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• CLINICAL RESEARCH •

Therapeutic efficacy of high-dose vitamin C on acute pancreatitis and its potential mechanisms

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Abstract

AIM: To observe the therapeutic efficacy of high-dose Vitamin C (Vit. C) on acute pancreatitis (AP), and to explore its potential mechanisms.

METHODS: Eghty-four AP patients were divided into treatment group and control group, 40 healthy subjects were taken as a normal group. In the treatment group, Vit. C (10 g/day) was given intravenously for 5 days, whereas in the control group, Vit. C (1 g/day) was given intravenously for 5 days. Symptoms, physical signs, duration of hospitalization, complications and mortality rate were monitored. Meanwhile, serum amylase, urine amylase and leukocyte counts were also determined. The concentration of plasma vitamin C (P-VC), plasma lipid peroxide (P-LPO), plasma vitamin E (P-VE), plasma β-carotene (P-β-CAR), whole blood glutathione (WB-GSH) and the activity of erythrocyte surperoxide dimutase (E-SOD) and erythrocyte catalase (E-CAT) as well as T lymphocyte phenotype were measured by spectrophotometry in the normal group and before and after treatment with Vit. C in the treatment and the control group.

RESULTS: Compared with the normal group, the average values of P-VC, P-VE, P-β-CAR, WB-GSH and the activity of E-SOD and E-CAT in AP patients were significantly decreased and the average value of P-LPO was significantly increased, especially in severe acute pancreatitis (SAP) patients (P <0.05. P-VC, P =0.045; P-VE, P =0.038; P =0.041; P-β-CAR, P =0.046; WB-GSH, P =0.039; E-SOD, P =0.019; E-CAT, P =0.020; P-LPO, P =0.038). Compared with the normal group, CD_3 and CD_4 positive cells in AP patients were significantly decreased. The ratio of CD_4/CD_8 and CD_4 positive cells were decreased, especially in SAP patients (P<0.05. CD_4/CD_8, P =0.041; CD_4, P =0.019). Fever and vomiting disappeared, and leukocyte counts and amylase in urine and blood become normal quicker in the treatment group than in the control group. Moreover, patients in treatment group also had a higher cure rate, a lower complication rate and a shorter in-ward days compared with those in he control group. After treatment, the average value of P-VC was significantly higher and the values of SIL-2R, TNF-α, IL-6 and IL-8 were significantly lower in the treatment group than in the control group (P<0.05 P-VC, P =0.045; SIL-2R, P =0.012; TNF-α, P =0.030; IL-6, P =0.015; and IL-8, P =0.043). In addition, the ratio of CD_4/CD_8 and CD4 positive cells in the patients of treatment group were significantly higher than that of the control group after treatment (P<0.05. CD_4/CD_8, P =0.039; CD_4, P =0.024).

CONCLUSION: High-dose vitamin C has therapeutic efficacy on acute pancreatitis. The potential mechanisms include promotion of anti-oxidizing ability of AP patients, blocking of lipid peroxidation in the plasma and improvement of cellular immune function.

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INTRODUCTION

In the occurrence and progress of acute pancreatitis (AP), system inflammatory response syndrome (SIRS) often appears as a complication, and may result in pyemia and multiple organ dysfunction (MODS), and death may be the last consequence[1,2]. Many investigations have made it clear that over-activation of leucocytes and their cytokines, the imbalance between release and clearance of free radicals and other pathophysiological changes play important roles in this progress[3-5]. The prognosis of AP patients has a close correlation with infection and pyemia, whereas the occurrence and progress of infection and pyemia also have a correlation with the changes of host immune function[6]. It has been confirmed that vitamin C is an important antioxidant which protects the body from damage of inflammation[7,8], and high-dose vitamin C can improve the immune function[9]. In the present, randomized control study, we observed the clinical efficacy on a high-dose of vitamin C (10 g/day, intravenously) on AP and also monitored its influence on plasma vitamin C (P-VC), plasma lipid peroxide (P-LPO) and other biochemical and immunological markers in order to explore its underlying mechanisms.

