Comparison between theophylline, N-acetylcysteine, and theophylline plus N-acetylcysteine for the prevention of contrast-induced nephropathy

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Original Article

Abstract

BACKGROUND: Few studies compared the efficacy of theophylline with N-acetylcysteine or evaluated the efficacy of combination therapy in the prevention of contrast-induced nephropathy (CIN). We compared the efficacy of theophylline, N-acetylcysteine, and the combination of these agents in the prevention of CIN.

METHODS: This randomized controlled trial was conducted on 96 patients referring consecutively to the Shahid Chamran University Hospital in Isfahan, Iran, for elective coronary angiography (with our without angioplasty). Patients with at least moderate risk for CIN were included and were randomized to receive theophylline (200 mg), N-acetylcysteine (600 mg), or theophylline + N-acetylcysteine, twice a day, from 24 h before to 48 h after administration of the contrast material. A non-ionic, low-osmolar contrast material was used. Serum creatinine was measured before and 48 h after contrast material injection.

RESULTS: Serum creatinine was increased by 6.83 ± 15.32% with theophylline, 13.09 ± 14.63% with N-acetylcysteine, and 5.45 ±1 3.96% with theophylline + N-acetylcysteine after contrast material injection (between group P = 0.072). Controlling for Mehran risk score, baseline serum creatinine, and contrast volume, the change in serum creatinine level was lower with theophylline compared with N-acetylcysteine (F = 4.79, P = 0.033), and with theophylline + N-acetylcysteine compared with N-acetylcysteine (F = 5.78, P = 0.020). CIN (increase in creatinine of ≥ 0.5 mg/dl or ≥ 25% from the baseline) was occurred in 20%, 21.9%, and 7.1% of patients in the theophylline, N-acetylcysteine, and theophylline + N-acetylcysteine groups, respectively (P = 0.260).

CONCLUSION: Theophylline is superior to N-acetylcysteine in preventing contrast-induced renal dysfunction, but the combination with N-acetylcysteine is not superior to theophylline alone in this regard. Further trials with larger sample of patients are warranted.

Keywords: Acute Kidney Injury, Theophylline, Acetylcysteine, Coronary Angiography, Contrast Media

Date of submission: 4 Apr 2014, ***Date of acceptance:*** 29 Oct 2014

Introduction

Contrast-induced nephropathy (CIN) is the third most common cause of acute renal failure in hospitalized patients.[1] It is defined as an impaired kidney function after administration of intravascular contrast agent within 48-72 h of contrast injection, in the absence of other cause.[1] Previous studies showed that the incidence of CIN in patients who have no risk factor for CIN is < 2%, but the incidence in patients who are at a high risk for CIN is increased to 90%.[2] CIN is associated with morbidity, mortality, and high medical care costs.[2-4] Therefore, screening for high-risk patients and taking appropriate preventive measures have an important role in reducing the incidence and burden of CIN.

Previous studies proposed some preventive strategies for CIN including appropriate hydration before angiography, minimizing the dose of contrast material, using non-ionic contrast medium with low osmolarity, and administration of some medications

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such as sodium bicarbonate, N-acetylcysteine, theophylline, and high-dose statins.[5-7] Theophylline and N-acetylcysteine are among the most common studied agents in this regard.[8] Theophylline is shown to have a protective effect for kidney by increasing renal blood flow through selective renal adenosine antagonism and increasing the glomerular filtration rate (GFR).[9] N-acetylcysteine is an antioxidant and may also induce renal vasodilation by increasing intrarenal prostaglandin E2 level.[10] Meta-analyses have shown that N-acetylcysteine[8], and theophylline[11] are effective in the prevention of CIN, though controversy on the efficacy of N-acetylcysteine is still exist.[12]

Despite several randomized trials on the preventive efficacy of theophylline and N-acetylcysteine for CIN, only few studies on a head-to-head comparison between these drugs or the efficacy of combination therapy with these agents are available.[13-15] Considering different mechanisms of N-acetylcysteine and theophylline in preventing CIN, combination therapy with these two agents may be beneficial. Accordingly, we aimed to compare the efficacy of combined oral theophylline and N-acetylcysteine with theophylline and N-acetylcysteine alone in the prevention of CIN. We hypothesized that (1) the efficacy of theophylline and N-acetylcysteine in preventing CIN is different, and (2) combination of theophylline and N-acetylcysteine is more effective than each medication alone in preventing CIN.

