

EXPERIMENTAL STUDY

Yiguanjian cataplasm attenuates opioid dependence in a mouse model of naloxone-induced opioid withdrawal syndrome

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Supported by Shandong Foundation for Development of Science and Technology, China (Research and Development of Umbilical Treatment Cataplasm for Drug Rehabilitation, No. 2009GG10008007)

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Accepted: January 25, 2016

morphine administration on day 3 and subsequently removed at the end day 5. On day 6, naloxone (8 mg/kg) was intraperitoneally injected to precipitate opioid withdrawal syndrome. Behavioral observation was performed in two 30-min phases immediately after naloxone injection.

RESULTS: The YGJ cataplasm significantly and dose-dependently attenuated morphine-naloxone-induced experimental opioid withdrawal, in terms of withdrawal severity score and the frequencies of jumping, rearing, forepaw licking, and circling behaviors. However, YGJ cataplasm treatment did not alter the acute analgesic effect of morphine.

CONCLUSION: YGJ cataplasm could attenuate opioid dependence and its associated withdrawal symptoms. Therefore, YGJ cataplasm could serve as a potential therapy for opioid addiction in the future.

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Abstract

OBJECTIVE: To investigate the effect of Yiguanjian (YGJ) cataplasm on the development of opioid dependence in a mouse model of naloxone-induced opioid withdrawal syndrome.

METHODS: One hundred Swiss albino mice, of equal male to female ratio, were randomly and equally divided into 10 groups. A portion (3 cm²) of the backside hair of the mice was removed 1 day prior to the experiment. Morphine (5 mg/kg) was intraperitoneally administered twice daily for 5 days. YGJ cataplasm was prepared and pasted on the bare region of the mice immediately before

Key words: Yi Guan Jian; Paste; Morphine; Naloxone; Opioid dependence

INTRODUCTION

Opioid drugs are used primarily for pain control and can produce a state of euphoria or well-being during their use. Owing to these mood-enhancing effects, opioid drugs have become the most commonly abused psychoactive substances worldwide. Continuous administration of opioid drugs can elicit opioid dependence, while their abrupt withdrawal may result in the precipitation of an abstinence syndromes.¹ Opioid dependence is usually associated with serious medical, le-

gal, social problems, and is associated with comorbid psychiatric disorders. In 2002, the cost of opioid dependence to society was approximately 181 billion US dollars.²

Until now, several approaches have been proposed for the management of opioid dependence. Opioid replacement therapy is an effective method in preventing acute withdrawal and maintaining long-term abstinence; however, acceptance of this therapy has been rather slow.³ Other treatment approaches, such as the administration of α_2 -adrenergic agonists, were also examined in previous studies.⁴ Unfortunately, none of these therapies have promised to conclusively treat opioid dependence and its related abstinence syndromes. Therefore, new approaches for the management of opioid dependence are urgently needed.

Traditional Chinese Medicine (TCM) has been applied in medical care throughout East Asia for thousands of years.^{5,6} Although the active ingredients in most mixed herbal formulas/medications have not been fully identified, it has been widely recognized that synergism among all components within the prescription is an important characteristic.^{7,8} The Yiguanjian recipe (YGJ) is a traditional Chinese herbal formula that possesses the medical function of nourishing liver-*Yin* and dispersing stagnated liver-*Qi*. It has been widely used in China for the treatment of diseases with liver-*Yin* deficiency.⁹⁻¹¹ We found that liver-*Yin* deficiency was a common clinical syndrome of TCM in opioid dependence in clinical examinations. Therefore, we examined the use of YGJ for the treatment of opioid dependence and showed good effect.

Transdermal drug delivery refers to the topical application of drugs to healthy intact skin, either for localized treatment or systemic therapy.¹² The potential of skin to serve as a pathway for drug administration has already been demonstrated previously.¹³ Compared with conventional drug administration routes, the transdermal drug delivery system (TDDS) has several additional advantages. It can maintain constant drug levels in the blood, while minimizing first-pass metabolism associated with gastro-intestinal administration of drugs.¹⁴⁻¹⁶ It is more convenient and has increased patient compliance compared with oral administration routes. To date, the transdermal drug delivery of traditional herbal medicine has been used to treat many diseases.¹⁷

In this study, we established a mouse model of naloxone-induced opioid withdrawal syndrome and analyzed the effectiveness of YGJ cataplasm in treating opioid dependence.

MATERIALS AND METHODS

Preparation of YGJ cataplasm

The YGJ formula consists of Dihuang (*Radix Rehmanniae*), Beishashen (*Radix Glehniae*), Danggui (*Radix An-*

gelicae Sinensis), Maidong (*Radix Ophiopogonis Japonici*), Gouqizi (*Fructus Lycii*), Dangshen (*Radix Codonopsis*) and Baizhu (*Rhizoma Atractylodis Macrocephalae*). All crude herbs were the products of Jianlian TCM Co., Ltd. (Jinan, China).⁷ The herbs were chopped finely and extracted twice with 10-fold 75% ethanol (Tianjin Guangcheng Chemical Reagent Co., Ltd., Tianjin, China) under reflux. The 75% ethanol extract was then filtered through absorbent gauze, and the filtrate was concentrated under reduced pressure to remove the ethanol and produce the dried extract powder. Then, the extract powder, artificial moschus (Beijing Lianxin Pharmaceutic Co., Ltd., Beijing, China), emodin (Shanghai Yantuo Biosciences Co., Ltd., Shanghai, China) and borneol (Hebei Jinmu Pharmaceutic Group Co., Ltd., Hebei, China) were mixed into a cream with excipients, including plasdone K-90, polyplasdone XL-10, and viscomate NP700 (Guangzhou Biours Biosciences Co., Ltd., Guangzhou, China), according to the requirements of the medicinal paste detailed in the Pharmacopoeia of the People's Republic of China.¹⁷ The cream was then coated onto rubberized fabric with herb extract powders at a concentration of 1 mg/cm² and the resulting plaster was cut into 1 cm², 2 cm² and 3 cm² pieces, which were stored in desiccators until use.¹⁸ The procedure generally corresponded to the pharmaceutical quality standards currently under the guidance of pharmaceutical experts from Qilu Hospital of Shandong University. The manufacturing procedure of placebo cataplasm was the same as that of YGJ cataplasm. The placebo cataplasm contained all of the excipients that were used in YGJ cataplasm without the herb extracts.

Animals

One hundred Swiss albino mice of specific pathogen-free grade (50 males and 50 females), aged 7 weeks old, weighing (25 ± 2) g, were used in this study. The mice were obtained from the Laboratory Animal Center of Shandong University (Certificate of quality number: SCXK [Lu] 20090001). The mice were fed on standard laboratory diet and tap water and were housed in the Laboratory Animal Center of Shandong University. The mice were divided into 10 groups using a random number table method. The experiments were conducted in a semi-soundproof laboratory. The mice were exposed to a 12 h/12 h light/dark cycle, with the light period between 08:00 to 20:00 h. Behaviors were observed using a 30 cm³ large transparent Perspex observation chamber. Two observers who were blind to the treatment schedule simultaneously observed the withdrawal measurements. The mean value of both observations was recorded. The experimental protocol was performed in accordance with the Institutional Animal Ethics Committee. The study was approved by the local Research and Ethics Committee at Qilu Hospital of Shandong University, in accordance with the guidelines of the 1975 Declaration of Helsinki.

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