Short Communication

Therapeutic Effect of Chinese Herbal Ointment Liu-He-Dan in Patients with Acute Pancreatitis

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INTRODUCTION
Severe acute pancreatitis (AP) remains a challenge in clinical practice, and there are no internationally agreed specific therapies.\(^1\) Severe AP typically presents with epigastric pain, abdominal distention, vomiting, and constipation at the early stage and is similar to the Yangming-Fushi syndrome of traditional Chinese medicine (TCM). The Chinese herbal ointment Liu-He-Dan (LHD) has been adapted for the treatment of AP with Yangming-Fushi syndrome externally on belly for many years in our hospital. However, the potential mechanism of LHD in the treatment of severe AP has not been elucidated. Therefore, the present study sought to evaluate the effect of LHD on AP patients and preliminarily investigate its anti-inflammatory mechanism.

METHODS

Study design and ethics
This study was performed in patients hospitalized with predicted severe AP from January to December 2011 at the Department of Integrated Traditional Chinese and Western Medicine, Sichuan Provincial Pancreatitis Center, West China Hospital. The study protocol was reviewed and approved by the Ethical Committee of West China Hospital of Sichuan University and was registered at the Chinese Clinical Trial Registry (No. ChiCTR-TRC-13003845). The study was conducted in accordance with the Declaration of Helsinki (as revised in Edinburgh, 2000). Informed consent was obtained within 6 h for all the patients or their authorized next of kin.

Patients’ allocation and treatment
The diagnosis of AP based on 1992 Atlanta Symposium and severity was defined as Ranson score ≥3 and/or Balthazar computed tomography (CT) severity index ≥5.\(^2\) Enrolled patients were randomized into AP group and LHD group by a random number table generated from PEMS software (Package for Encyclopedia Medical Statistics, Sichuan University, China). Patients in the two groups received fluid resuscitation and use of TCM for both oral intake and enema. Prophylactic use of antibiotics, parenteral nutrition, somatostatin, and narcotic drugs were used if needed according to the Chinese Acute Pancreatitis Practice Guideline.\(^3\) For patients in LHD group, LHD ointment, 50 g/application, was immediately applied from the xiphoid to the pubic symphysis, between the anterior axillary lines, covering the projection on the body surface of pancreas. LHD was used for 6 h/d for 7 days or before discharge if the hospitalization was <7 days. The LHD powder was authenticated as previously reported.\(^4\)

Data collection
Demographic data, clinical and CT severity scores, time of disease onset to admission, and treatment baselines were recorded. Serum white blood cell count, procalcitonin, interleukin (IL)-6, and C-reactive protein (CRP) were recorded at day 7 or at discharge (if <7 days). Endpoints were duration of abdominal pain, time to oral refeeding, length of hospital stay, local complications, organ failure, infection, Intensive Care Unit (ICU) admission, surgery, and mortality. Side effects of LHD were also recorded.

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### Statistical analysis

All statistical analyses were performed with PEMS 3.1. Data were expressed as mean ± standard deviation (SD) or number (percentage). The Kolmogorov–Smirnov test was used to determine the pattern of data distribution, the Student’s unpaired *t*-test was used to compare normally distributed data between two groups, and Chi-square test and Fisher’s exact test were used for quantitative data analysis. The values of *P* < 0.05 were considered statistically significant.

### RESULTS

#### Enrollment of patients and baseline characteristic comparison on admission

The process of patient enrollment is described in Figure 1. There were no significant differences in age, gender, etiological factors, clinical and CT scores, and time of abdominal onset to admission between groups (all *P* > 0.05). The inflammatory markers of IL-6 and CRP had no significant difference between the two groups.

#### Comparison of serological data and clinical outcomes

Compared to AP group, LHD treatment lowered the serum levels of IL-6 and CRP significantly (*P* < 0.05). It also shortened the time to oral refeeding (7.3 vs. 9.9 days, *t* = 2.035, *P* = 0.048) and reduced the length of hospital stay (11.4 vs. 14.9 days, *t* = 2.159, *P* = 0.037). There was no significant difference in terms of duration of abdominal pain, rates of local complications, organ failure (both transient and persistent), infection, ICU admission, surgery, and mortality between the two groups (all *P* > 0.05) [Table 1]. After the external usage, the contact dermatitis with erythematous rash occurred in one patient in LHD group.

### DISCUSSION

Transdermal delivery has a variety of advantages compared with other routes of herbal ointment administration. The main disadvantages of transdermal delivery include potential skin sensitization or irritation. Only one patient in our study developed slight itching and an erythematous rash on the 6th day of treatment, but the dermatitis was alleviated after discontinuing the use of LHD.

This study showed that topical application of LHD could significantly reduce IL-6 and CRP, curtail time to oral refeeding, and shorten length of hospital stay, despite little impact on the major complications of the disease. These findings suggest LHD was protective against AP patients through inhibiting the inflammatory response. In our study, we provided a novel method of administration of the Chinese herb formula in the treatment of AP and demonstrated its efficacy. The beneficial effect of LHD in clinical outcomes may be due to the reduced serum proinflammatory cytokines, thereby reducing the abdominal pain duration. However, a statistically significant difference was not reached for local complications possibly due to relatively small sample size; therefore, further replications are needed.

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### Conflicts of interest

There are no conflicts of interest.

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### Table 1: Comparison of clinical outcomes between the two groups after treatment

| Items                              | AP group (n = 22) | LHD group (n = 22) | *P*   |
|------------------------------------|------------------|--------------------|-------|
| White blood cell (*×10^9^/L), mean ± SD | 12.33 ± 3.07     | 11.77 ± 4.13       | 0.612 |
| IL-6 (pg/ml), mean ± SD            | 121.5 ± 31.6     | 100.23 ± 24.8      | 0.017 |
| CRP (mg/L), mean ± SD              | 195.3 ± 24.5     | 176.9 ± 17.9       | 0.007 |
| Duration of abdominal pain (days), mean ± SD | 7.6 ± 5.0         | 6.3 ± 4.1          | 0.351 |
| Time to oral refeeding (days), mean ± SD | 9.9 ± 5.4         | 7.3 ± 2.6          | 0.048 |
| Length of hospital stay (days), mean ± SD | 14.9 ± 6.2       | 11.4 ± 4.4         | 0.037 |
| Local complications*, n (%)        | 10 (46)          | 6 (27)             | 0.210 |
| Transient organ failure, n (%)     | 11 (50)          | 13 (59)            | 0.545 |
| Persistent organ failure, n (%)    | 1 (5)            | 0                  | 0.312 |
| Any infection, n (%)               | 1 (5)            | 0                  | 0.312 |
| ICU admission, n (%)               | 1 (5)            | 0                  | 0.312 |
| Surgery, n (%)                     | 1 (5)            | 0                  | 0.312 |
| Side effect of LHD, n (%)          | 0                | 1 (5)              | 0.312 |
| Mortality, n (%)                   | 0                | 0                  | 0.312 |

*Local complications: Pancreatic fluid collection and/or pancreatic necrosis. AP: Acute pancreatitis; LHD: The Chinese herbal ointment Liu-He-Dan; -: Not applicable; SD: Standard deviation; ICU: Intensive Care Unit.
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