Materials and Methods

This study was conducted on patients referring for elective coronary angiography (with or without angioplasty) from September 2013 to January 2014 to Shahid Chamran Hospital in Isfahan, Iran. This University Hospital is a cardiac specialized and referral center affiliated to the Isfahan University of Medical Sciences and includes two elective angiography units. Patients with at least moderate risk for CIN as defined by the Mehran risk score were included in the study.[16] Patients with the following characteristics were not included in the study; unstable angina, myocardial infarction, cardiac arrhythmias, acute or chronic renal failure, intravascular administration of contrast material in the past month, using theophylline or N-acetylcysteine in the past month, and known hypersensitivity to theophylline or N-acetylcysteine. The study was approved by the Ethics Committee of the Isfahan University of Medical Sciences and informed consent was obtained from patients before entering the study.

The study was designed as a randomized, double-blind, comparative trial with three parallel arms including theophylline, N-acetylcysteine, and theophylline plus N-acetylcysteine. An alphabetical code was assigned for each of the study arms (A, B, C). Using the Random Allocation Software,[17] a set of sequential numbers was generated in one block among which the study arms were randomly distributed. An independent investigator placed drugs in sequentially numbered, opaque and stapled, drug pockets. Patients were consecutively entered into the study and were assigned an order number and received the intervention based on the allocation sequence. The allocation sequence was concealed from the investigators who enrolled patients into the study. Blinding the attending physicians and patients was achieved by administering a placebo tablet identical in appearance with theophylline into the N-acetylcysteine arm and a placebo tablet identical in appearance with N-acetylcysteine into the theophylline arm. The trial was registered in clinicaltrials.gov (ID: NCT02088502). Sample size was calculated using the G*Power software (version 3.1.7, Universität Kiel, Germany). Considering the effect size of 0.3,[11] significance level of 0.05, and study power of 0.8, a total sample of 32 patients in each group was required.

Patients in the theophylline group received200 mg slow-release theophylline tablet (Darupakhsh Co., Tehran, Iran) plus placebo, and patients in the N-acetylcysteine group received600 mg non-effervescent N-acetylcysteine tablet (Shafa Co., Tehran, Iran) plus placebo, twice daily, from 24 h before to 48 h after administration of contrast material. Patients in theophylline plus N-acetylcysteine group received both drugs in the same order. All patients were hydrated with 0.9% sodium chloride (1 ml/kg/h) for 24 h, started 12 h before operation. Patients with left-ventricular ejection fraction of less than 40% or New York Heart Association functional class of III-IV were hydrated at rate of 0.5 ml/kg/h. Angiography ± angioplasty was done according to the clinical standards, by trans-femoral or trans-radial approach. In all cases, Iodixanol (Visipaque™, Amersham Healthcare, Cork, Ireland) was used as a non-ionic contrast media with low contrast osmolality.

Before the operation, all the patients underwent a detailed history and physical examination by a cardiologist. Age, gender, and history of hypertension, diabetes mellitus, dyslipidemia, and

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smoking were recorded, and weight was measured. Cardiopulmonary examination was done for the evaluation of heart failure and systolic/diastolic blood pressure. Complete blood count was checked for anemia before operation. The volume of contrast material used was recorded for each patient. Serum creatinine was measured before and 48 h after contrast material injection in a hospital laboratory and the amount of change was considered as the study outcome. CIN was defined as an increase in serum creatinine level of ≥ 0.5 mg/dl or ≥ 25% of the baseline creatinine after 48 h of contrast material injection.[18]

Data were analyzed using the SPSS software for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation or number (%). The chi-square test was applied for comparison of qualitative data between groups. Quantitative data were checked if normally distributed in each group using the Kolmogorov–Smirnov Test. If data were normally distributed, the ANOVA test (with Tukey post-hoc) was applied for comparisons among the three study groups. If data was not normally distributed, the Kruskal-Wallis test was applied, followed by the Mann–Whitney U-test for comparisons between each two pairs. The Wilcoxon test was applied for within-group comparisons. Furthermore, the ANCOVA test was done for controlling the effects of covariates. $P < 0.050$ was considered as significant.

