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Original Article

Peptic ulcer hemorrhage combined with acute gout: analyses of treatment in 136 cases

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Abstract: This study aims to compare the safety and curative effect of celecoxib and small-dose methylprednisolone sodium succinate in patients with peptic ulcer hemorrhage combined with acute gout. In this randomized, controlled trial, a total of 136 patients with peptic ulcer hemorrhage combined with acute gout were divided into the celecoxib group or the small-dose methylprednisolone sodium succinate group. These patients underwent gastroscopy hemostasis and proton pump inhibitor (PPI) therapy. Moreover, for the treatment of gout, the patients were administered either celecoxib or small-dose methylprednisolone sodium succinate. Adverse reactions and the visual analogue scale (VAS) score were recorded for the two groups. The difference in adverse reactions between the two groups was not significant (χ^2 = 0.002, P = 0.967). The duration of evident pain relief after the first dose of treatment showed a significant difference between the two groups (t = 13.728, P < 0.01). The VAS scores before treatment were not significantly different between the two groups (t = -1.786, P = 0.076). The VAS scores at 6 h, 2 days, 4 days, 6 days, and 8 days after treatment were significantly different between the two groups (t = 3.239, 6.586, 6.280, 3.737, 3.215; P = 0.002, 0.000, 0.000, 0.000, 0.002, respectively). In cases that receive effective gastroscopy hemostasis and PPI therapy, small-dose methylprednisolone sodium succinate exhibits a greater clinical curative effect for peptic ulcer hemorrhage combined with acute gout as compared to celecoxib, and is associated with greater safety.

Keywords: Peptic ulcer, hemorrhage, acute gout

Introduction

Peptic ulcer indicates the presence of an inflammatory reaction and a necrotizing lesion in the mucous membrane due to many different pathogenic factors. The lesion may be as deep as the mucosa muscularis, and the stomach and duodenum are the most common locations. Peptic ulcer is one of the most common chronic gastroenteric dysfunction diseases worldwide, with a morbidity of up to 10% [1]. The accepted pathogenesis of peptic ulcer is infection with *Helicobacter pylori*, which then leads to the reduction of the protective capabilities of certain factors (including gastric acid and pepsin) and of the axolemma [2]. Peptic ulcer bleeding (PUB) is the most common reason for the treatment of upper gastrointestinal hemorrhage [3], and almost 50% of all peptic ulcer bleeding cases are attributed to peptic ulcer [4]. The morbidity of the disease is approximately 5.4%, and the morbidity of peptic ulcer hemorrhage combined with acute gout is approximately 10% [5, 6]. Gout is a type of metabolic rheumatism associated with purine metabolic disorders and/or hyperuricemia. Acute gout leads to red, swollen, and tight skin; haphalgesia; and limited function in the damaged joint. Pain is always progressively aggravated, and the maximum pain usually occurs at approximately 12 h. Patients may experience tearing, lancinating, or biting pain, and they typically opt for immediate pain treatment because the pain takes a long duration to resolve.

PUB combined with acute gout is commonly noted in the clinical setting, primarily because of the use of irregular doses of nonsteroidal anti-inflammatory drugs (NSAIDs) or traditional Chinese medicine with illegally added NSAIDs. NSAIDs can inhibit the generation of prostaglandin, which has an anti-inflammatory effect

and reduces thrombosis; NSAIDs also can lead to gastrointestinal ulceration and bleeding [7]. The occurrence rate of peptic ulcer is > 15% in patients with long-term use of NSAIDs [8], and these drugs are the most important causative factor of PUB [9]; in particular, elderly patients with NSAID use are very susceptible to upper gastrointestinal hemorrhage [10, 11]. PUB induced by NSAIDs accounts for approximately 50% of PUB cases in the elderly population [12]. The second reason underlying the combined presentation of PUB and acute gout is that PUB is induced by acute gout. Bleeding can reduce blood volume, decrease the glomerular filtration rate, and increase the reabsorption of uric acid by the proximal convoluted tubule, which can further induce acute gout.

However, it is difficult to treat peptic ulcer hemorrhage combined with acute gout. The first-line drugs for acute gout [13], including NSAIDs, colchicines, and glucocorticoids, can lead to digestive tract symptoms. First, patients with PUB may have a higher rebleeding risk despite their treatment with a proton pump inhibitor (PPI) along with nonselective NSAIDs. Second, colchicines have obvious gastrointestinal adverse effects, and the therapeutic dose is similar to the toxic dose. Furthermore, nearly 80% of patients show adverse reactions. Finally, glucocorticoids can induce peptic ulcer disease, which is also one of the factors that lead to PUB.

