

Effect of traditional Chinese medicine *Bupleurum* in the treatment of influenza A (H1N1)

Jihong Yao¹, Haiyan Zhang², Li Ma¹, Xiaoli Mu³, Yonghong Wang³, Yuanzhen Lu³, Pengfei Yu⁴ and Hong Dai^{3*}

¹The department of traditional Chinese medicine of Yantaishan Hospital, Yantai, China

²The Medicine department of Yantaishan Hospital, Yantai, China

³The Respiratory department of Yantaishan Hospital, Yantai, China

⁴The Respiratory department of Yuhuangding Hospital, Yantai, China

Abstract: The treatment of influenza A (H1N1) is mainly antiviral treatment, symptomatic treatment or traditional Chinese medicine treatment. Previous studies showed that the extract of *Bupleurum* has the functions of anti-inflammatory, antiviral, regulating the immune system and so on, which can be used to treat influenza. In this paper, we analyze the drug effect of *bupleurum* compound medicine, at the same time, using oseltamivir as control group. The results showed that the Chinese medicine *chima qingwen decoction* had certain antiviral effects. No adverse reactions occurred during the treatment period, and the overall effective rate was 93.3%. It shows that combination therapy of Chinese and Western medicine is feasible for mild cases of influenza A (H1N1). Therefore, the research and development of Chinese medicine preparations has positive research significance and sufficient market potential.

Keywords: Antiviral drugs, *bupleurum*, oseltamivir, clinical symptoms, traditional Chinese medicine.

INTRODUCTION

In recent years, the epidemic of influenza A (H1N1) has spread in many countries and regions around the world (Ning *et al.*, 2012, Monto 2017). In a few months, the pandemic in the world (Balasubramaniam *et al.*, 2014). Most cases are mainly light symptoms. With the spread of the epidemic, the number and number of critical cases are increasing (Pistevou *et al.*, 2015, Hsuan 2016). The influenza virus is a new strain of influenza A (H1N1) and has a fast transmission speed. The infection cases in China changed from input to localization and from sporadic cases to clustered outbreaks (Ozgur *et al.*, 2015). At present, the epidemic of influenza A (H1N1) influenza in the mainland of China is still in a low period. Experts believe that there will not be a large outbreak in the near future (Reber *et al.*, 2013). However, there may still be a small cluster of epidemic situations in local areas and population centers (such as schools, etc.) and cases and cases of death are still possible (Fuu *et al.*, 2017). The first clinical treatment of influenza A (H1N1) is mainly antiviral treatment, and then to transition to symptomatic treatment or directly using traditional Chinese medicine (Cahill *et al.*, 2015).

Bupleurum is commonly used in traditional Chinese medicine, bitter, acrid, slightly cold, it can promote sweating, and has liver catharsis function (Dan *et al.*, 2015). It is found that *Bupleurum* has the functions of anti-inflammatory, antiviral, anti-tumor, regulating endocrine and immune system. *Bupleurum saponin* has

effects on many inflammatory processes, including exudation, capillary permeability, release of inflammatory mediators, leukocyte migration and connective tissue hyperplasia (Gaopeng *et al.*, 2015). Thromboxane and leukotrienes are the main inflammatory mediators, which can cause platelet aggregation (Bulut *et al.*, 2015; Chang *et al.*, 2016). It is found that *Bupleurum saponin* can significantly inhibit the platelet aggregation induced by adenosine triphosphate, which is equivalent to aspirin (Chang *et al.*, 2016). In addition, the researchers also found that *Bupleurum saponin* is an effective inhibitor of Na⁺-K⁺-ATP enzyme (Hsuan *et al.*, 2016), which can cause a significant increase in blood sugar, ACTH, aldosterone, vasopressin, corticosterin and strengthen the metabolism of sugar, salt and water and also produce anti-inflammatory, anti allergic, anti ulcer, antiviral and other effects (Stephen *et al.*, 2016). Based on the traditional Chinese medicine *chima qingwen decoction*, which mainly includes *bupleurum*, *Pueraria lobata*, *ephedra*, *Scutellaria baicalensis*, *honeysuckle*, etc. Then We analyze the application of *Bupleurum compound* and its clinical effect in the treatment of influenza A (H1N1).

