

Analysis of Animal Models of Oral Ulcers Based on the Characteristics of Clinical Symptoms of Chinese and Western Medicine

Huan LI, Ming BAI, Yan-yan MIAO and Ming-san MIAO *

Henan University of Traditional Chinese Medicine, Zhengzhou, China

*Corresponding author

Keywords: Chinese and Western medicine, Oral ulcers, Animal model.

Abstract. Objective: To analyze the methods and characteristics of animal model of oral ulcer and the characteristics of Chinese and Western medicine oral ulcer disease anastomosis. **Methods:** To summarize the characteristics of animal models of oral ulcers, modeling methods, analysis of oral ulcer animal model and clinical features of the anastomosis, according to oral ulcers in Western medicine diagnostic criteria and clinical features, to discuss the advantages and disadvantages of the existing oral ulcer animal model and improve the recommendations. **Results:** At present, there are many methods of oral ulcer modeling, which reflects the characteristics of clinical symptoms of oral ulcer, but lacks the animal model which can reflect the characteristics of traditional Chinese medicine and western medicine, and lacks the method of evaluating oral ulcer model. **conclusions:** The establishment of a reliable oral ulcer evaluation method, establishing a disease - associated oral ulcer model is the focus of future research.

Introduction

Oral ulcers (oral ulcer) is one of the most common oral mucosal diseases. The prevalence rate of more than 10%. Mouth ulcers refers to oral mucosal epithelial cells shedding after epithelial damage, it is a common disease. Round or oval ulceration on the oral mucosa, superficial ulceration, pale yellow or white, central depression, neat edges, around to flush, is the main clinical manifestations of oral ulcers, additionally, ulcers can occur in the oral mucosa any site [1]. According to the depth of ulceration, ulceration in clinical divided into shallow and deep ulcers. Shallow ulceration attack mere to the epithelial surface, generally do not leave scars after healing. However, deep ulceration was able to damage the deep connective tissue, leaving scars after healing. Clinical oral ulcers can be divided into: recurrent oral ulcers, behcet's disease, oral mucosal injury ulcers, vesicular stomatitis, erythema multiforme, tuberculous ulcers, contact stomatitis, necrotizing gingivostomatitis and cancerous ulcer. Wherein the recurrent oral ulcers, traumatic ulcers and herpetic stomatitis most common. Cancerous ulcer is the most dangerous [2]. Currently, the methods to establish the model of oral ulcers are mainly immune induction method, chemotherapy method, burning method, mechanical method, inducing bacterial infection method, radiation method, chemical burning method [3]. Oral ulcers, although not severe, but can affect the patient's eating, talking, and easy to relapse, affecting the quality of life of patients. Because the cause of the disease is not entirely clear, clinical efficacy has yet to be improved. Clinically, to extend the cycle of ulcers, shorten the onset time, systemic medication and local symptomatic treatment to relieve pain and promote ulcer healing [4].

Oral Ulcers Etiology and Pathogenesis

Oral Ulcers Modern Medicine Etiology and Pathogenesis

Western medicine perspective, oral ulcers may be associated with immune dysfunction, bacterial or viral infections, metabolic disorders, vitamin deficiency, endocrine abnormalities, digestive disorders and mental factors. Principle of treatment is to prevent secondary infection, relieve pain, promote healing and shorten the course of treatment, to avoid recurrence [5]. At present oral ulcer drugs commonly used in clinical treatment are: vitamin, antibacterial drugs, topical application promote epithelial healing drugs, designed to alleviate pain, promote ulcer healing. Severe cases, the use of immunosuppressive agents, however, such drugs toxic side effects.

Etiology and pathogenesis and treatment of Traditional Chinese Medicine (TCM) of oral ulcers

Oral ulcers belonging "aphtha", "mouth ulcers" category in the field of TCM. The Plain Question · Gas Alternating Large Theory He said: "The golden years less, flames upward people sick mouth sores, and even the heartache, shows that fire-evil is a causative factor of aphthous. To Treat Patients On The Tongue Door written by Chao Yuan Fang Sui Dynasty ,Say: "Hand lack of Yin, through the heart, the heart air through the tongue; full lunar, after the spleen, spleen gas reaches the mouth, internal organs excessive heat, heat to the Heart and gas rushed mouth and his tongue, it makes mouth sores. "This indicates that there is hot and humid in the heart has a close relationship with oral ulcers, heat toxin upside into the mouth, which led to occurrence of oral ulcers. While Chinese medicine believes that oral dirty and susceptible to foul toxicity causes mouth ulcers, tongue is the the seedlings of heart, Splenic pulse in the tongue, heat toxin filled, intrinsic Heart and after Heat toxin susceptible to heart along Meridians, the Yin and Blood consumption, Qi stagnation, the skin lost in Ruyang, Firelight on inflammation, splenic fever upstream steam fumigation tongue, oral ulcers generated.