According to both international and Asia-Pacific studies, treatment with cyclooxygenase 2 (COX-2) selective inhibitors (such as celecoxib) along with PPI is the safest solution for patients with peptic ulcer hemorrhage combined with acute gout that require NSAID treatment. However, we found that the clinical effect of celecoxib occurs only gradually, whereas patients desire immediate analgesic effects because of the intense, unbearable pain. To quickly relieve pain, increase patient compliance, reduce the hospitalization period, and eliminate potential doctor-patient conflicts, a safer and faster treatment is needed. Therefore, in the present study, we adopted a new treatment method using small doses of methylprednisolone sodium succinate plus PPI and compared the safety and efficacy of this method with those of celecoxib plus PPI in the treatment of peptic ulcer hemorrhage combined with acute gout.

Materials and methods

Participants

The participants were selected from patients in our hospital between January 2008 and December 2012. These patients met all of the following conditions: I a definite diagnosis of PUB based on stomachoscopy results; II acute gout that occurred before or after 48 h of acute PUB, which is consistent with the diagnostic criterion of acute gouty arthritis by the American College of Rheumatology [14]; III no combined serious heart, lung, liver, or renal insufficiency; and IV no intake of clopidogrel antiplatelet drugs. A total of 136 patients were selected, including 131 men and 5 women. Their ages were 39-82 years (average age, 61.1 ± 8.0 years). The Forrest classification of these patients was defined using stomachoscopy, as follows [15]: 61 patients with PUB (I a: 4, I b: 39, and II a: 18), 47 patients with duodenal ulcer and bleeding (I a: 1, I b: 31, and II a: 15), and 28 patients with compound ulcer and bleeding (I a: 1, I b: 20, and IIa : 7). This study was conducted in accordance with the declaration of Helsinki, and conducted with approval from the Ethics Committee of Shenzhen People's Hospital. Written informed consent was obtained from all participants.

General treatment

All patients stayed in bed and avoided strenuous activities. In patients with anemia, transfusion therapy was provided to replenish blood volume and maintain the hemoglobin level at > 75 g/L. These patients were administered a low-purine liquid diet.

Hemostatic treatment

Emergency endoscopic treatment was used for hemostasis [16-19]. An Olympus GIF-XQ260 electronic gastroscope, a rotary-type Olympus HX-110LR titanium clamp device, an HX-610 endoscopic hemoclip, and an NH-200L-0423 gastroscope needle were used. The need for hemostatic treatment was detected using an emergency gastroscopy within 24 h. The detected ulcer surface was flushed with physiological saline, and the focus of the ulcer was adequately exposed and injected with hemostatic drugs [20]. Adrenaline sodium chloride solution (1:10,000) was injected in the ulcer mucous

Table 1. Comparison of clinical data in the two groups

Group	Number	Age (±s, years)	Affected joints	
			Single-Joint	Multi-joint
A	75	60.9 ± 7.8	39	46
B	61	61.3 ± 8.3	26	35
t/χ^2		-0.355	0.153	
P		0.723	0.696	

membrane around the focus at three to six points; each point was injected with 1-2 mL of solution (the total amount was < 10 mL). If the injected mucosa was swollen and white in color, and there was no active bleeding within 5 min, the injection was stopped. If active bleeding persisted, endoscopic hemoclipping was conducted to stop the bleeding [21] by clamping the bleeding blood vessels and surrounding tissues, closing the titanium clamp, and removing the titanium placer. Then, the local area of the ulcer was sprayed with saline solution, and gastroscopy was performed to confirm the cessation of bleeding. The success rate of the endoscopic hemostatic procedure was 100%.

Hemostatic drug treatment

Pantoprazole was the selected PPI because it can treat PUB and prevent further hemorrhage [22, 23]. Pantoprazole was obtained from Nai Comin Pharmaceutical Co., Ltd. (injection of 40 mg/branch and 40 mg/tablet).

Drug treatment for gout

After the successful endoscopic hemostasis, patients were randomly divided into two groups: group A, celecoxib + pantoprazole group (n = 75), wherein patients were administered 200 mg bid celecoxib (trade name: celecoxib, 200 mg/grain; Pfizer Pharmaceuticals Ltd.) and 40 mg bid pantoprazole, or group B, small-dose methylprednisolone sodium succinate + pantoprazole group (n = 61), wherein patients were administered intravenous prednisolone and sodium succinate (trade name: methylprednisolone, 40 mg; Pfizer Pharmaceuticals Ltd) and 20 mg qd + pantoprazole 40 mg bid. Both groups were treated for 7 days.