Results

A total of 436 candidates of coronary angiography with and without angioplasty were evaluated during the study period. One hundred patients were eligible for the study. Four patients were unwilling to participate. Ninety-six patients were equally randomized into the three study groups. All patients received the assigned intervention, but six patients did not refer for the post medication evaluation (Figure 1). Demographic data and baseline characteristics of the patients are summarized in table 1. There was some difference between the study groups regarding frequency of diabetes and heart failure, but the Mehran risk score for CIN was the same among the three groups.

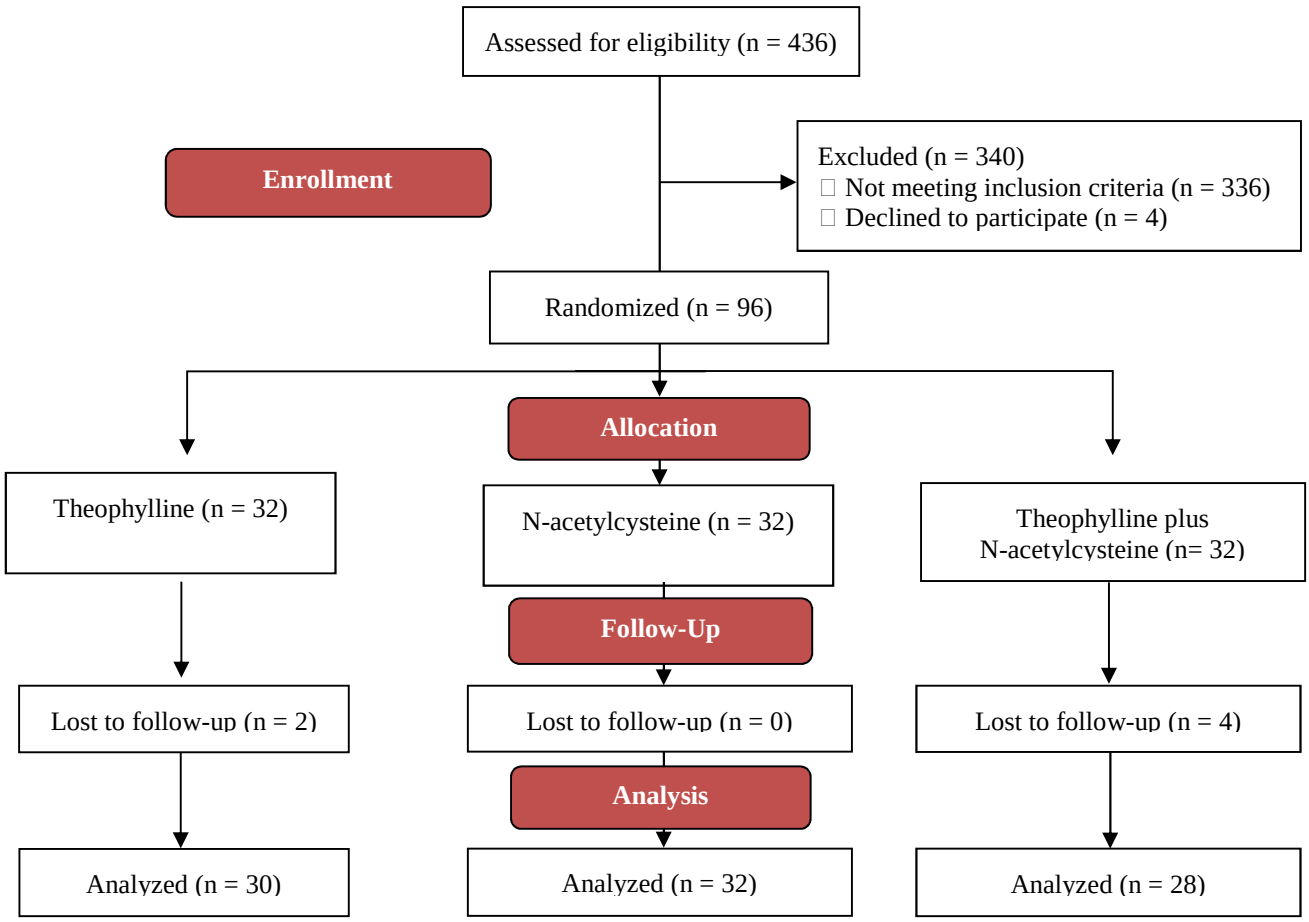

Figure 1. Patients' flow diagram

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Table 1. Demographic data and baseline characteristics of the patients

Variables	Theophylline (n = 30)	N-acetylcysteine (n = 32)	Theophylline plus N-acetylcysteine (n = 28)	P
Male/Female	13 (43.3)/17 (56.7)	15 (46.9)/17 (53.1)	11 (39.3)/17 (60.7)	0.839*
Comorbidity				
Hypertension	19 (63.3)	16 (50.0)	13 (46.4)	0.390*
Diabetes	17 (56.7)	27 (84.4)	17 (60.7)	0.041*
Dyslipidemia	13 (43.3)	18 (56.3)	9 (32.1)	0.171*
Heart failure	18 (60.0)	9 (28.1)	12 (42.9)	0.041*
Anemia	14 (46.7)	18 (56.3)	17 (60.7)	0.544*
Smoking	8 (26.7)	9 (28.1)	5 (17.9)	0.615*
CIN risk				
Moderate	23 (76.7)	27 (84.4)	24 (85.7)	0.647*
High	6 (20.0)	5 (15.6)	4 (14.3)	
Very high	1 (3.3)	0	0	
Weight	68.9 ± 8.7	71.0 ± 11.4	70.6 ± 7.8	0.655†
Age	65.0 ± 9.5	59.7 ± 13.3	64.5 ± 12.0	0.153†
Contrast volume (cc)	124.0 ± 115.2	155.6 ± 114.9	128.9 ± 89.4	0.318‡