Clinical Characteristics of Oral Ulcers

Oral Ulcers Diagnostic Criteria and Clinical Manifestations of Western Medicine is Shown In Table 1 [2]

Table 1. oral ulcers diagnostic criteria and clinical manifestations of Western medicine

	Recurrent oral ulcer	Damage of the oral mucosa ulcer
Diagnostic criteria	① female susceptible;② occurs throughout the oral mucosa;③ shallow ulcers, round or oval, generally 7 - 10 days of healing, no scar after healing, but can relapse.	① more common in adults, especially the elderly susceptible; ② lesions are located in the stimulus contact or adjacent parts; ③ early stimulation by mucosal redness, heavy stimulation caused by ulcer formation; ④ ulcer shape and the shape of the stimulus consistent; ⑤ long-term stimulation, the formation of deep ulcers, central depression, the surface has yellow and white pseudomembrane; ⑥ ulcer pain is not obvious; ⑦ to remove the local mechanical stimulation, ulcers soon disappeared.
Biochemical index	①TNF- α levels increased in the serum; ②CD4 + cells was significantly reduced in the peripheral blood; ③ superoxide dismutase SOD activity decreased in the serum; ④ malondialdehyde (MDA) content increased; ⑤IL-8 was significantly increased.	

Note: Recurrent oral ulcers in line with a item of 33.33%, (the diagnostic criteria set at 100%, three criteria, each about 33.33%);oral mucosal injury ulcer in line with a 14.285%, (the diagnostic criteria for the 100%, seven criteria, each about 14.285%); biochemical indicators do not participate in the evaluation of the degree of compliance, as a reference

Diagnostic Criteria and Clinical Manifestations of Oral Ulcers of TCM

Diagnostic criteria [6]

- ① the main symptoms: oral ulcers, pain, irritation pain.
- ② secondary symptoms: upset irritable, hot mouth, dry mouth, dark urine, dry stool.
- ③ examination: ulcer site congestion and edema, pseudomembranous bleeding ulcer surface, neat edges, round or oval, surrounded by flush.

Clinical manifestations

TCM believes that this disease in the oral topical but is closely related to body organs dysfunction, ancient physicians believe that brimming heat of the heart and spleen, fire excess from Yin deficiency, deficiency of qi and blood deficiency of both lung and stomach yin, flaring up of deficient fire, deficiency of spleen and stomach, virtual fire pan. Chinese medicine-discrimination analysis of oral ulcer is shown in table 2.

Table 2. Chinese medicine-discrimination analysis of oral ulcer[7]

Syndrome	Differentiation	Classification Symptoms	Tongue vein
Real disease	Brimming heat of the heart and spleen	Oral pain, thirst, bad breath, constipation urinate red, aphthous was yellow, surrounding mucosa red, slightly swollen and protruding, central depression.	Tongue red, tip of the tongue burrs, yellow tongue coating, pulse counting.
Deficiency syndrome	Fire excess from Yin deficiency	Oral pain, dry mouth and throat, dysphoria hot, palpitations, night sweats. microredness and swelling around the aphthous.	Red tongue, tongue coating thin, pulse counting.
	Deficiency of qi and blood	Chills, pale complexion, mental fatigue, fatigue and shortness of breath, loose stools. aphthous gray surface, mucosa around the color pink.	Pale tongue, thin white tongue coating, weak pulse.
intermingled deficiency and excess	Qi and blood deficiency of both lung and stomach yin, flaring up of deficient fire	Tongue edge ulcers on both sides, particularly the right side, large rupture surface, the center of projection, white surface mucosal erosion, swelling and pain, inconvenience language, drooling.	Red tongue, Thin white tongue coating less fluid,
	Deficiency of spleen and stomach, virtual fire pan	Emaciation, malnutrition, malaise and fatigue, loss of appetite ,oral cheeks, tongue edge ulcers shows multiple points, yellowish pseudomembrane covering the surface,hyperemia, consciously burning pain.	Tongue coating thin, pink tongue, less moss, pulse counting.

