

# Clinical Effect, Analysis of Amoxicillin Clavulanate Potassium Combined with Shenling Baizhu Powder in the Treatment of Gastric Ulcer with *Helicobacter pylori* Infection

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**Wang et al.: Efficacy of Amoxicillin Clavulanate Potassium and Shenling Baizhu Powder in Gastric Ulcer Treatment**

We attempt to investigate the improvement of clinical efficacy of amoxicillin-clavulanate potassium combined with Shenling Baizhu powder in treating gastric ulcer patients with *Helicobacter pylori* infection and the effect on related serum indexes. We selected 90 patients with gastric ulcer complicated with *Helicobacter pylori* infection in our hospital from January 2019 to May 2021 and randomly divided them into observation group (45 cases treated with amoxicillin clavulanate potassium combined with Shenling Baizhu powder) and control group (45 cases treated with amoxicillin-clavulanate potassium), compared both groups on the clinical effective rate and *Helicobacter pylori* eradication rate (per-protocol analysis) before and after treatment, the serum mucosal cytokines (vascular endothelial growth factor, epidermal growth factor, cyclooxygenase-2), matrix metalloproteinase and infection indicators (procalcitonin, C-reactive protein, interleukin-6) concentration level changes. After treatment, observation group possessed remarkably higher serum levels of vascular endothelial growth factor, epidermal growth factor and cyclooxygenase-2 than control group ( $p < 0.05$ ); it possessed remarkably lower procalcitonin, C-reactive protein and interleukin-6 serum levels than control group ( $p < 0.05$ ); and it possessed remarkably lower matrix metalloproteinase-7, matrix metalloproteinase-9 and matrix metalloproteinase plasma levels than control group ( $p < 0.05$ ); after per-protocol analysis, *Helicobacter pylori* radical cure rate of observation group (86.67 %) was remarkably higher than control group (66.67 %) ( $p < 0.05$ ). Amoxicillin-clavulanate potassium combined with Shenling Baizhu powder can significantly improve the clinical efficacy of gastric ulcer complicated with *Helicobacter pylori* infection, increase the clearance rate of *Helicobacter pylori*, increase the level of cellular and mucosal cytokines in serum and reduce the level of serum cytokines. The concentration levels of procalcitonin, C-reactive protein and interleukin-6 can provide clinical guidance value for effectively treating gastric ulcer with *Helicobacter pylori* infection.

**Key words:** Amoxicillin-clavulanate potassium, Shenling Baizhu powder, gastric ulcer, *Helicobacter pylori*, clinical efficacy

Stomach ulcer is one type of the commonest disease of upper gastrointestinal tract. Gastric ulcer prevalence in Western population is 2.4 %, with annual incidence ranging from 0.10 % to 0.19 %<sup>[1]</sup>. In parts of mainland China, gastric ulcer prevalence in general population reaches high as 6.07 %, 22.5 % of gastrointestinal symptoms patients have gastric ulcer<sup>[2]</sup>. Gastric ulcers are more common in smoking people, use Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), or alcohol drinkers and have a recurrence rate of up to 60 % after

treatment<sup>[3]</sup>. Gastric ulcer has a remarkable impact on national economy. In United States, the average annual medical cost for stomach ulcer is \$23 819. In Korea, the medical cost for gastric ulcer every year ranges is about from \$959.6 to \$2553.10<sup>[4]</sup>. Although studies have indicated that *Helicobacter pylori* (*H. pylori*) eradication therapy has cost benefit, but there is another more systematic study showed eradication therapy and placebo possess no remarkable difference in per subject's cost<sup>[5]</sup>. Although routine procedure