MATERIALS AND METHODS

Patients

Based on the AP diagnostic criteria worked out by the Pancreatic Surgery Subgroup of Chinese Medical Association, we selected 84 cases of AP patients. They included 53 males and 31 females, and were aged from 25 to 71 (mean ± SD, 42±13) years. Patients with serious diseases in main visceral organs such as the heart, brain, liver and kidney, peptic ulcer disease, diabetes mellitus, auto-immune diseases ,and tumors were excluded. According to the classification criteria (2nd edition 1996), 70 patients were mild AP (MAP) cases, 14 patients were severe (SAP) cases. Forty healthy volunteers (male 26, female 14, age 28-66 (47±14) years old) were included in the study as a normal group. There was no

significant difference in age and gender between AP patients and healthy volunteers (P>0.05).

Methods

Treatment regimen the routine therapy was used in both treatment and control groups, which consisted of pancreatic excretion inhibition, anti-spasm, analgesia, maintenance of the water-electrolyte balance, prevention and cure of infection and other complications, and if necessary, fasting and gastrointestinal decompression. The patients were randomly divided into two groups. In the treatment group (n=40), vitamin C (10 g/day) was given intravenously for 5 days, while in the control group (n=44), vitamin C (1 g/day) was given intravenously for 5 days. There was no significant difference in age (40±12 *vs*. 43±14 years old), gender (M/F, 25/15 *vs*. 28/16) and disease severity (MAP/SAP, 33/7 *vs*. 37/7) between the treatment and control groups (all P>0.05).

Detection of clinical, biochemical and immunological markers Symptoms such as abdominal pain, fever, vomiting, and hospitalization duration were monitored. Serum amylase, urine amylase, leukocyte counts, concentrations of plasma vitamin c (P-VC), plasma lipid peroxide (P-LPO), plasma vitamin E (P-VE), plasma β-carotene (P-β-CAR), whole blood glutathione (WB-GSH) and the activity of erythrocyte surperoxide dimutase (E-SOD), erythrocyte catalase (E-CAT), serum interleukin-2 receptor (SIL-2R), tumor necrosis factor-alpha (TNF-α), IL-6, IL-8 and complement reaction protein (CRP), as well as T lymphocyte phenotypes CD_3, CD_4, and CD_8 were measured. P-VC and P-VE (μmol/L) were measured by spectrometry using ferrocyanide. P-LPO (μmol/L) was measured by spectrometry using sulfbarbitone. P-β-CAR (μmol/L) was measured with alcohol-petroleum ether spectrometer. WB-GSH (mmol/L) was measured by spectrometry using disulfhydry-dinitrobenzoic acid. E-SOD (U/g*Hb) was measured by spectrometry using pyrocatechol. E-CAT (K/g*Hb) was measured by spectrometryusing oxydol-acetic diachromic acid potassium. SIL-2R, TNF-α, IL-6 and IL-8 (pmol/L) were measured by enzyme-linked immunosorbent assays (ELISA). All reagents were supplied by the Roche Company (Swiss). CRP (mg/L) was measured by the quick immune extinction spectrometry. T-lymphocytephenotypes (%) were determined by spectrometry using anti-AKP monoclonal antibody AKP.

Clinically, cure of the disease was defined if symptoms such as abdominal pain, vomiting and fever disappeared, serum amylase, urine amylase and leukocyte counts returned to normal, and imaging examinations showed no abnormality. Improvement of the disease was defined if symptoms relieved or disappeared, and laboratory examinations showed almost normal results. The disease was defined to be unchanged if symptoms, physical signs and laboratory examinations had remained unchanged since hospitalization, and to be deteriorated if patient' s condition was getting worse, with occurrence of severe complications and death.

Statistics analysis

All the data were expressed as mean ± SD, when appropriate. SPSS 10.0 statistical package was used for statistical analysis. T-test and χ^2-test were used for the analysis, and P<0.05 was regarded as statistically significant.

RESULTS

Comparison of the results between patients and healthy volunteers

As shown in tables 1, 2 and 3, the serum levels of SIL-2R, TNF-α, IL-6, IL-8 and CRP in AP patients were much higher than those in healthy volunteers (P<0.05 or P<0.01). The average contents of P-VC, P-VE, P-β-CAR, WB-GSH, E-SOD and E-CAT were significantly lower, while the level of P-LPO was significantly higher in patients than in healthy volunteers. More importantly, all the above variables were higher in SAP patients than in MAP patients (P<0.05). The percentage of CD_3 and CD_4 positive cells in AP cases was significantly lower in AP patients compared to the healthy group (both P<0.05), CD_4 and the ratio of CD_4/CD_8 were much lower in SAP patients than in healthy group (both P<0.05).