MATERIALS AND METHODS

Research object

We choose 120 cases who have mild influenza A (H1N1) and admitted in our hospital in 2016 as research object. Including 62 males and 58 females, aged 14~65 years, with an average of (22.5±8.6) years. The diagnosis of influenza A (H1N1) is carried out according to the criteria for diagnosis and treatment of influenza A, which is issued by the Ministry of health. They were randomly

*Corresponding author: e-mail: daihong_sd@163.com

divided into TCM group (experimental group) 60 cases and antiviral group (control group) 60 cases. There was no significant difference in the average age, sex, disease and past history between the two groups. All patients were approved by ethics committee of our hospital, approval number of the ethics committee as 2015TCMYH5D and all patients signed on the informed consent.

Diagnostic criteria

The main symptoms include fever, aversion to wind, headache, stuffy nose and yellow nose, red throat sore throat, cough. Local symptoms include sneezing, stuffy nose, runny nose, cough, sore throat, hoarseness with tears. Systemic symptoms include fever, malaise, headache, dizziness, limb or back pain (Schmidt *et al.*, 2013).

Inclusion criteria: (1) Conforms to the diagnostic standard of Western medicine. (2) Conforms to the standard of TCM syndrome diagnosis. (3) 48 hours after the onset of the disease. (4) The age is 18-65 years old. (5) Sign informed consent. And exclusion criteria as: (1) Women in pregnancy and lactation. (2) Patients with psychosis. (3) Combined with heart, liver and kidney function and severe hematopoietic diseases. (4) People who have used other drugs. (5) Anaphylaxis or allergic to a variety of drugs. Expulsion or shedding standard: (1) Those who met the inclusion criteria, failed to take the prescribed medication or withdrew from the hospital, could not decide whether the efficacy or information was incomplete or not. (2) Adverse events, complications or special treatments should not be accepted.

Therapeutic method

The Chinese medicine group was treated with *chima qingwen decoction*, 2 times a day for 5 days, and the children's dosage should be reduced by half. *Chima qingwen decoction*: Bupleurum 20g, *Scutellaria baicalensis* 10g, *Pinellia ternate* 10g, *Radix pseudostellariae* 10g, Ginger 10g, Jujube 10g, Licorice 6g, on this basis, adding gypsum, honeysuckle, forsythia, *Folium isatidis*. Antiviral group took oral oseltamivir, every 75 mg (50 mg children), 2 times a day, a course of 5 days.

Observation index

The clinical features of the patients were observed: fever, fear of wind and cold, sweat, pharynx symptoms and nasal congestion; the observation time of the two groups was 5 days, and the improvement of the symptoms was observed and the effect was evaluated and the adverse reaction was observed. The clinical efficacy was evaluated by 4 levels (Sheng *et al.*, 2015). (1) Recovery: The treatment effect and signs disappeared, symptom scores reduce more than 95%. (2) Effect: treatment effect and signs of significant improvement, reduce the

syndrome score is greater than or equal to 70%. (3) Partially effective: The treatment effect and signs were improved, symptom scores reduce more than 30%. (4) Invalid: treatment effect and signs did not improve significantly, or even increased, and the score of syndromes decreased by less than 30%.

STATISTICAL ANALYSIS

SPSS 10 statistical software was used for data processing, and the sample size was compared with t test. The efficacy of the two groups was compared with the χ^2 test.

RESULTS

Clinical symptoms

120 cases of mild H1N1 influenza were diagnosed as fever (108 cases, 90%), cough (95 cases, 79.1%) and sore throat (74 cases, 61.6%), followed by headache (52 cases, 43.3%) and whole body aches and fatigue (45, 37.5%), nasal congestion, runny (41, 34.1%), upper respiratory symptoms, lung signs obviously, as shown in table 1. The two groups of sex, age, and body temperature are compared as shown in table 2.