Animal Model of Oral Ulcers Research Status (table 3)

Table 3. Description of oral ulcers model establishment and clinical degree matching

Methods	Drug	Features and application	Matching degree of clinical Symptoms
Chemical burning method	Phenol burning method [8,9]	Oral mucosal injury ulcer model. Advantages: modeling method is simple and easy, does not cause other secondary reactions, symptoms and clinical close. Disadvantages: the faster the model, not suitable for recurrent oral ulcers.	Meet the diagnostic criteria for TCM① ③, Meet the diagnostic criteria for Western medicine② ③ ④ ⑥⑦, biochemical indicators ①; anastomosis $\geq 71.43\%$; High anastomosis.
	Glacial acetic acid cauterization [3]	Oral mucosal injury ulcer model. Advantages: easy to operate, ulcer parts, size, depth easy to control, repeatability, high success rate. Disadvantages: chemical agents contact with mucosal easy to spread, leading to mucosal damage to expand the area, the area was not easy to fix the ulcer, ulcer size instability, not as a recurrent oral ulcer animal experiments.	Meet the diagnostic criteria for TCM① ③, Meet the diagnostic criteria for Western medicine② ③ ④ ⑥⑦, biochemical indicators ①; anastomosis $\geq 71.43\%$; High anastomosis.
Immune induction method	Injecting Freund's adjuvant added oral mucosal tissue homogenates [10]	Recurrent oral ulcer model. Advantages: Immunological modeling, and human oral ulcers occurred very similar. Disadvantages: more complex, time-consuming, ulcer number and location is not easy to control, for the low immune caused by oral ulcers.[11]	Consistent with traditional Chinese medicine diagnostic criteria ① ③, Western diagnostic criteria ② ③, biochemical indicators ② ③ ④ ⑤; anastomosis $\geq 66.66\%$; low anastomosis, less application.
Chemotherapy combined with chemotherapy burn Burning method	5-FU combined NaOH crystal burning [2]	Oral mucosal injury ulcer. Advantages: easy to operate, easy to repeat, pathological changes similar to humans; ulcers clear boundary, surrounded by congestion and edema, the ulcer surface size, shape and depth is relatively close. Disadvantages: Not suitable for animal experiments with recurrent oral ulcers.	In line with Western diagnostic criteria ② ③ ④ ⑤ ⑥ ⑦; anastomosis $\geq 85.71\%$. High anastomosis, widely used. Can be used as a study to promote oral mucosal healing.
Mechanical methods		Oral mucosal injury ulcer model. Advantages: mechanical method of manufacturing animal oral mucosal traumatic ulcers, ulcer size, depth easy to control, can observe the healing time and size of ulcers. Disadvantages: mechanical stimulation modeling, the size of its strength and the role of the length of time is different, is bound to lead to the emergence of the disease have their own characteristics. Uses: Applicable to a method of treatment of simple trauma caused by ulcer effect of the screening model.[12,13]	In line with traditional Chinese medicine diagnostic criteria ① ③, Western diagnostic criteria: ② ③ ④ ⑤ ⑥ ⑦; anastomosis $\geq 85.71\%$. High anastomosis, widely used.

Note: the level of anastomosis that Western diagnostic criteria and clinical relevance of the relationship.
 High anastomosis: $> 70\%$; moderate anastomosis: $> 50\%$, $<70\%$; low anastomosis: $<50\%$. Chinese medicine diagnostic criteria as a reference.

Discussions

Oral ulcers Western etiology and pathogenesis is unknown, at present, it is related to many factors such as heredity, autoimmune, imbalance of copper and zinc in the human body, iron deficiency, microcirculation disturbance, local trauma and infection. The disease is mostly in the category of "sores" of traditional Chinese medicine, Local treatment combined with systemic therapy [14]. Oral ulcers are not only associated with these factors, but also with environmental factors, systemic diseases (gastric ulcer, duodenal ulcer, cirrhosis, biliary tract disease[15], etc.), psychological factors [16] (interpersonal sensitivity, depression, anxiety, etc.) related. Most of the existing models showed significant tenderness, ulcer around the mucosal congestion, ulcers were round or oval, surrounded by flush around; but the biochemical indicators failed to show it. At present, the common animal model of oral ulcer model rabbits, rats, guinea pigs, golden hamster and so on. There are many methods for the preparation of animal models of oral ulcers, such as immune induction method, chemotherapy, electrocautery method, mechanical method, bacterial infection induction method, radiation method, chemical burning method and so on. , Has not yet formed a unified standard animal model, nor oral ulcer animal model evaluation method. Oral ulcer model is mostly Western medicine pathological model, oral ulcer animal model of the study, although there are many, but not based on traditional Chinese medicine to reproduce the oral ulcer animal model. Superimposed on the basis of the existing model of oral ulcers, the establishment of disease with animal model which has the characteristics of TCM syndromes, more suitable for Chinese medicine related research.