Table 1 Comparison of cytokines between patients and healthy volunteers

	Patients (n=84)	Healthy volunteers (n=40)	P
SIL-2R (pmol/L)	213.42±54.68	72.34±23.17	<0.01
TNF-α (pmol/L)	3.67±1.01	0.58±0.15	<0.01
IL-6 (pmol/L)	92.43±25.67	29.57±11.64	<0.01
IL-8 (pmol/L)	267.58±121.88	60.49±25.35	<0.01
CRP (mg/L)	18.30±7.35	8.34±4.17	<0.01

Table 2 Comparison of oxidation and anti-oxidation levels between patients and healthy volunteers

	Patients (n=84)		Healthy volunteers (n=40)
	MAP (n=70)	SAP (n=14)	
P-VC(μmol/L)	32.56±6.73	43.51±2.15	55.12±13.24
P-VE(μmol/L)	19.21±1.75	13.26±3.14	24.01±5.28
P-LPO(μmol/L)	12.95±3.91	15.41±2.15	11.21±2.76
P-β-CAR(μmol/L)	1.38±0.25	0.94±0.11	1.61±0.23
WB-GSH(mmol/L)	1.08±0.27	0.70±0.33	1.21±0.21
E-SOD(U/g*Hb)	1 804.42±100.14	1 495.27±152.87	2 084.39±191.53
E-CAT(K/g*Hb)	221.54±20.47	174.76±34.56	280.42±77.26

Comparison between patients and healthy volunteers and between mild acute panceatitis (MAP) and severe acute panceatitis (SAP), all P<0.05.

Table 3 Comparison of cellular immunity between patients and healthy volunteers ($\bar{x}$±s)

	MAP (n=70)	SAP (n=14)	Healthy group (n=40)
CD_3(%)	46.73±10.15	45.23±12.24[a]	57.65±10.28
CD_4(%)	34.27±9.52[a]	23.65±7.53[ab]	43.23±7.65
CD_8(%)	22.32±7.29	27.18±4.56	26.18±4.79
CD_4/CD_8	1.84±0.78	0.80±0.67[ab]	2.13±0.66

[a]P<0.05 *vs* healthy volunteers, [b]P<0.05 *vs* MAP.

Table 4 Comparison of clinical symptoms and laboratory examinations between treatment and control groups ($\bar{x}$±s, h)

	Treatment group (n=40)	Control group (n=44)	P
Disappearance of fever	65.75±14.26	89.71±16.25	<0.05
Release of abdominal pain	23.43±5.66	25.31±6.37	>0.05
Disappearance of abdominal pain	55.23±10.08	54.23±11.73	>0.05
Disappearance of vomiting	43.19±12.65	51.67±10.93	<0.05
Normalization of serum amylase	79.14±19.64	91.45±10.45	<0.05
Normalization of urine amylase	100.22±19.22	122.38±13.56	<0.05
Normalization of leucocyte counts	69.59±15.41	81.34±14.05	<0.05

Table 5 Comparison of clinical efficacy between treatment and control groups (day, %)

	Case	Cure	Improvement	No change	Deterioration	Hospitalization
Treatment group	40	30 (75.00)	4(10.00)	4 (10.00)	2 (5.00)	9.34±4.24
Control group	44	18 (40.91)	10(22.73)	6 (13.64)	6 (13.64)	13.45±3.21
P		<0.05	<0.05	<0.05	<0.05	<0.05

Table 6 Comparison of cytokines between treatment and control groups before and after therapy ($\bar{x}\pm s$)

	Treatment group (*n*=40)		Control group (*n*=44)	
	Before therapy	After therapy	Before therapy	After therapy
SIL-2R (pmol/L)	221.67±87.30	118.37±43.68[a]	196.52±63.28	178.84±30.56
TNF-α (pmol/L)	3.65±1.25	1.52±0.78[b]	3.99±1.34	2.46±1.04
IL-6 (pmol/L)	95.58±18.64	39.53±10.36[b]	89.22±12.03	59.83±9.48
IL-8 (pmol/L)	273.49±88.50	127.35±49.86[a]	261.47±64.97	198.31±28.50
CRP (mg/L)	19.19±9.37	8.70±4.65	17.56±5.62	9.42±5.84

Before therapy: $P>0.05$ for each index in the two group. After therapy: [a]$P<0.05$, [b]$P<0.01$ *vs* treatment and control groups.