Comparison of two groups of curative effects

The main mechanism of the antiviral drug oseltamivir is to interfere with the replication of influenza virus and its distribution in mucosal secretions, and reduce the infection activity of viruses. Oral oseltamivir treatment period, no adverse gastrointestinal reactions occur. Chinese medicine *chima qingwen decoction* has a certain non specific antiviral effect, to regulate the immune function of the body, enhance the resistance of the human body to the virus and achieve the purpose of treatment. No adverse reactions occurred during treatment, and patients' compliance was good. This shows that the combination of traditional Chinese and Western medicine is completely feasible for the cases of influenza A (H1N1) avoiding the phenomenon of resistance caused by the mutation of virus genes that may be caused by antiviral drugs alone.

DISCUSSION

Influenza A (H1N1) is an acute respiratory infectious disease caused by a new influenza virus H1N1 subtype strain (Tural *et al.*, 2015). Early symptoms of mild cases are similar to seasonal influenza, with influenza like symptoms as the main manifestation, and some cases can develop rapidly, even secondary severe viral pneumonia, respiratory failure, or multiple organ failure (Xiong *et al.*, 2015, Vekov *et al.*, 2015). For severe cases, antiviral and anti-inflammatory combined therapy and basic diseases should be treated. The clinical symptoms of influenza A (H1N1) patients are mainly fever, coughing, sore throat, expectoration, or slight headache, nasal congestion, runny

Table 1: Main clinical symptoms

Symptom	Cases	Percentage
Fever	108	90.0
Cough	95	79.1
Sore throat	74	61.6
Headache	52	43.3
Malaise	45	37.5
Nasal congestion, runny nose	41	34.1

Table 2: Patient condition

Factor		Treatment group (n=60)	Control group (n=60)	t-value	p-value
Gender	male	28	31	1.32	0.057
	female	32	29		
Average age		25.4±7.6	24.2±7.1	2.64	0.024
temperature	Before treatment	37.53±0.58	37.62±0.64	2.37	0.003
	After treatment	36.71±0.27	36.68±0.32		

Table 3: Comparison of two groups of curative effects

Group	Classification of curative effect				total effective rate
	Recovery	Effective	Partial validity	Invalid	
Treatment group	19	24	13	4	93.3
Control group	17	25	11	7	88.3

Table 4: Symptomatic signs after treatment

Symptom	Treatment group (n=60)		Control group (n=60)		χ^2
	Before treatment	After treatment	Before treatment	After treatment	
Fever	60	1	60	0	
Cough	42	8	38	9*	3.56
Sore throat	35	4	42	5*	5.12
Headache	39	2	35	4	
Malaise	32	0	30	0	
Nasal congestion, runny nose	41	2	45	6*	6.48

Note: *P < 0.05, there were statistical differences.

nose, whole body ache, fatigue and so on, and the pulmonary signs are often not obvious (Yanyan *et al.*, 2017). The main mechanism of the antiviral drug oseltamivir in the treatment of influenza is to interfere with the replication of influenza virus and its distribution in mucosal secretions, and reduce the infection activity of viruses (Zhu *et al.*, 2015). The results showed that a very few elderly people could have severe complications such as trachea spasm, dyspnea, rash, urticaria, oropharynx edema after the treatment of oseltamivir (Reber *et al.*, 2013). The control group was treated with oseltamivir adverse drug reactions did not occur during treatment.

Bupleurum chinese has certain non-specific antiviral effects (Umar *et al.*, 2017). It can achieve the purpose of treatment by regulating the immune function of the body and enhancing the body's resistance to the virus. *Chima Qingwen decoction* includes bupleurum, *Scutellaria* and other herbs, while adding gypsum, honeysuckle, forsythia,