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has effects, it is hard to avoid their side effects and it will limit clinical application. However, both clinical and experimental studies have shown that traditional Chinese medicine has a therapeutic effect on gastric ulcer, at the same time, there are fewer side effects. Moreover, Chinese herbal medicine cost for gastric ulcer treatment only reaches about 1/6<sup>th</sup> of Western medicine<sup>[6]</sup>. The combination of amoxicillin and the beta-lactamase inhibitor clavulanic acid is frequently used in respiratory infections and otitis media treatment because of it has bactericidal to common beta-lactamase producing pathogens (including *H. pylori*, *Haemophilus influenza* and *Moraxella catarrhalis*) and to penicillin-sensitive strain of *Streptococcus pneumoniae*<sup>[7]</sup>. Shenling Baizhu powder mainly regulates gastrointestinal peristalsis, improves human metabolism and immunity<sup>[8]</sup>. Therefore, this study attempts to investigate the clinical effect of amoxicillin-clavulanate potassium combined with Shenling Baizhu powder in gastric ulcer patients with *H. pylori* infection treatment. We selected 90 patients with gastric ulcer complicated with *H. pylori* infection in our Department of Gastroenterology from January 2019 to May 2021 as a research cohort. Inclusion criteria, meet the diagnostic criteria of “Chinese consensus on chronic gastritis”<sup>[9]</sup>, gastro scope showed gastric ulcer and positive *H. pylori* detected by 14C urea breath test method and no communication disorder or mental illness patients without systemic immune system diseases. In exclusion criteria patients had liver, kidney or other organ damages; patients had cardiovascular disease; patients with unstable vital signs; a history of cancer; patients with other digestive diseases such as duodenal ulcer and Crohn’s disease and patients allergic to amoxicillin-clavulanate potassium. We got approval from the ethics committee of our hospital. We divided the patients in this study into control group (45 cases) and an observation group (45 cases). 28 males and 17 females included in control group, ages were from 46 y to 68 y old, average was about (60.52±7.04) y old. 24 males and 21 females included in observation group, ages were from 48 y to 67 y old, average was about (59.25±8.67) y old. Both groups possessed comparability on general data (p>0.05). After admission, both groups received routine treatment. We treated control group with amoxicillin clavulanate potassium (Manufacturer: Xiangbei Welman Pharmaceutical Co., Ltd.; approval number: gyzz h20 051 710), 250 mg/time, twice a day. After receiving the same treatment as control group,

we added with Shenling Baizhu powder decoction. The main prescriptions of Shenling Baizhu powder decoction were Dangshen 15 g, yam 12 g, *Atractylodes macrocephala* 15 g, Poria 12 g, lotus seed 12 g, white lentil 20 g, *Cyperus* 10 g, *Coix* seed 10 g, *Coptis* 6 g and licorice 5 g. We decocted them with 200 ml water; the patients warmly took them both in the morning and in the evening, 1 dose/d. We evaluated the clinical efficacy of both groups after continuous treatment for 15 d. We collected 10 ml of fasting cubital veins of both groups’ patients in the early morning of the 2<sup>nd</sup> d after admission and distribute them into 3 centrifuge tubes, each tube 3 ml. After standing at room temperature for 30 min, centrifuged each tube at 3500 r/min centrifuge (4°) for 10 min, extracted the supernatant. Adopted enzyme-linked immunosorbent assay to detect mucosal cytokines (Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor (EGF), Cyclooxygenase-2 (COX-2)) in peripheral blood serum, Matrix Metalloproteinases (MMP)-7, MMP-9, Tissue Inhibitor Matrix Metalloproteinase-1 (TIMP-1) and inflammatory factors (C-Reactive Protein (CRP), Procalcitonin (PCT) and Interleukin-6 (IL-6)) levels. After 15 d treatment, detected the same indicators in the patient’s serum again. We observed the eradication rate of *H. pylori* in both groups and analyzed by Per-Protocol (PP). *H. pylori* eradication rate is equal to the number of successful eradication of *H. pylori* in each group/the number of people in each group meeting the research requirements×100 %. Adopted Statistical Package for Social Sciences (SPSS) 22.0 to process and analyze enumeration data and measurement data. Expressed enumeration data by constituent ratio (%), adopted Chi-square ( $\chi^2$ ) test to make comparison of both groups. The measurement data conformed to normal distribution and homoscedasticity and use mean±standard deviation ( $\bar{x}\pm s$ ) to indicate it. Adopted t-test to compare both groups. p<0.05, indicating that the divergence possessed statistical significance. Before treatment, both groups possessed no remarkable difference in plasma mucosal factor (VEGF, EGF, COX-2) levels (p>0.05), so it was of statistical significance; after treatment, observation group possessed remarkably higher plasma mucosal factors (VEGF, EGF, COX-2) than control group (p<0.05), it had statistical significance, as shown in Table 1. After both groups received treatment, the decrease value of MMP-7 content in observation group was 33.31±6.56 (ng/l),