Acknowledgements

The research work is supported by The national "eleven five" supported program (2008BAI53B09); Henan Science and Technology Innovation Team (TCJ2014-391); science and technology innovation team of Zhengzhou city (131PCXTD612). [1]J.

van der Geer, J.A.J. Hanraads, R.A. Lupton, The art of writing a scientific article, J. Sci. Commun. 163 (2000) 51-59.

References:

- [1] Pei-pei Tang, Ming Bai, Ming-san Miao, Effect on guinea pig Oral ulcers model of *artemisia argyi* decoction for external use, J. Journal of Chinese medicine. 27(2012)1286-1289.
- [2] Jin-liang Deng, Common clinical classification and diagnosis of oral ulcers, J.China's practical medicine. 5(2010) 230-231.
- [3] Qi Chen, Cheng Luo, Hong Chen, Etc, Progress of animal models of oral ulcer , J. Sichuan medical.36 (2015) 234-236.
- [4] Cheng Yao, Min-he Shen, Shan-mingYuan , Establishment of animal model Oral ulcers , J. Shanxi traditional Chinese medicine. 30 (2014) 46-47.
- [5] Kai Xiao, Xin Yan, Ming-sanMiao, Effect on guinea pig Oral ulcers model of *nitidum* for external use, J.Traditional Chinese medicine new medicine With clinical pharmacology. 23(2012) 533-537.

- [6] Xiao-yu Zheng. Chinese medicine clinical research guidelines for new drugs, chinese medical science and technology press, Beijing, The first edition, 2002, pp.333-337.
- [7] Jian-dong Hu, Jing Sun, Yuan Xue, Etc, Study Recurrent oral ulcers TCM syndrome and clinical factors, J. Journal of Chinese medicine. 30(2012)2348-2351.
- [8] Dan-dan Liu, Ming Bai, Ming-san Miao, Effect of Asarum vinegar paste for external use Oral ulcers on guinea pig model, J. Journal of Chinese medicine. 27(2012) 334-337.
- [9] Dan-dan Liu, Xiao-fang Guo, Ming-san Miao, Araceae vinegar paste, paste affect wine for external use oral ulcers in guinea pigs, J. Traditional Chinese medicine pharmacology And clinical. 28(2012) 93-96.
- [10] Fang Zhou, Dong Li, Dan-yang Wang, Etc, Analysis of changes in Recurrent oral ulcers rats immunological function and serum factors, J. Shanxi medical journal. 43(2014) 942-944.
- [11] Jin-feng Wang, Wen-hui Liu, Xue-ning Jin, Etc, Role of licorice Ze Xie Tang formula granules for recurrent oral ulcers in rats, J. Chinese journal of experimental formulas of Chinese medicine. 20(2014) 143-146.
- [12] Sukhitashvili N, Imnadze I, Tabaghua G, et al, Characterization of Oral ulcer and pathological scar in nude mice model, J. Georgian MedNews. 20 (2012) 82-87.
- [13] Tanideh N, Namazi F, Andisheh Tadbir A, et al, Comparative assessment of the therapeutic effects of the topical and systemic forms of Hype-ricumper stratum extract on induced oral mucositis in golden hamsters, J. Int J Oral Maxillofac Surg. 5(2014) 1-7.
- [14] Shi Pengzhan, Progress on therapy for the treatment of recurrent oral ulcers, J. Shanxi traditional Chinese medicine. 32(2011) 247-249.
- [15] Suwimon Jettanacheawehankit, Siriruk Sasithanasate. Acemannan Stimulates Gingival Fibroblast Proliferation; Expressions of Keratino-cyte Growth Factor-1, Vascular Endothelial Growth Factor, and Type I Collagen; and Wound Healing, J. Sci, Journal of Pharmacological. 10(2009) 525-531.
- [16] Cowan D, Oral Aloe vera as treatment for osteoarthritis: a summary, J. Br Community Nurs. 15(2010) 280-282