Folium isatidis. It plays a significant role in enhancing cellular immunity, humoral immunity and macrophage phagocytosis (Wei *et al.*, 2017). *Chima Qingwen decoction* has obvious anti influenza virus effect, and its side effect is small, its effect is better than the disassembly group; in *Chima Qingwen decoction*, the anti influenza effect of *Radix bupleuri* and *Scutellaria baicalensis* is the strongest, which also indicates that *Bupleurum* and *Scutellaria* may play a major role in the anti influenza virus infection (Wang 2016). Chinese patent medicine has its unique advantages in the treatment of acute upper respiratory tract infection, not only improving clinical symptoms, but also has significant effect (Fuu *et al.*, 2017). At the same time, it has the dual function of enhancing or regulating the immune system of the body (Cahill *et al.*, 2015). Therefore, the research and development of Chinese medicine or traditional Chinese medicine preparation has positive research significance and sufficient market potential (Ning *et al.*, 2012, Monto

2017). The drug has a certain non-specific antiviral effect to regulate the immune function of the body, enhance the body's resistance to the virus and achieve the purpose of treatment (Pistevou *et al.*, 2015). No adverse reactions occurred during treatment, and patients' compliance was good. Compared with antiviral group, there was no significant difference in the experimental group ($P > 0.05$). This shows that the combination of traditional Chinese and Western medicine is completely feasible for the cases of influenza A (H1N1) avoiding the phenomenon of resistance caused by the mutation of virus genes that may be caused by antiviral drugs alone (Hsuan, 2016). There is a certain limitation on the resistance to the pandemic of the flu, and the traditional Chinese medicine has a unique advantage in the treatment of viral infection, and it has a definite effect, which makes up for the shortage of antiviral drugs.

CONCLUSION

The incidence of influenza A is not optimistic, and is still at a stalemate. In autumn, winter and even next spring, a more serious epidemic may occur, and its incidence, severe illness and death toll may increase. The same research shows that there is no difference in curative effect between traditional Chinese medicine and Western medicine combined with antiviral therapy. Therefore, we take *Chima Qingwen decoction* to treat mild cases of influenza A (H1N1) and discuss the therapeutic effect of traditional Chinese medicine. The results showed that Chinese medicine has the advantage of treating viral infection, and the effect was exact, which made up for the shortage of antiviral drugs. Chinese medicine has a complete theoretical system for treating exogenous febrile diseases. The flexibility of TCM syndrome differentiation can cope with the variability of influenza virus.

ACKNOWLEDGEMENTS

Technical development project of Yantai Municipal Science and Technology Bureau 2010149-6.

REFERENCES

- Balasubramaniam A and Kuperstein E (2014). Update on oral herpes virus infections. *Dent. Clin. N. Am.*, **58**: 265-280.
- Bulut N and Altundag K (2015). Excellent clinical outcome of triple-negative breast cancer in younger and older women. *J. BUON.*, **20**(5): 1276-1281.
- Chang SY, Deu JM, Yoonae K and Ji M (2016). Identification of pyrrolo[3,2-c]pyridin-4-amine compounds as a new class of entry inhibitors against influenza viruses *in vitro*. *Bioche. Biophys. Res. Comm.*, **478**(4): 1594-1601.
- Cahill G, Tran L, Baker RA, Brown A, Huang YC and Ou CW (2015). Principles of radiation oncology. *Medi. J.*,

