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RAPID COMMUNICATION

Optimal injection volume of epinephrine for endoscopic treatment of peptic ulcer bleeding

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Abstract

AIM: To define the optimal injection volume of epinephrine with high efficacy for hemostasis and low complication rate in patients with actively bleeding ulcers.

METHODS: This prospective, randomized, comparative trial was conducted in a medical center. A total of 228 patients with actively bleeding ulcers (spurting or oozing) were randomly assigned to three groups with 20, 30 and 40 mL endoscopic injections of an 1:10 000 solution of epinephrine. The hemostatic effects and clinical outcomes were compared between the three groups.

RESULTS: There were no significant differences in all background variables between the three groups. Initial hemostasis was achieved in 97.4%, 98.7% and 100% of patients respectively in the 20, 30 and 40 mL epinephrine groups. There were no significant differences in the rate of initial hemostasis between the three groups. The rate of peptic ulcer perforation was significantly higher in the 40 mL epinephrine group than in the 20 and 30 mL epinephrine groups ($P < 0.05$). The rate of recurrent bleeding was significantly higher in the 20 mL epinephrine group (20.3%) than in the 30 (5.3%) and 40 mL (2.8 %) epinephrine groups ($P < 0.01$). There were no significant differences in the rates of surgical intervention, the amount of transfusion requirements, the days of hospitalization, the deaths from bleeding and 30 d mortality between the three groups. The number of patients who developed epigastric pain due to endoscopic injection, was significantly higher in the 40 mL epinephrine group (51/76) than in the 20 (2/76) and 30 mL (5/76) epinephrine groups ($P < 0.001$). Significant elevation of systolic blood pressure after endoscopic injection was observed in the 40 mL epinephrine group ($P < 0.01$). Significant decreasing and normalization of pulse rates after endoscopic injections were observed in the 20 mL and 30 mL epinephrine groups ($P < 0.01$).

CONCLUSION: Injection of 30 mL diluted epinephrine (1:10 000) can effectively prevent recurrent bleeding with a low rate of complications. The optimal injection volume of epinephrine for endoscopic treatment of an actively bleeding ulcer (spurting or oozing) is 30 mL.

Key words: Endoscopic injection; Epinephrine; Volume; Peptic ulcer bleeding

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INTRODUCTION

Endoscopic injection of epinephrine is considered a highly effective and simple hemostatic technique for non-variceal upper gastrointestinal (GI) bleeding[1-3]. Although the rate of initial hemostasis is high, rebleeding occurs in 6% - 36% of patients[4-7]. Rebleeding after initial endoscopic hemostasis remains an important determinant of poor prognosis in patients with hemorrhaging ulcers[8, 9]. The wide variation in rates of recurrent bleeding may result from the different volumes (2-30 mL) of epinephrine injected to achieve hemostasis in various studies[4-7]. Clinical trials in patients with bleeding ulcers disclosed that injection of normal saline solution[10] or distilled water[11] is as effective as absolute alcohol[10] or an epinephrine[11] solution for endoscopic therapy. These findings suggest that tamponade plays a primary role in hemostasis with endoscopic injection therapy, and that injection of larger volumes of epinephrine may be beneficial for preventing recurrent bleeding by prolonging the hemostatic effect of local compression. Lin *et al*[12] found that injection of a large volume (13-20 mL) of 1:1 0000 solution of epinephrine can reduce the rate of recurrent bleeding in patients with high-risk peptic ulcers and is superior to an injection of lesser volumes (5-10 mL) of epinephrine (15.4% *vs* 30.8%). Park *et al*[13] also reported that injection of 35-45 mL of an 1:10 000 solution of epinephrine is more effective in preventing recurrent bleeding from ulcers in the gastric body than injection of 15-25 mL of the same solution (0% *vs* 17.1%). However,

what is the "optimal injection volume" of epinephrine for the prevention of recurrent bleeding is not clear. The aim of our study was to define the optimal injection volume of epinephrine with high efficacy for hemostasis and low complication rate in patients with actively bleeding ulcers.