Table 7 Comparison of oxidation and anti-oxidation between treatment and control groups before and after therapy

	Treatment group (*n*=40)		Control group (*n*=44)	
	Before therapy	After therapy	Before therapy	After therapy
P-VC(μmol/L)	41.54±2.91	53.25±10.11[a]	41.78±1.96	45.21±9.25[1)]
P-VE(μmol/L)	18.47±3.45	19.97±4.26[b]	18.67±2.13	19.24±2.46[2)]
P-LPO(μmol/L)	13.53±2.12	11.54±1.45[a]	13.68±2.31	12.98±2.75[1)]
P-β-CAR(μmol/L)	1.25±0.17	1.37±0.71[b]	1.28±0.21	1.34±0.65[2)]
WB-GSH(mmol/L)	0.97±0.18	1.39±0.41[a]	0.98±0.21	1.04±0.35[1)]
E-SOD(U/g*Hb)	1 749.01±50.55	1 997.42±145.33[1)]	1 726.28±71.37	1 807.22±120.21[1)]
E-CAT(K/g*Hb)	217.34±19.51	269.52±65.32[1)]	220.18±20.14	239.17±70.15[1)]

Before therapy: each index in the two group, $P>0.05$. After therapy: [a]$P<0.05$, [b]$P<0.01$ *vs* treatment and control groups.

Comparison of results between treatment and control groups

As shown in in tables 4 and 5, except for abdominal pain, all symptoms disappeared and serum and urine amylase normalized at a much faster speed in the treatment group than in control group (all $P<0.05$). The treatment group had a higher cure rate and lower deterioration rate than the control group 5 days after therapy (both $P<0.05$).

Comparison of cytokines between treatment and control groups before and after therapy

There was no significant difference in the levels of SIL-2R, TNF-α, IL-6, IL-8 and CRP between the two groups before treatment (all $P>0.05$) (Table 6). However, the levels of cytokines decreased significantly 5 days after therapy in both groups ($P<0.05$), although they were still higher compared with the healthy group. The contents of SIL-2R, TNF-α, IL-6 and IL-8 were significantly lower in the treatment group than in the control group (all $P<0.05$) 5 days after therapy. The CRP level was lower compared with the control group, but the difference was not statistically significant ($P>0.05$, Table 6).

Comparison of oxidation and anti-oxidation levels between treatment and control groups before and after therapy

No notable difference in levels of P-VC, P-VE, P-LPO, P-β-CAR, WB-GSH, E-SOD and E-CAT was observed between the two groups ($P>0.05$) before treatment (Table 7). The average concentration of P-VC, WB-GSH, E-SOD and E-CAT was elevated significantly and P-LPO level was decreased in treatment group 5 days after therapy compared with the control group (all $P<0.05$, Table 7). The contents of P-VE and P-β-CAR had no remarkable difference between the two groups ($P>0.05$).

Comparison of cellular immunity between MAP cases in treatment and control groups before and after therapy

There was no significant difference in CD_3, CD_4 CD_8 and the ratio of CD_4/CD_8 between the MAP patients in the two groups before treatment (Table 8). The mean count of CD_3 and CD_4 and the ratio of CD_4/CD_8 were higher 5 days after treatment than those before treatment in both groups (all $P<0.05$). As far as the comparison of the CD_3 and CD_4 positive cells and the ratio of CD_4/ CD_8 between these two group was concerned, the levels in the former group were slightly higher than that in the latter group ($P>0.05$, Table 8).