that of MMP-9 content was  $22.56 \pm 1.39$  (ng/l) and that of TIMP-1 content was  $1.92 \pm 0.26$  (ng/l), compared with control group, observation group possessed remarkably higher decrease range than control group ( $p < 0.05$ ), it had statistical significance, as shown in Table 2. Before treatment, PCT, IL-6 and CRP levels of both groups had no difference, so it was of no statistical significance ( $p > 0.05$ ); after treatment, compared PCT, IL-6, CRP levels of both groups, observation group had bigger downtrend than control group, they

were remarkably different, so it possessed statistical significance ( $p < 0.05$ ), as shown in Table 3. According to PP analysis results of both groups after treatment, the eradication rate of *H. pylori* in observation group was 86.67 %, it was remarkably higher than control group (66.67 %), the difference possessed statistical significance ( $p < 0.05$ ) as shown in Table 4. *H. pylori* infection is very common in gastric ulcers. In a survey of blood donors from patients with gastrointestinal disease, 68 % were found to be serologically positive for *H. pylori*.

**TABLE 1: COMPARISON OF MUCOSAL CYTOKINE LEVELS OF BOTH GROUPS**

Group	Number of cases	VEGF (ng/l)		EGF (ng/l)		COX-2 (U/l)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	40	$56.03 \pm 6.91$	$131.63 \pm 23.37$	$127.64 \pm 30.04$	$276.62 \pm 24.44$	$25.09 \pm 9.60$	$33.31 \pm 10.44$
Control group	40	$54.44 \pm 6.85$	$113.61 \pm 21.46$	$126.54 \pm 31.69$	$223.16 \pm 30.61$	$26.64 \pm 10.07$	$28.73 \pm 8.41$
t		0.44	34.56	0.17	56.24	0.08	21.91
p		0.71	0.001	0.87	0.001	0.93	0.001

**TABLE 2: COMPARISON OF THE DECREASED VALUES OF MMP-7, MMP-9 AND TIMP-1 IN PLASMA PF BOTH GROUPS AFTER TREATMENT**

Group	Number of cases	MMP-7 drop value	MMP-9 drop value	TIMP-1 drop value
Observation group	45	$33.31 \pm 6.56$	$22.56 \pm 1.39$	$1.92 \pm 0.26$
Control group	45	$16.74 \pm 5.57$	$12.01 \pm 1.12$	$1.33 \pm 0.16$
t		43.71	37.31	14.03
p		0.001	0.001	0.001

**TABLE 3: COMPARISON OF PCT, IL-6 AND CRP OF BOTH GROUPS BEFORE AND AFTER TREATMENT**

Group	Number of cases	PCT (ug/l)		IL-6 (pg/ml)		CRP (mg/l)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	35	$16.56 \pm 6.45$	$9.21 \pm 3.42$	$232.31 \pm 72.31$	$73.6 \pm 23.7$	$90.09 \pm 32.60$	$52.35 \pm 15.9$
Control group	35	$16.22 \pm 6.94$	$12.46 \pm 4.56$	$230.38 \pm 82.17$	$123.6 \pm 34.5$	$89.63 \pm 36.12$	$69.73 \pm 22.7$
t		0.56	8.55	0.31	12.32	0.23	13.32
p		0.63	0.001	0.72	0.001	0.81	0.001

**TABLE 4: COMPARISON OF *H. pylori* ERADICATION RATES BY PP ANALYSIS**

Item	n	<i>H. pylori</i> positive	<i>H. pylori</i> negative	$\chi^2$	p
Observation group	45	39 (86.67 %)	6 (14.33 %)	4.31	0.002
Control group	45	30 (66.67 %)	15 (34.33 %)	8.36	0.001