Gout pain severity score

A 10-point visual analogue scale (VAS) was used to score the pain as follows [24]: 0, no pain; < 3, tolerable slight pain; 4-6, tolerable pain that affects sleep; 7-9, severe pain that prevents sleep; and 10, sharp pain.

Comparison of safety

Comparisons of rebleeding and other digestive system symptoms (such as bleeding, stomach ache, sour regurgitation, nausea, and emesis) and/or adverse symptoms were conducted between the two groups. Bowel movements were monitored daily, blood pressure and heart rate were monitored, blood parameters were dynamically monitored, and changes in hemoglobin level were observed (reexamination was performed after 1, 3, and 7 days, and in critical situations). Patients were instructed to report adverse events at any time during the treatment. Follow-up and recording of adverse events were performed at 1, 2, 4, 7, and 10 days after treatment.

Comparison of curative effect

The observation points were 6 h, 2 days, 4 days, 6 days, and 8 days after the first drug dosage. The patient-reported scores were recorded. The definite onset of the cure of acute gout (reduction of the VAS score by 2 points) was recorded by each patient, and the data were used to compare the effects of the two drugs.

Statistical analysis

Demographic and clinical data of two groups were compared, including age and damaged joints. Safety and curative effect were estimated using SPSS 20.0 (IBM Corp, Armonk, NY, USA). The onset time is reported as $\bar{x} \pm s$. A *t*-test was used to estimate the difference between the therapeutic evaluation before and after treatment for each group as well as the differences between the two groups. $P < 0.05$ indicated a significant difference.

Results

General clinical data

No significant difference was detected between the ages of patients in the two groups with the *t*-test ($P = 0.723$), and no significant difference in damaged joints was detected with the χ^2 test ($P = 0.696$). The general clinical data were also not significantly different between the two

Table 2. Comparison of adverse reactions in the two groups

Group	Number	Digestive system						Other systems	Total
		bleeding	stomachache	sour regurgitation	nausea	emesis	others		
A	75	0	3	1	2	0	0	0	6 (8.0%)
B	61	0	2	2	1	0	0	0	5 (8.2%)
χ^2								0.002	
P								0.967	

Table 3. Comparison of obvious pain relief time in the two groups

Group	Number	Obvious pain relief time (h)
A	75	17.49 ± 5.61
B	61	6.52 ± 3.03
t		13.728
P		< 0.01

groups (**Table 1**). Of the 136 patients, 119 completed the study. Eight patients (10.7%) in group A and 6 patients (11.8%) in group B stopped the treatment. Of these, one patient in group A stopped treatment because of intolerance to adverse reactions, and seven patients changed their treatment from small-dose methylprednisolone sodium succinate because of poor treatment effect and intense pain. In the other group, none of the patients stopped treatment because of intolerance to adverse reactions, and six patients stopped the drugs ahead of schedule because of significant effects.

Drug safety

The incidence of adverse drug reactions was 8.0% and 8.2% in group A and group B, respectively. No significant difference was detected in adverse drug reactions between the two groups with the χ^2 test (P = 0.967) (**Table 2**). No rebleeding was detected in either group. In group A, one patient stopped the treatment with celecoxib because of pain in the upper abdomen. The adverse reactions were mild in other patients, and the symptoms gradually improved and disappeared when they continued to use pantoprazole, which did not influence subsequent treatments.

Curative effect

The duration of pain was markedly reduced after the initial prescription in both groups (VAS score was reduced by 2 points); however, no significant difference was detected between the two groups based on the *t*-test (**Table 3**). In group A, the duration was 17.49 ± 5.6 h, whereas in group B the duration was 6.52 ± 3.03 h (P < 0.01). Moreover, pain was relieved faster in group B than in group A.

The VAS scores were compared between the two groups at different time points using *t*-tests (**Table 4**), and the change in VAS scores was compared using paired *t*-tests (**Table 5**). The VAS scores before treatment were not significantly different between the groups (P = 0.076), whereas the VAS scores were different after 6 h, 2 days, 4 days, 6 days, and 8 days (P = 0.002, 0.000, 0.000, 0.000, and 0.002, respectively). The changes (decrease) in the VAS scores were different at 6 h and 2, 4, 6, and 8 days after treatment (all P = 0.000).