MATERIALS AND METHODS

Patients

This prospective, randomized, comparative trial was conducted in a medical center. Patients with active bleeding ulcers between January 2003 and June 2005 were admitted to our hospital. Emergency endoscopies were performed in the first day of admission, patients were enrolled in this study if the endoscopy revealed an ulcer with active bleeding defined by the Forrest classification[14] as stage Ia (spurting bleeding) or stage Ib (oozing). Patients were excluded if they were under 18 years of age, pregnant, unable or unwilling to give written informed consent, on anticoagulation therapy, or had a bleeding tendency (platelet count < 20 000/mm^3, prothrombin time >2.0 by international normalized ratio [INR], and activated partial thromboplastin time > 60 s), bleeding gastric malignancy and multiple potential sources of bleeding. Possible complications of endoscopic treatment were discussed with patients and their relatives, and written informed consent was obtained before entry into the trial. The protocol was approved by the Clinical Research Committee of our hospital. Clinical characteristics, including age, gender, use of non-steroidal anti-inflammatory drugs (NSAID), blood pressure, pulse rate, comorbid diseases, coagulopathy (platelet count 20 000/mm^3-50 000/mm^3, prothrombin time 1.3-2.0 by INR), and Hb level were recorded. Shock was defined as systolic pressure less than 100 mmHg and pulse rate greater than 100 beats/min accompanying cold skin, sweating, pallor, and oliguria. Endoscopic characteristics, including type of stigma, ulcer size and location were recorded. One biopsy was obtained from the gastric antrum and one from the gastric body after cessation of bleeding. The presence of *helicobacter pylori* infection was assessed with a rapid urease test.

Methods

Patients were randomly assigned to three groups with 20, 30 and 40 mL endoscopic injections of an 1:10 000 solution of epinephrine. Randomization was performed by using a computer-generated randomization list and sealed envelopes. A single experienced senior gastroenterologist performed all endoscopic hemostatic treatments. The post-procedure care of the patients was conducted by other physicians. A commercially available endoscope (GIF-XQ240, Olympus Optical Co., Ltd., Tokyo, Japan) and a 4 mm, 23 G injector needle (NM-8L, Olympus) were used. An 1:10 000 solution of epinephrine was injected around the bleeding site (2 mL/injection at 2 mm-3 mm from the point of bleeding) until a total volume of 20, 30 and 40 mL respectively in three groups. Initial hemostasis was defined as endoscopically verified cessation of bleeding for at least 5 min. Pain in the epigastric area that developed during endoscopic injection and lasted for more than one hour after the injection was considered to be induced by the epinephrine injection. Patients who complained of epigastric pain due to endoscopic injection were recorded. Throughout the period of endoscopic injection, electrocardiographic monitoring and pulse oximeter monitoring were used to detect arrhythmia and signs of ischemia or hypoxemia. Patients who continued bleeding, despite an injection of the total volume of epinephrine, underwent additional endoscopic treatment with heater probe thermocoagulation, and were then given emergent surgery if they failed to achieve successful hemostasis. After initial endoscopic hemostasis, all patients received acid suppressive therapy with 40 mg omeprazole, intravenously every 12 h for 3 d, then orally (20 mg/d) for 2 mo. If *Helicobacter pylori* infection was confirmed by the rapid urease test, the patient was treated for 1 wk with a triple drug regimen (omeprazole, amoxicillin and clarithromycin) as soon as possible. Recurrent bleeding was defined as a subsequent ulcer bleeding that occurred after the initial bleeding stopped. "Rebleeding" was suspected if one or more signs of ongoing bleeding were found, including fresh hematemesis, melena or bloody stools, aspiration of fresh blood via nasogastric tube, unstable vital signs, and a reduction of Hb by more than 20 g/L within 24 h after initial hemostasis. Patients with rebleeding were confirmed by endoscopy and treated with a second therapeutic endoscopy (epinephrine injection plus heater probe thermocoagulation), and then underwent surgery if they failed to achieve successful hemostasis. The end points of this study were (a) endoscopic therapy failure, i.e., a combination of persistent bleeding and recurrent bleeding during follow-up or (b) death of the patient.