In China, an estimated 840 million people are currently infected with *H. pylori*<sup>[10]</sup>. If we consider that 10 % of those infected have peptic ulcer disease or gastric cancer, 84 million of them require complete clearance of *H. pylori*<sup>[11]</sup>. Although the combination of omeprazole, amoxicillin and clarithromycin has achieved good *H. pylori* eradication rates, 10 % to 15 % of patients still experience eradication failure. Under these conditions, it is very meaningful to pursue alternative treatment options with satisfactory *H. pylori* eradication rates, low adverse reactions rates and low cost<sup>[12]</sup>. The efficacy of different regimens varies according to patient compliance and bacterial resistance to antibiotics. Clarithromycin, quinolones and metronidazole should not be used more than once because *H. pylori* can induce its drug resistance<sup>[13]</sup>. For patients who failed in initial treatment, it is ideal to detect the antimicrobial susceptibility of *H. pylori*, but there is limit because of high cost and lack of laboratories that can fully test the sensitivity. In China, the resistance of *H. pylori* strain to antibiotics including metronidazole has reached 50 %, under this condition, it reduces the efficacy of the regimen containing this drug or other nitroimidazole drugs<sup>[14]</sup>. Studies have indicated that lower doses of amoxicillin clavulanate potassium can reduce the adverse symptoms rates, but this strategy may also reduce the eradication rate<sup>[15]</sup>. The treatment of gastric ulcer with Shenling Baizhu powder is partly due to their antibacterial properties. Studies have indicated that oral administration of Shenling Baizhu powder could reduce bacterial colony forming units in gastric ulcer caused by gastric acid by about 30 %<sup>[16]</sup>. The extracts of some traditional Chinese medicines have anti-inflammatory activity and can inhibit myeloperoxidase activity at the site of gastric ulcer. Myeloperoxidase is a marker of neutrophil infiltration during inflammation. There is one clinical study, shown that oral herbal compounds for 1 mo can remarkably increase mucosal Mucin5AC (MUC5AC) (human mucin gene) levels in gastric ulcer patients<sup>[17]</sup>. Studies have also indicated that anti-gastric ulcer drugs can reduce the content of pepsin and the activity of *H. pylori*. Ulcer healing requires mucosal proliferation and some traditional Chinese medicines that promote ulcer healing work by stimulating cell proliferation. A study showed that oral administration of ginseng for 3 d could stimulate the proliferation and angiogenesis of gastric mucosal cells and increase the expression of basic fibroblast growth factor<sup>[18]</sup>. This study also found that observation group possessed remarkably

higher increase of serum mucosal cytokines (VEGF, EGF and COX-2) than control group. Amoxicillin-clavulanate potassium combined with Shenling Baizhu powder has synergistic effect on gastric ulcer treatment complicated with *H. pylori*. Therefore, Shenling Baizhu powder alone or combined with routine drugs can be used as a substitute for gastric ulcer treatment or the prevention of recurrence<sup>[19]</sup>. This study also shows that the combination can achieve the eradication rate of *H. pylori* to a greater extent. This study has some limitations. Due to the small sample size of our study, only 90 cases and individual differences among patients, the test results are not convincing. It is necessary to design scientifically rigorous large-sample randomized controlled trials in the future. This study confirmed that erythromycin combined with oseltamivir phosphate granules in treating elevated serum VEGF, EGF and COX-2 in children with mycoplasma pneumonia, remarkably reduced PCT, CRP and IL-6 levels in serum and remarkably reduced MMP-7, MMP-9 and MMP levels in plasma; PP analysis showed that the radical cure rate of *H. pylori* in observation group was 86.67 %, so it was remarkably higher than control group (66.67 %). Amoxicillin-clavulanate potassium combined with Shenling Baizhu powder can remarkably improve the clinical effective rate of gastric ulcer with *H. pylori* infection, improve the clearance rate of *H. pylori*, increase the level of mucosal cytokines in serum and reduce the concentration of PCT, CRP and IL-6 in serum. It can provide clinical guiding value for effectively treating gastric ulcer with *H. pylori* infection.

#### Conflict of interests:

The authors declared no conflict of interest.

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**This article was originally published in a special issue, "Modern Applications in Biomedical Research and Pharmaceutical Sciences" Indian J Pharm Sci 2022;84(3) Spl Issue "131-135"**