- 1**: 27-38.
- Dan L, Jie W, Li L, Ying W, Ling L and Xiao H (2015). Cytotoxic triterpenoid glycosides (saikosaponins) from the roots of *Bupleurum chinense*. *Bioor. & Medi. Chem. Let.*, **25**(18): 3887-3892.
- Fuu T, Tsung H, Chi C, Xiang Lu and Hsinyi T (2017). Effect of Chinese herbal medicine on stroke patients with type 2 diabetes. *J. Ethnop.*, **200**: 31-44.
- Gaopeng S, Xintian S, Sumei L, Yibin L, Yunpeng L and Yushan Z (2015). Structure-activity relationships of 3-O- β -chacotriosyl ursolic acid derivatives as novel H5N1 entry inhibitors. *Euro. J. Medi. Chem.*, **93**: 431-442.
- Ghoneum M, Felo N, Nwaogu OM, Fayanju IY, Jeffe JA, Margenthaler DB(2015). Clinical Trials in Surgical Oncology. *Asian Pac. J. Surg. Oncol.*, **1**(2): 73-82.
- Hsuan C, Shu M, Dino T, Yuh C, Li W (2016). Oral Ulcers as an Initial Presentation of Juvenile Pemphigus: A Case Report. *Pedia. & Neon.*, **57**(4): 338-342.
- Luo X (2015). Clinical research of azithromycin in treatment of acute enteritis. *Guangzhou Medi. J.*, **22**(3): 80-81.
- Monto A (2017). Moving toward improved influenza vaccines. *J. Infect. Dis.*, **215**: 500-502.
- Ning D, Qing C, Wei Z, Sumei R and Ying G (2012). Structure-activity relationships of saponin derivatives: A series of entry inhibitors for highly pathogenic H5N1 influenza virus. *Euro. J. Medi. Chem.*, **53**: 316-326.
- Ozgun Aytac H and Colacoglu T (2015). Predictors determining the status of axilla in breast cancer: Where is PET/CT on that? *J. Buon.*, **20**(5): 1295-1303.
- Pistevou K, Zygogianni A, Kantzou I (2015). Splenic irradiation as palliative treatment for symptomatic splenomegaly due to secondary myelofibrosis: A multi-institutional experience. *J. Buon.*, **20** (4): 1132-1136.
- Reber A and Katz J (2013). Immunological assessment of influenza vaccines and immune correlates of protection. *Expert Rev. Vaccines*, **12**(2): 519-536.
- Stephen C, Lee I, Min Y, Chun L and Chiang L (2016). Anti-melanoma activity of *Bupleurum chinense*, *Bupleurum kaoi* and nanoparticle formulation of their major bioactive compound saikosaponin-d. *J. Ethnop.*, **179**: 432-442.
- Schmidt A, Xu A, Khan T, 'Donnell S and Khurana L (2013). Preconfiguration of the antigen-binding site during affinity maturation of a broadly neutralizing influenza virus antibody. *Proc. Natl. Acad. Sci. USA*, **110**(13): 264-269.
- Sheng W, Zhang B, Chen W, Gu D and Gao W (2015). Laparoscopic colectomy for transverse colon cancer: comparative analysis of short- and long-term outcomes. *Int. J. Clin. Exp. Med.*, **8**(9): 16029-16035.
- Tural D and Kivrak Salim D (2015). Is there any relation between PET-CT SUV max value and prognostic factors in locally advanced breast cancer? *J. Buon.*, **20**(5): 1282-1286.

- Umar F, Sara K, Sadia N, Ajmal K and Afsar Khan (2017). A Three new anthraquinone derivatives isolated from *Symplocos racemosa* and their antibiofilm activity. *Chin. J. Nat. Med.*, **15**(12): 944-949.
- Vekov T and Lebanova H (2015). Pharmacotherapeutic recommendations for application of target oncological drug therapies for treatment of breast cancer in Bulgaria - therapeutic efficacy and cost effectiveness. *J. Buon.*, **20**(6): 1420-1425.
- Wang K (2016). Comparison of clinical efficacy of azithromycin and pefloxacin in treatment of acute enteritis. *Anti-Infection Phar.*, **12**(2): 371-374.
- Wei F, Yin Y, Bao G (2017). Anti-influenza triterpenoid saponins (saikosaponins) from the roots of *Bupleurum marginatum* var. *stenophyllum*. *Bioorg. & Med. Chem. Lett.*, **27**(8): 1654-1659.
- Xiong X, Corti D, Liu J, Pinna D, Foglierini M, Calder R and Martin Y (2015). Structures of complexes formed by H5 influenza hemagglutinin with a potent broadly neutralizing human monoclonal antibody. *Proc. Natl. Acad. Sci. USA*, **112**: 9430-9435.
- Yanyan W, Qiang G, Zhongbin C, Kewu Z, Hong L and Pengfei T (2017). New saikosaponins from the roots of *Bupleurum chinense*. *Phytoch. Lett.*, **21**: 183-189.
- Zhu H, Zhai D (2015). Clinical efficacy of azithromycin in treatment of acute enteritis. *Medical J. Chi. Peop. Hea.*, **24**(20): 17-18.