Statistical analysis

Unless otherwise indicated, values were expressed as mean ± SD. The Student *t* test was used to compare the mean values of continuous variables. The chi-square test with Yates correction for continuity and the Fisher's exact test were used when appropriate to compare the categorical variables. Clinical, laboratory and endoscopic parameters were analysed. All statistical analyses were performed using SPSS statistical package (version 11.0) on a personal computer. A p value less than 0.05 was considered statistically significant. Any frequency of death was considered as an adverse outcome. Therefore, if a death occurred, the cause was determined. If death was due to recurrent bleeding, a decision of whether to stop the study early was made. Clinical outcomes compared between the three groups were initial hemostatic rate, recurrent bleeding rate, perforated peptic ulcer, need for emergency operation, transfusion requirements, bleeding-related deaths, 30-day mortality, and admission duration.

RESULTS

A total of 284 patients with actively bleeding ulcers (spurting or oozing) were enrolled in the study. Of these, 56 were excluded because of the absence of informed consent, bleeding tendency, gastric malignancy, or multiple potential bleeding sources at endoscopy. There were 228 patients who were included in the study, 76 in each group. Clinical and endoscopic data obtained for patients at study

Table 1 Clinical and endoscopic variables of patients at study entry (n = 76, mean ± SD)

	Epinephrine (20 mL) n (%)	Epinephrine (30 mL) n (%)	Epinephrine (40 mL) n (%)
Age (yr)	61.5 ± 12.8	60.2 ± 13.3	62.3 ± 12.5
Gender (M/F)	56/20	53/23	55/21
NSAID ingestion	26 (34.2)	24 (31.6)	27 (35.5)
Shock	20 (26.3)	23 (30.3)	21 (27.6)
Comorbid illness	43 (56.6)	41 (53.9)	45 (59.2)
Hb level (g/dL)	7.2 ± 2.8	7.5 ± 2.6	7.6 ± 2.7
Coagulopathy	12 (15.8)	10 (13.2)	13 (17.1)
Positive *H pylori*	44 (57.9)	43 (56.6)	47 (61.8)
Forrest class			
Ia	18 (23.7)	20 (26.3)	19 (25.0)
Ib	58 (76.3)	56 (73.7)	57 (75.0)
Ulcer size			
⩾2 cm	20 (26.3)	22 (28.9)	23 (30.3)
<2 cm	56 (73.7)	54 (71.1)	53 (69.7)
Location of ulcer			
Stomach	41 (53.9)	40 (52.6)	44 (57.9)
Duodenum	32 (42.1)	34 (44.7)	30 (39.5)
Stoma	3 (3.9)	2 (2.6)	2 (2.6)

NSAID: non-steroid anti-inflammatory drug. $P > 0.05$ for all variables between the three groups.

Table 2 Clinical outcomes of endoscopic injection therapy

	Epinephrine (20 mL) n (%)	Epinephrine (30 mL) n (%)	Epinephrine (40 mL) n (%)
Initial hemostasis	74 (97.4)	75 (98.7)	76 (100)
Recurrent bleeding	15/74 (20.3)[b]	4/75 (5.3)	2/72 (2.8)
Perforated peptic ulcer	0 (0)	0 (0)	4 (5.3)[a]
Surgical intervention	4 (5.3)	2 (2.6)	5 (6.6)
Transfusion requirement (units)	4.7 ± 3.4	4.5 ± 3.2	4.2 ± 3.6
Total hospital stay (days)	10.8 ± 3.3	9.7 ± 3.5	10.2 ± 3.1
Deaths from bleeding	0 (0)	0 (0)	0 (0)
30-d mortality	3 (3.9)	2 (2.6)	4 (5.3)
No. of patients that felt pain'	2 (2.6)	5 (6.6)	51 (67.1)[d]

[a]$P < 0.05$ *vs* the 20 mL and 30 mL epinephrine groups; [b]$P < 0.01$ *vs* the 30 mL and 40 mL epinephrine groups; [d]$P < 0.001$ *vs* the 20 mL and 30 mL epinephrine groups;' Epigastric pain induced by endoscopic injection of epinephrine.

entry are outlined in Table 1. There were no significant differences in age, gender, NSAID ingestion, shock, comorbid diseases, Hb level, coagulopathy, positive H pylori status, bleeding stigma, ulcer size or ulcer location between the three groups. The 3 groups were well matched for factors that could potentially affect outcomes (Table 1).

