	1.000
Statins, n (%)	60 (13.5%)	23 (15.2%)	37 (12.5%)	0.464
CCBs, n (%)	157 (35.2%)	50 (33.1%)	107 (36.3%)	0.531
Diuretics, n (%)	11 (2.5%)	4 (2.6%)	7 (2.4%)	1.000
Hypoglycemic agents, n (%)	72 (16.1%)	25 (16.6%)	47 (15.9%)	0.892
TG, mmol/L	1.42 (1.04-1.96)	1.40 (1.00-2.09)	1.42 (1.09-1.87)	0.936
TC, mmol/L	5.21 ± 1.04	5.25 ± 1.01	5.19 ± 1.06	0.546
HDL-C, mmol/L	1.40 (1.21-1.63)	1.40 (1.23-1.66)	1.40 (1.20-1.61)	0.683
LDL-C, mmol/L	3.20 ± 0.95	3.19 ± 0.93	3.20 ± 0.97	0.905
Cr, μmol/L	65.75 (56.45-77.00)	65.60 (56.00-77.00)	66.00 (56.60-77.00)	0.617
Ccr§, mL/min	79.07 (66.92-92.51)	77.03 (64.89-93.56)	80.27 (67.91-92.08)	0.199
eGFR§, mL/min/1.73 m^2	88.80 (78.42-95.83)	88.97 (79.98-96.63)	88.71 (78.76-95.30)	0.858

Normally distributed, continuous variables are mean ± SD and non-normally distributed, continuous variables are median (IQR); categorical variables are n (%). BMI, body mass index; CVD, cardiovascular disease; PCI, percutaneous coronary intervention; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blocking agents; CCBs, calcium channel blockers; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein; LDL-C, low density lipoprotein; Cr, creatinine; Ccr, creatinine clearance; eGFR, estimated glomerular filtration rate. †Prior vascular disease was defined as history of peripheral artery disease or prior stroke. §Creatinine clearance and estimated glomerular filtration rate was estimated using Cockcroft-Gault and CKD-EPI equation. *$p < 0.05$ *vs*. 50 mg aspirin group.

of aspirin on LTA-AA were observed after two weeks (81.63%, 71.44-88.68% *vs.* 6.08%, 3.75-10.85%; $p < 0.001$). The levels of LTA-AA were markedly decreased in subjects after taking 50 mg and 100 mg aspirin daily (aspirin 50 mg group: 84.21%, 74.90-89.96% *vs.* 6.65%, 4.03-12.07%; aspirin 100 mg group: 80.55%, 69.64-88.30% *vs.* 5.77%, 3.66-10.48%; both $p < 0.001$, Table II). No significant differences were observed in LTA-AA levels between the two dosage groups after aspirin treatment ($p > 0.05$, Table II). The results indicated that both 50 mg and 100 mg aspirin could effectively inhibit platelet aggregation in people aged 60 years or older.

Changes in SUA Levels After Aspirin Administration

Compared with baseline, SUA levels were decreased after the use of aspirin for two weeks (311 μmol/L, 256-375 μmol/L *vs.* 302 μmol/L, 248-356 μmol/L; $p < 0.001$, Table II). Similar results were observed in the two dosage groups (50 mg aspirin group: 314 μmol/L, 266-371 μmol/L *vs.* 303 μmol/L, 248-344 μmol/L; 100 mg aspirin group: 309 μmol/L, 253-376 μmol/L *vs.* 298 μmol/L, 249-363 μmol/L; both $p < 0.001$, Table II). The distribution of the change in SUA levels is presented in Figure 2A.

Subgroup Analysis Categorized by SUA Levels

As shown in Table III , SUA levels were slightly decreased in subjects after taking aspirin for two weeks in the hyperuricaemia subgroup (429 μmol/L, 398-466 μmol/L *vs.* 392 μmol/L, 348-432 μmol/L; $p < 0.001$), while no change was observed in the normouricaemia subgroup (284 μmol/L, 242-325 μmol/L *vs.* 280 μmol/L, 238-

Table II. Comparison of LTA-AA and SUA levels before and after aspirin administration.

Variable	Overall (n = 446)	50 mg aspirin (n = 151)	100 mg aspirin (n = 295)
LTA-AA, %			
Baseline	81.63 (71.14-88.68)	84.21 (74.90-89.96)	80.55 (69.64-88.30)
2 wk	6.08 (3.75-10.85)*	6.65 (4.03-12.07) *	5.77 (3.66-10.48) *
SUA, μmol/L			
Baseline	311 (256-375)	314 (266-371)	309 (253-376)
2 wk	302 (248-356) *	303 (248-344) *	298 (249-363) *

LTA-AA: arachidonic acid-induced platelet aggregation performed by light transmission aggregometry. SUA: serum uric acid. Data are median with IQR. *$p < 0.001$ *vs*. baseline.

Table III. Comparison of SUA levels before and after aspirin administration stratified by hyperuricaemia.

Variable	Normouricaemia			Hyperuricaemia		
	Overall (n = 342)	50 mg aspirin (n = 117)	100 mg aspirin (n = 225)	Overall (n = 104)	50 mg aspirin (n = 34)	100 mg aspirin (n = 70)
SUA, μmol/L						
Baseline	284 (242-325)	284 (248-325)	285 (239-324)	429 (398-466)	422 (395-445)	432 (400-469)
2 wk	280 (238-322)	289 (239-321)	273 (237-322)	392 (348-432)*	378 (346-404)*	404 (348-441)*

SUA: serum uric acid. Data are median with IQR. Data are median with IQR. *$p < 0.001$ *vs*. baseline.