Hemoglobin (g/dl)	13.0 ± 1.2	12.6 ± 1.2	12.9 ± 1.2	0.424†
Hematocrit (%)	39.0 ± 3.9	37.8 ± 3.9	38.8 ± 3.7	0.426†
SBP (mmHg)	136.5 ± 18.2	125.4 ± 16.7	128.8 ± 21.3	0.066†
DBP (mmHg)	82.0 ± 10.5	80.2 ± 10.3	80.0 ± 9.9	0.720†
eGFR (ml/min/1.72 m^2)	61.6 ± 18.4	71.1 ± 27.7	65.8 ± 25.9	0.312†
Risk score	9.4 ± 2.9	8.2 ± 2.5	8.8 ± 2.4	0.332‡

Data are presented as mean ± SD or number (%); CIN: Contrast-induced nephropathy; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SD: Standard deviation; GFR: Glomerular filtration rate
* Chi-square test; † ANOVA (with Tukey post-hoc); ‡ Kruskal–Wallis test

There was no difference among the study groups regarding baseline creatinine level (Table 2). Creatinine level significantly increased in all groups after 48 h (all P < 0.050). The Kruskal-Wallis test showed a difference among the study groups regarding the amount of changes in creatinine level after 48 h (P = 0.048). In pair-wise comparisons, there was no significant difference between the theophylline group compared with N-acetylcysteine group (Mann–Whitney test, P = 0.117) or compared with theophylline plus N-acetylcysteine group (Mann–Whitney test, P = 0.604) regarding the amount of change in serum creatinine level after angiography. More increase was observed in serum creatinine level in the N-acetylcysteine group compared with the theophylline plus N-acetylcysteine group after angiography (Mann–Whitney test, P = 0.025) (Figure 2). Frequency of CIN was 20, 21.9, and 7.1% in the theophylline, N-acetylcysteine, and theophylline plus N-acetylcysteine groups, respectively, but the difference was not significant (P = 0.260).