Initial hemostasis was achieved in 74 of 76 patients (97.4%) in the 20 mL epinephrine group, 75 of 76 patients (98.7%) in the 30 mL epinephrine group and 76 of 76 patients (100%) in the 40 mL epinephrine group. There were no significant differences in the rate of initial hemostasis between the three groups (Table 2). Three patients with spurting bleeding from gastric ulcers, two in the 20 mL epinephrine group and one in the 30 mL epinephrine group, failed to achieve initial hemostasis after injection of 20 mL or 30 mL of the 1:10 000 solution of epinephrine. Bleeding was controlled in all patients by additional heater probe thermocoagulation. Four patients in the 40 mL epinephrine group developed perforation of peptic ulcers and underwent emergent operations within 24 h after endoscopic injection. The rate of peptic ulcer perforation was significantly higher in the 40 mL epinephrine group than in the 20 mL and 30 mL epinephrine groups ($P < 0.05$, Table 2). The rate of recurrent bleeding was 20.3% (15/74) in the 20 mL epinephrine group, 5.3% (4/75) in the 30 mL epinephrine group and 2.8 % (2/72) in the 40 mL epinephrine group. The rate of recurrent bleeding was significantly higher in the 20 mL epinephrine group than in the 30 and 40 mL epinephrine groups ($P < 0.01$, Table 2). Fifteen patients in the 20 mL epinephrine group had recurrent bleeding. Bleeding was controlled in 11 patients by epinephrine injection plus heater probe thermocoagulation, and in 4 by surgical intervention. Four patients in the 30 mL epinephrine group had recurrent bleeding. Bleeding was controlled in 2 patients by epinephrine injection plus heater probe thermocoagulation, and in 2 by surgical intervention. Two patients in the 40 mL epinephrine group had recurrent bleeding. Bleeding was controlled in one patient by epinephrine injection plus heater probe thermocoagulation, and in the other by surgical intervention. The rate of 30-d mortality was 3.9% (3/76), 2.6% (2/76) and 5.3% (4/76) in the 20, 30 and 40 mL epinephrine groups respectively. The causes of death included severe pneumonia with respiration failure in 3 patients, terminal lung cancer in 1 patient, advanced hepatoma with hepatic failure in 3 patients, advanced colon cancer with sepsis in 1 patient and uremia in 1 patient. There was no death due to peptic ulcer bleeding in the three groups. There were no significant differences in the rates of surgical intervention, the amount of transfusion requirements, the days of hospitalization, the deaths due to bleeding and 30-d mortality between the three groups (Table 2). The number of patients who complained of epigastric pain during the procedure of endoscopic injection, was significantly higher in the 40 mL epinephrine group (51/76) than in the 20 mL (2/76) and 30 mL (5/76) epinephrine groups ($P < 0.001$, Table 2).

There was no procedure-related cardiovascular or respiratory complication in three groups. Electrocardiographic monitoring did not record any cardiac arrhythmia, and no abrupt change occurred in oxygen saturation. However, significant elevation of systolic blood pressure after endoscopic injection was observed in the 40 mL epinephrine group ($P < 0.01$), while there were no significant changes in systolic blood pressure after endoscopic injection in the 20 and 30 mL epinephrine groups (Table 3). Significant decreasing and normalization of pulse rates after endoscopic injections were also observed in the 20 and

Table 3 Changes in systolic blood pressure and pulse before and after endoscopic injection therapy (n = 76, mean ± SD)

	Epinephrine (20 mL) n (%)	Epinephrine (30 mL) n (%)	Epinephrine (40 mL) n (%)
Pressure (mmHg)			
Before treatment	108.2 ± 31.8	109.3 ± 29.3	106.2 ± 30.7[b]
After treatment	110.3 ± 21.9	112.7 ± 22.5	129.3 ± 25.8[b]
Pulse (/min)			
Before treatment	96.5 ± 14.7[d]	98.2 ± 15.3[d]	96.7 ± 14.3
After treatment	84.8 ± 12.8[d]	86.3 ± 12.5[d]	101.4 ± 15.2

[b]$P < 0.01$ (paired t-test) in the 40 mL epinephrine group; [d]$P < 0.01$ (paired t-test) in the 20 mL and 30 mL epinephrine groups.

30 mL epinephrine groups ($P < 0.01$) as compared to the 40 mL epinephrine group (Table 3).