Table 8 Immunity change before and after therapy in MAP cases of two groups ($\bar{x}\pm s$)

	Treatment group (*n*=33)		Control group (*n*=37)	
	Before therapy	After therapy	Before therapy	After therapy
CD_3(%)	45.99±9.75	52.34±6.87	47.48±10.35	50.18±7.10
CD_4(%)	36.43±8.56	38.79±7.65	36.01±9.47	37.25±6.92
CD_8(%)	21.98±6.85	20.46±3.53	22.45±7.11	21.33±4.88
CD_4/CD_8	1.88±0.64	1.97±0.74	1.75±0.76	1.85±0.43

Before therapy: $P>0.05$ *vs* the two groups. After therapy: $P>0.05$ *vs* the two groups.

Comparison of cellular immunity between SAP cases treatment and control groups before and after therapy

There was no significant difference in CD_3, CD_4 CD_8 and the ratio of CD_4/CD_8 between the MAP patients in the two groups before treatment (Table 9). The mean count of CD_3 and CD_4 and the ratio of CD_4/CD_8 were higher 5 days after treatment than those before treatment in both groups (all $P<0.05$).

Moreover, the CD_3 and CD_4 positive cells and the ratio of CD_4/CD_8 were remarkably higher in the treatment group than in the control group (all $P<0.05$).

Table 9 Immunity changes in SAP cases of two groups before and after therapy ($\bar{x}\pm s$)

	Treatment group (n=7)		Control group (n=7)	
	Before therapy	After therapy	Before therapy	After therapy
P-VC(μmol/L)	31.93±7.21	49.27±10.12[a]	32.89±2.17	38.17±9.41[a]
CD_3(%)	45.65±11.18	51.39±7.17	44.90±10.47	47.45±10.72
CD_4(%)	22.48±6.35	36.93±8.51[a]	23.85±7.52	25.67±7.57[a]
CD_8(%)	23.32±6.43	23.64±5.50	26.84±5.92	22.58±6.74
CD_4/CD_8	0.85±0.23	1.41±0.47[a]	0.86±0.45	1.17±0.52[a]

Before therapy: $P>0.05$ *vs* the two groups. After therapy: [a]$P<0.05$ *vs* the two groups.

DISCUSSION

Many free radicals are produced in body metabolic procedure. It is estimated that oxygen-derived free radicals account for 95 %. They are cleaned by antioxidants and antioxidases rapidly, and thus the production and clearance keep a homeostasis in normal conditions. Free radicals could exert physiological functions to some degree, such as taking part in biosynthesis, detoxification and microorganism clearance[10,11]. However, overdose free radicals could lead to tissue and cell injuries in pathologic conditions through different approaches[12]: (1) Free radicals attacked bio-membrane, which led to unsaturated fatty acid lipid peroxidation (LPO) and affected the function of membrane of cells and cell organelle. (2) Free radicals might destroy the major enzymes and other molecules, making them lose their functions. (3) Free radicals might disturb the synthesis and replication of DNA. (4) LPO could produce more toxic substances and free radicals. Usually the free radicals produced in metabolism can be cleared by the defence system of anti-oxidation. This system is mainly composed of anti-oxidases and antioxidants. These materials catch and clear the excessive free radicals, prevent the chain reaction of a serial of free radicals from pathologic acceleration and keep the homeostasis of antioxidation from imbalance. Vit. C, Vit. E and β-CAR were the most important anti-oxidases and antioxidants, and played an important role in anti-infection[7-9].

The occurrence and development of acute pancreatitis were related to the disturbance in release and clearance of free radicals, which resulted in the imbalance between oxidation and anti-oxidation[13]. Many studies have indicated that excessive free radicals could lead to tissue and cellular injury in pathological conditions[11]. Free radicals took part in the edema of AP, and probably in the necrosis process[13]. When AP happened, vitamin C was depleted at first by reacting with superoxide, anion hydroperoxide anion and hydroxylperoxide anion, and then by forming vitamin C free radicals to prevent DNA and membrane lipid from damage[14]. The concentration of vitamin C in AP cases decreased to various extents[15], reached the lowest level in the first 1-5 days of the disease course, and the vitamin C level correlated with the severity of the disease[16]. The output of free radicals was increased, and peroxidation reaction was reinforced, therefore a large amount of vitamin C, vitamin E, β-CAR, WB-GSH, E-SOD and E-CAT were depleted so that they could hardly prevent pancreas and other organs from damage caused by lipid peroxidation. Furthermore, the elevation of cytokines is a frequent phenomenon and the extention was closely associated with the severity of AP[17]. The reason why MAP developed into SAP was a chain and amplification reaction (so-called waterfall effect) of inflammatory agents that led to SIRS and MODS[18]. Therefore, the serum levels of cytokines SIL-2R, TNF-α, IL-6, IL-8 and CRP could be regarded as the biomarkers of therapeutic efficacy[19].