Considering some differences among the study groups in baseline characteristics, ANCOVA was conducted controlling for the Mehran risk score, baseline serum creatinine concentration, and contrast volume used as covariates. The amount of change in creatinine level was considered as the dependent variable. Compared with theophylline, those who received N-acetylcysteine experienced more increase in creatinine level after contrast injection [95% confidence interval (CI) of delta Cr = 0.009 to 0.196, F = 4.79, P = 0.033]. Compared with N-acetylcysteine, receiving theophylline plus N-acetylcysteine resulted in less increase in creatinine level after contrast injection (95% CI of delta Cr = -0.168 to -0.015, F = 5.78, P = 0.020). No difference was observed between the theophylline and theophylline plus N-acetylcysteine groups in this regard (95% CI of delta Cr = −0.105 to 0.088, F = 0.03, P = 0.862).

Discussion

Various interventions are evaluated for the prevention of CIN. Among the most studied medications, theophylline and N-acetylcysteine are shown to be effective in this regard,[8] with controversy on the efficacy of N-acetylcysteine.[12] Our study was aimed to compare the efficacy of theophylline, N-acetylcysteine, and their combination therapy in the prevention of CIN in patients with at least moderate risk. In overall, we found that theophylline is superior to N-

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Table 2. Change of serum creatinine level among the study groups

	Theophylline (n = 30)	N-acetylcysteine (n = 32)	Theophylline plus N-acetylcysteine (n = 28)	P
Baseline Cr (mg/dl)	1.14 ± 0.40	1.08 ± 0.22	1.08 ± 0.22	0.987*
48 h Cr (mg/dl)	1.21 ± 0.46	1.22 ± 0.28	1.14 ± 0.23	0.457*
Delta Cr (%)	6.83 ± 15.32	13.09 ± 14.63	5.45 ± 13.96	0.072*
Delta Cr (mg/dl)	0.06 ± 0.20	0.14 ± 0.14	0.05 ± 0.15	0.048*
P†	0.003	< 0.001	0.020	
Occurrence of CIN	6 (20)	7 (21.9)	2 (7.1)	0.260‡

Data are presented as mean ± SD or number (%); CIN: Contrast-induced nephropathy; Cr: Creatinine; SD: Standard deviation
* Kruskal–Wallis test; † Wilcoxon test; ‡ Chi-square test

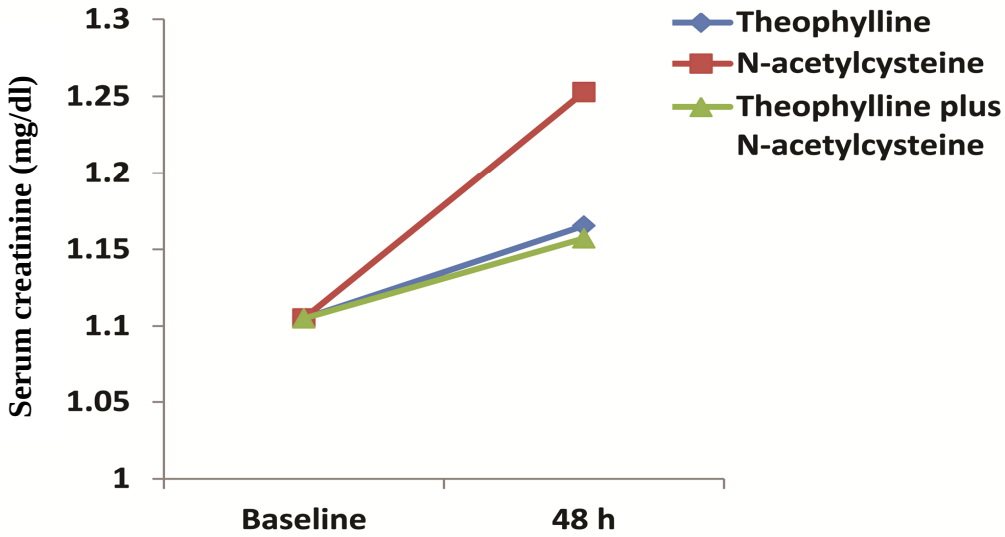

Figure 2. Changes in serum creatinine concentration from baseline to 48 h after angiography

acetylcysteine in preventing CIN, in terms of less increase in serum creatinine level after contrast material injection. Furthermore, we found that the combination of theophylline plus N-acetylcysteine is superior to N-acetylcysteine alone but not theophylline alone in this regard. However, we found no difference among the study groups in the incidence of CIN.