DISCUSSION

Peptic ulcer bleeding remains a disease with a considerable morbidity and mortality. The mortality rate is high especially for patients with spurting or oozing bleeding[2, 3, 15]. Endoscopic injection of epinephrine, which is the most widely used method, can significantly reduce rates of further bleeding in non-variceal upper GI[1-3]. Although high rates of initial hemostasis have been obtained, rebleeding occurs in 6% to 36% of patients[4-7]. The wide variation in rates of recurrent bleeding may result from the different clinical features and endoscopic findings between enrolled patients and also the different volumes (2-30 mL) of epinephrine injected to achieve hemostasis in various studies[4-7]. Some factors may be associated with the rate of recurrent bleeding in actively bleeding ulcers after endoscopic injection, including age, shock, comorbid illness, ulcer size, ulcer location and stigmata of hemorrhage[2, 9, 16], which were similar between the 3 groups in the present study, suggesting that the outcomes of endoscopic therapy are unlikely influenced by these factors.

A number of agents have been used to achieve hemostasis in endoscopic therapy. However, what is the best solution for the prevention of recurrent bleeding remains unclear. Lai *et al*[11] demonstrated that a local tamponade with distilled water is as effective as epinephrine solution (11.3 ± 4.7 mL) in endoscopic injection therapy. Lin *et al*[10] have also disclosed similar hemostatic effects of injection with normal saline solution, 3% NaCl solution, 50% glucose water, and pure alcohol. These studies suggested local tamponade is the major effect on sustained hemostasis. Although the mechanisms of hemostasis are different among various agents, clinical studies comparing various agents have demonstrated that no single solution is superior to the others[2, 10, 11]. Laine and Estrada[17] found that local tamponade with normal saline (30 ± 3 mL) solution is less effective than thermal therapy. However, Chung *et al* [18] found that epinephrine injection (1.5 to 19.5 mL) and thermocoagulation have comparable rebleeding rates, indicating that epinephrine injection is technically easier to perform and has a higher initial hemostatic rate. Although the most important mechanism underlying hemostasis in response to epinephrine solution is local tamponade, which is similar to normal saline solution, epinephrine solution offers additional hemostatic effects, including vasoconstriction and platelet aggregation[19]. In a patient with massive active bleeding, it is often difficult to achieve hemostasis with the application of contact devices or laser emergently when visualization of the bleeding site is unsatisfactory. In addition, these methods may not be available in rural hospitals. In our study, the initial hemostatic rate in the 20 mL epinephrine group (97.4%) was as high as that in the 30 mL (98.7%) and 40 mL (100%) epinephrine groups, suggesting that epinephrine solution can be used as a first-line injection solution and hemostatic method for the initial arrest of active bleeding.

Because epinephrine produces vessel compression, vasoconstriction, and platelet aggregation, but not induce vessel thrombosis, the addition of sclerosing agents such as ethanol, ethalonamie or polidocanol would be advantageous in theory. However, clinical trials have not definitively demonstrated a benefit for this combination therapy[6, 20-22]. Likewise, the addition of thrombin or fibrin sealant also dose not reduce the risk of rebleeding[23, 24]. Lin *et al* [12] found that injection of a large volume (13-20 mL) of epinephrine can reduce the rate of recurrent bleeding in patients with high-risk peptic ulcer and is superior to injection of lesser volumes (5-10 mL) of epinephrine (15.4% *vs* 30.8%). Park *et al* [13] also reported that injection of 35-45 mL of an 1:10 000 solution of epinephrine is more effective in preventing recurrent bleeding from ulcers in the gastric body than an injection of 15-25 mL of the same solution (0% *vs* 17.1%). These findings suggest that a continuous injection of larger volumes of epinephrine even after the bleeding stopped is beneficial for preventing recurrent bleeding by prolonging the hemostatic effect of local tamponade, vasoconstriction, and platelet aggregation. However, what is the optimal volume of epinephrine that can achieve permanent hemostasis still remains unknown. In our study, the rate of recurrent bleeding was significantly higher in the 20 mL epinephrine group than in the 30 mL and 40 mL epinephrine groups ($P < 0.01$), while there was no significant difference in the rate of recurrent bleeding between these two groups. The studies of Lin *et al*[12] and Park *et al*[13] enrolled peptic ulcers with spurting, oozing or non-bleeding visible vessels, and found that only 48.7% (38/78) and 52.8% (19/36) of ulcers are active bleeders (spurting or oozing) in the larger-volume injection group respectively. Because our study only enrolled patients with active bleeding (spurting or oozing), the rates of recurrent bleeding in the 30 and 40 mL epinephrine groups were higher than those reported by Park *et al*[13]. However, with a larger injection volume, the rebleeding rate in our study was lower than that reported by Lin *et al*[12] Our study disclosed that an injection of 30 mL epinephrine was an optimal volume for sustained hemostasis and equally beneficial for preventing recurrent bleeding as a 40 mL epinephrine injection.