Discussion

Small doses of methylprednisolone sodium succinate are safe for the treatment of peptic ulcer hemorrhage combined with acute gout. The basis of this treatment is the inhibition of the effect of NSAIDs on COX-2, which could lead to adverse reactions. Celecoxib is a COX-2 inhibitor that plays a role in relieving pain and confers anti-inflammatory effects by selectively inhibiting COX-2 and reducing the synthesis of prostaglandin in human monocytes that are activated by sodium uric acid crystals. Simultaneously, it also reduces the adverse effects (such as gastrointestinal reactions) caused by the nonselective inhibition of COX-1. When traditional NSAIDs are not tolerated or are contraindicated, a COX-2 inhibitor can be used in the treatment [25]. Methylprednisolone sodium succinate artificially synthesizes the effect of glucocorticoids, and it has the following advantages over prednisone [26]: I the binding rate of methylprednisolone sodium succinate and plasma proteins is stable, and the amount of unbound drug and dose have a linear relationship; II its plasma clearance rate is stable and

Table 4. Comparison of VAS scores before and after treatment in the two groups

Group	Number	Before treatment	After treatment				
			6 h	2th day	4th day	6th day	8th day
A	75	6.45 ± 1.20	6.27 ± 1.21	4.41 ± 1.23	3.00 ± 1.31	1.51 ± 0.86	0.31 ± 0.47
B	61	6.82 ± 1.18	5.61 ± 1.14	3.26 ± 0.79	1.77 ± 0.88	0.98 ± 0.65	0.09 ± 0.29
t		-1.786	3.239	6.586	6.280	3.737	3.215
P		0.076	0.002	0.000	0.000	0.000	0.002

Table 5. Comparison of changes of VAS scores before and after treatment in the two groups

Group	Number	6 h	2th day	4th day	6th day	8th day
A	75	-0.19 ± 0.39	-2.04 ± 0.71	-3.45 ± 1.03	-4.82 ± 0.89	-6.02 ± 1.02
B	61	-1.21 ± 0.93	-3.56 ± 0.90	-5.05 ± 1.18	-5.86 ± 1.16	-6.75 ± 1.17
t		8.034	10.717	8.319	5.573	3.672
P		0.000	0.000	0.000	0.000	0.000

does not increase with longer treatment duration; III it has high lipid solubility and better penetrability; and IV it is not metabolized by the liver, has strong anti-inflammatory effects, and has fewer adverse reactions. As a first-line drug for acute gout, methylprednisolone sodium succinate can also cause increased secretion of hydrochloric acid in gastric juice, similar to other glucocorticoids; however, small doses of PPI-that inhibits gastric acid-do not significantly increase digestive tract symptoms. This study indicates that the safety of the treatment was not significantly different between patients treated with small doses of methylprednisolone sodium succinate and those treated with celecoxib in cases where endoscopic hemostasis is effective and PPI treatment is regulated for peptic ulcer hemorrhage combined with acute gout, the digestive tract symptoms are not aggravated, and alimentary tract hemorrhage and perforation are not induced.

Compared with celecoxib, small-dose methylprednisolone sodium succinate is more effective in treating acute gout. Our findings suggest that 6 h after the first dose of small-dose methylprednisolone sodium succinate, the self-assessed pain of patients was significantly reduced. However, after 6 h of the first celecoxib dose, the self-assessed pain of patients did not show significant changes. The evident effective time was approximately 6.5 h after the first dose of small-dose methylprednisolone sodium succinate, whereas the effective time for celecoxib was 17.5 h. This result suggests that the onset time of cure for small-dose methylprednisolone sodium succinate is shorter than that for celecoxib. Patients with acute gout typically experience sharp pain that restricts their activity, and rapid pain relief is important for improving patient adherence to treatment. Based on the changes in the self-assessed scores at 2-8 days after treatment compared with those before treatment, it was noted that small-dose methylprednisolone sodium succinate is more effective than celecoxib. The self-assessed score of pain in six patients who used small-dose methylprednisolone sodium succinate was 0, and they stopped the drug ahead of schedule because of a marked curative effect. Therefore, we believe that treatment with small doses of methylprednisolone sodium succinate has a more significant effect and also has a relatively shorter course.

From these collective findings, treatment with small-dose methylprednisolone for patients with peptic ulcer hemorrhage combined with acute gout has a clinically superior curative effect over that of celecoxib and has good safety in cases where endoscopic hemostasis is effective and the use of gastric acid-inhibiting drugs is regulated. The short-term use of this drug does not cause serious digestive system effects and other adverse events, and thus provides a new method of treatment for acute PUB combined with gout.

Disclosure of conflict of interest

None

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