Few studies are conducted on head-to-head comparisons between theophylline and N-acetylcysteine or on combination therapy with these agents. Baskurt et al. compared the efficacy of N-acetylcysteine, N-acetylcysteine plus theophylline, and hydration alone. Considering the incidence of CIN, author found no benefit for N-acetylcysteine over hydration alone (9.6 vs. 6.9%). However, the incidence of CIN in those who received N-acetylcysteine plus theophylline (0%) was significantly lower than those who received N-acetylcysteine or hydration alone. Also, eGFR at 48 h after contrast material injection was higher with N-acetylcysteine plus theophylline compared with other interventions.[14] Huber et al. compared the preventive efficacy of acetylcysteine, theophylline, and their combination in an intensive care unit. Authors reported CIN in 2, 12, and 4% of patients who received theophylline, acetylcysteine, and combination therapy, respectively, revealing superiority of theophylline over acetylcysteine.[13] In another study, Bilasy et al. compared the efficacy of N-acetylcysteine plus hydration with N-acetylcysteine plus hydration and intravenous theophylline in patients with at least moderate risk for CIN. Authors found decreased serum creatinine and increase eGFR at 72 h after contrast administration with combination therapy that shows additional benefits of intravenous theophylline in preventing CIN when added to N-acetylcysteine.[15] These studies, as well as ours, suggest the superior efficacy of theophylline over N-acetylcysteine, which can also justify the beneficial effects of theophylline when added to N-acetylcysteine in preventing CIN. However, adding N-acetylcysteine to theophylline does not seem to increase the efficacy of theophylline.

While most of the previous trials, as well as meta-analyses, have supported the preventive efficacy of theophylline,[7,8,11] there is controversy on

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the efficacy of N-acetylcysteine in the prevention of CIN. Recent meta-analyses focusing on more qualified studies do not support the efficacy of N-acetylcysteine to prevent CIN.[12,19] Also, a recent large randomized trial on N-acetylcysteine which included about 2308 patients (1400 patients with diabetes mellitus) undergoing coronary and peripheral vascular angiography found no significant benefit for N-acetylcysteine in preventing CIN in all[20] or in diabetic patients.[21] According to the recent mete-analyses and large trials, it seems that N-acetylcysteine is not highly effective in preventing CIN. Therefore, as we also found in our study, N-acetylcysteine has no additional effects in combination therapy with theophylline.

Our study has some limitations. First, the trial was a single-center study, which may reduce its generalizability. Second, our study sample size was small, and we were not able to show statistical significant effects of the medications in terms of CIN incidence that is a clinical important outcome. Post-hoc power calculation showed that to achieve a study power of 0.8 we required at least 59 cases in each group. Finally, we monitored our patients for 48 h. Longer follow-ups can provide more information on the efficacy of preventive measures.

Conclusion

The results of this study showed that, in patients undergoing coronary angiography (with or without angioplasty) with at least moderate risk for CIN, theophylline is superior to N-acetylcysteine in preventing contrast-induced renal dysfunction, in terms of less increase in serum creatinine level after contrast material injection. Also, we found that the combination of theophylline plus N-acetylcysteine is superior to N-acetylcysteine alone but not theophylline alone in this regard. These results should be interpreted cautiously considering the study limitations. Further trials including larger sample of patients and longer follow-ups are warranted in this regard.

Acknowledgments

This study was supported by the Isfahan University of Medical Sciences (grant 392300). We are thankful for the Chamran Hospital Angiography Unit staff for helping us in data gathering and Dr. Ali Gholamrezaei for conducting data analyses and editing this report.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Arabmomeni M, Najafian J, Abdar Esfahani M, Samadi M, Mirbagher L. **Comparison between theophylline, N-acetylcysteine, and theophylline plus N-acetylcysteine for the prevention of contrast-induced nephropathy.** ARYA Atheroscler 2013; 11(1): 43-9.

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