Recent studies have shown that the prognosis of AP is closely associated with infection and pyemia. At the same time, the occurrence, development and conversion of infection and pyemia were intimately associated with the changes of immune function[20,21]. Because histamine, bradykinin and many other cytokines produced in AP progression could inhibit the immune function in AP cases, especially in those with SAP, the injuries of immune function took place. Theses injuries included decreased proliferation of T cells, especially Th cells, decreased IL-2 level, reduced monocytes in peripheral blood and increased prostaglandin E2 from monocytes[22-24]. Our study indicated that cellular immune function damage took place in AP patients. The percentage of CD_3 and CD_4 positive lymphocytes was higher in treatment group than in control group after treatment, while that of CD_4 positive lymphocytes and the ratio of CD_4/CD_8 were lower in SAP than in MAP[25]. CD_4 positive T-lymphocytes could excrete IL-2, which stimulated the silent T-lymphocytes to express IL-2 receptor, and thus IL-2 conjugated its receptor, leading to a series of immune reactions and increased DNA synthesis[26]. Therefore, the decrease of CD_4 positive T-lymphocytes certainly influenced the body immune function and resistibility, and the susceptibility to infection increase[27].

We found that the average concentration of P-VC, P-VE, β-CAR, WB-GSH, E-SOD and E-CAT was significantly lower while P-LPO level was significantly higher in AP patients than in healthy volunteers. All these indicate that free radical reaction and lipid peroxidation, and disturbance can speed up free radical elimination and anti-oxidation. We also found that high-dose of vitamin C at early stage could contribute to the improvement of the levels of P-VC, P-VE, WB-GSH, E-SOD and E-CAT, which took part in eliminating injurious free radicals and protecting cells from damage by the free radicals. Simultaneously, the P-LPO level was lower in treatment group than in control group, further confirming the preventive effect of high-dose vitamin C against lipid peroxidation. It was also revealed that there was no significant difference in CD4/CD8 ratio between the MAP patients and the control group. The possible reason is that the immune system of MAP cases has not been seriously impaired, so that the immune adjusting mechanism is able to adjust the CD_8 cells to keep the CD_4/CD_8 ratio at a normal level. However, in SAP patients this mechanism was seriously impaired and could no longer keep the CD_4/CD_8 ratio. Vitamin C could improve the immune function by increasing CD_3, CD_4 and the CD_4/CD_8 ratio, and decreasing CD_8[28], elevating transformation efficiency of lymphocytes, stimulating the production of IL-1, IL-2, IL-6 and other cytokines, and reinforcing cell-mediated immune reaction parameters[29]. In the present study, the percentage of CD4 positive lymphocytes and CD_4/CD_8 ratio in SAP cases were much lower compared with the healthy volunteers, but these indices were significantly higher than those of control group after high-dose vitamin C application. These findings indicate that severe cellular immune defection exists in SAP cases. However, high-dose vitamin C can not only eliminate free radicals and reduce the damage of lipid peroxidation, but also improve the cellular immune function in SAP patients, and thus is useful in reducing the incidence and mortality of pyemia and MODS. SIL-2R, TNF-α, IL-6, IL-8 and CRP concentrations in AP patients were significantly higher than those in healthy volunteers. However, SIL-2R, TNF-α, IL-6 and IL-8 levels decreased significantly after high-dose of vitamin C application, and were significantly lower than those in the control group. It took a shorter time to cure or improve

the clinical symptoms (fever, abdominal pain and vomiting) and to normalize serum amylase, urine amylase and leukocyte counts in patients taking high dose of vitamin C, compared with those taking low dose of vitamin C. Thus, the therapeutic efficacy of high dose of vitamin C was much better than that of low dose of vitamin C. Therefore, we conclude that high-dose vitamin C has therapeutic efficacy on acute pancreatitis. The potential mechanisms include promotion of anti-oxidizing ability of AP patients, blocking of lipid peroxidation in the plasma, and improvement of cellular immune function.

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