322 μmol/L; $p > 0.05$). The results were similar in the two subgroups of aspirin 50 mg or 100 mg (Table III). The distribution of the change in SUA levels is shown in Figure 2B and 2C.

Discussion

Low-dose aspirin is widely used in the prevention and treatment of CVD by inhibiting platelet thromboxane A_2 production[13]. In our study, platelet aggregation was detected before and after low-dose aspirin treatment. Consistent with the findings of previous studies[14,15], platelet aggregation was significantly inhibited by aspirin at both 50 mg and 100 mg daily in subjects aged 60 years or older.

Elevated SUA is increasingly being recognized as an important risk factor for CVD[8,16]. The effect of low-dose aspirin on SUA remains controversial. Caspi et al[3] showed that SUA levels were slightly increased after taking aspirin (75 mg/day) for one week in 49 elderly patients, presumably due to the inhibited uric acid excretion by aspirin. However, Akinwusi et al[7] showed that aspirin treatment (75 mg/day) for two weeks did not affect SUA levels in 30 elderly patients. We found that SUA levels

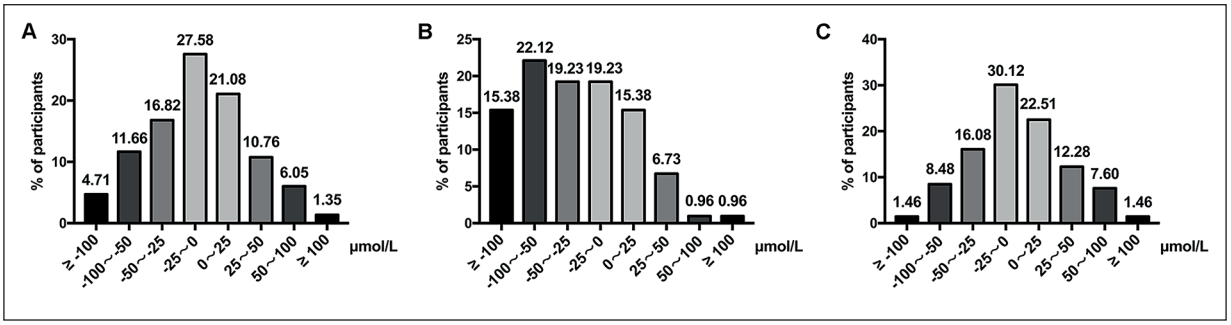

Figure 2. Distribution of the change in SUA levels after aspirin treatment. **A**, Change in SUA levels in the total population, n = 446. **B**, Change in SUA levels in hyperuricaemic subjects, n = 104. **C**, Change in SUA levels in normouricaemic subjects, n = 342. The results are presented as the percentage of subjects. (Abbreviation: SUA: serum uric acid).

were decreased in subjects with hyperuricaemia, whereas those with normal SUA levels had no significant changes after taking low-dose aspirin. Our findings showed no deleterious effects with short-term use of low-dose aspirin on SUA levels.

The kidney plays an important role in the regulation of uric acid, and approximately 70% of uric acid is excreted from the urine[17]. Renal insufficiency affects uric acid excretion, leading to an increase in SUA levels[18,19]. In Caspi et al[3], the average creatinine clearance rate (Ccr) was 47 mL/min. However, in our study, the average Ccr was 79 mL/min. It is speculated that the different effects of aspirin on SUA may be related to different renal functions.

We found that SUA levels were slightly decreased in subjects with hyperuricaemia after aspirin treatment. The underlying reason for the reduced SUA after taking low-dose aspirin was unclear. Massimi et al[20,21] reported that aspirin upregulated the expression of multidrug resistance-associated protein 4 (MRP4), an important uric acid efflux protein, in human embryonic kidney 293 cells and epithelial cells. Whether the aspirin-mediated upregulation of MRP4 could promote uric acid excretion and subsequently decease SUA levels remains unknown. A case-crossover study[22] showed that low-dose aspirin treatment for two consecutive days was associated with recurrent gout. However, the data were provided by the subjects, and levels of SUA were not collected before and after taking aspirin. In Zhang et al[22] study, it remained unclear whether SUA levels were changed after taking aspirin. The effect and the potential mechanisms of aspirin involved in uric acid metabolism under hyperuricaemia or gout deserve exploration.

To the best of our knowledge, this is the largest study to explore the effect of low-dose aspirin on SUA levels. The limitations of this study are as follows: (1) our findings were based on retrospective evidence; and (2) no data on uric acid excretion and diet were collected. To confirm our findings, it is necessary to conduct a futher larger-scale prospective study.

Conclusions

We showed that both 50 mg and 100 mg aspirin significantly inhibited platelet aggregation. After two weeks of low-dose aspirin treatment, the levels of SUA were not increased in individuals over 60 years of age. SUA levels were unchanged in subjects with normouricaemia after taking aspirin and were decreased in subjects with hyperuricaemia. The underlying mechanism remains to be further explored.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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