Sung *et al*[25] found that immediately after the endoscopic injection of a small volume (3-11 mL) of 1:10 000 epinephrine solution, the plasma epinephrine level is increased by 4-5 times above the basal level. In addition, hypertensive emergency and ventricular tachycardia after epinephrine injection have been reported[26]. In our study,

significant elevation of systolic blood pressure after endoscopic injection was observed in the 40 mL epinephrine group ($P < 0.01$), while there were no significant changes in systolic blood pressure after endoscopic injection in the 20 and 30 mL epinephrine groups. Significant decreasing and normalization of pulse rates after endoscopic injections were also observed in the 20 and 30 mL epinephrine groups ($P < 0.01$) as compared to the 40 mL epinephrine group. Therefore, the potential risk of inducing a hypertensive crisis and arrhythmia in patients with underlying cardiovascular diseases by using 40 mL of epinephrine as a hemostatic solution should not be overlooked. Although it has been confirmed that endoscopic injection of epinephrine is safe [6, 20, 23], the injection volume of epinephrine should not be unlimited, because the systemic absorption of epinephrine does occur during endoscopic injection. For large-volume epinephrine injection, electrocardiographic and pulse oximeter monitoring should be used to detect arrhythmias and signs of ischemia or hypoxemia. Our study demonstrated that injection of 30 mL epinephrine was safer than injection of 40 mL epinephrine concerning the potential risk of inducing a cardiovascular event.

The epigastric pain induced by large-volume epinephrine injection is rarely reported in literature. In our study, the number of patients who developed epigastric pain due to endoscopic injection, was significantly higher in the 40 mL epinephrine group (51/76) than in the 20 (2/76) and 30 mL (5/76) epinephrine groups ($P < 0.001$). The epigastric pain induced by large-volume epinephrine injection may be due to tissue ischemia as well as swelling of the ulcer. In addition, injection with a large volume of epinephrine may result in severe tissue necrosis[4, 22, 27] or GI perforation[21, 24, 28]. Perforation of duodenal ulcer in a patient injected a large-volume (35 mL) epinephrine has been reported by Park *et al*[13]. In our study, the rate of peptic ulcer perforation was significantly higher in the 40 mL epinephrine group than in the 20 and 30 mL epinephrine groups ($P < 0.05$). Among the four patients who developed perforation of peptic ulcers, three had deep duodenal ulcers (two with spurting bleeding and one with oozing), the other one had spurting bleeding from a deep and big ulcer (4 cm) in the antrum of the stomach. The size of all the perforated ulcers is greater than 2 cm before endoscopic injection. The cause of perforation may be due to severe tissue necrosis and prolonged inflation in the limited space of the duodenal bulb during the endoscopic procedure. Our study revealed that injection with 30 mL epinephrine was safer than 40 mL epinephrine concerning the potential risk of inducing severe tissue necrosis or peptic ulcer perforation.

In conclusion, diluted epinephrine (1:10 000) solution is good as a first-line injection solution for arrest of active bleeding with a high initial hemostatic rate. Injection of 30 mL epinephrine is optimal for sustained hemostasis with a low rebleeding rate. A 30 mL epinephrine injection is safer than a 40 mL epinephrine injection concerning the potential risk of inducing cardiovascular event and severe tissue necrosis or peptic ulcer perforation. Injection of 30 mL diluted epinephrine (1:10 000) can effectively prevent recurrent bleeding with a low rate of complications. The optimal injection volume of epinephrine for endoscopic treatment of an actively bleeding ulcer (spurting or oozing) is 30 mL.

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