Clinical Application of TCM External Therapy for Primary Dysmenorrhea: A Systematic Evaluation

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Keywords: Primary dysmenorrhea, External treatment of traditional Chinese medicine

Abstract: Primary dysmenorrhea (PD) is widespread in women of childbearing age and brings troubles to patients' lives. Modern medicine believes that primary dysmenorrhea is closely related to blood circulation disorders caused by factors such as an imbalance of prostaglandin levels and tilted uterus. Adjusting prostaglandin level by oral non steroidal anti-inflammatory drugs and contraceptives can achieve the purpose of alleviating pain symptoms, which is effective but effective In many adverse reactions, the long-term effect is not ideal. The theory of traditional Chinese medicine(TCM)in the treatment of primary dysmenorrhea is one and the methods are diverse. A large number of literature have proved that the external treatment of TCM such as acupuncture, massage and acupoint application has achieved satisfactory curative effect in the treatment of PD, with less side effects and a low recurrence rate. External treatment of TCM can help alleviate primary dysmenorrhea and enrich the treatment methods of primary dysmenorrhea. It has unique advantages and is worth further discussion and research.

1. Introduction

Dysmenorrhea is part of the most common gynecological diseases. It refers to the spasmodic uterine pain during menstruation. The pain is the most severe on the first day of menstruation. It is normally located in the suprapubic area of the lower abdomen and can radiate to the lumbosacral and inner thighs for 2-3 days[1]. Some patients may go hand in hand with headache, fatigue, dizziness, nausea and other discomforts. Dysmenorrhea is subdivided into primary and secondary. Generally speaking, secondary dysmenorrhea refers to pelvic pain caused by pelvic organic diseases such as endometriosis, hysteromyoma and pelvic inflammation, while primary dysmenorrhea refers to dysmenorrhea without organic lesions in the pelvic cavity through the relevant examination. Depending on the epidemiological investigation in different regions, about 50% of women suffer from dysmenorrhea in varying degrees, of which PD accounts for even 90%[2], especially young women of childbearing age.

Women of childbearing age shoulder the responsibility of occupational pressure and procreation. Endocrine dysfunction and low immunity are caused by factors such as extreme life pressure and heavy ideological burden, which may promote PD attack. Affected by symptoms such as menstrual pain, most women suffer from work absenteeism or decreased concentration, and related medical expenses increase[3-4]. Ju H, through a cross-sectional study of clinical cases, found that 29% of the investigated women had severe pain during menstruation, which had many negative impact on life quality, work efficiency and medical care use[5]. Therefore, it is particularly major to actively explore therapeutic measures that can effectively relieve PD symptoms.

2. Background of Pd

Modern medicine convinces that the pathogenesis of PD is mainly the activation of endometrial cyclooxygenase pathway, which results in the increase of prostaglandins and leukotrienes, and the contraction of myometrium blood vessels makes the uterus ischemia, hypoxia and pain[6].Progesterone levels stabilize lysosomes, but at the end of the luteal phase, when progesterone levels drop, lysosomes decompose and release phospholipase A2. Phospholipase A2 involves the cyclooxygenase pathway and produces prostaglandins. Among the prostaglandins, PGF2αand PGE2

have the greatest impact on menstrual pain. Fajrin I found that women with PD have elevated levels of PGF2αactivity, and the stronger the pain, the higher the level of prostaglandin PGF2α[7].The combined action of PGF2α, PGE2 and leukorrhea not only stimulates nerve endings and reduces pain threshold, but also causes vasoconstriction and uterine muscle contraction, further restricting blood flow and exacerbating pain.

PD is also affected by the increase of vasopressin and oxytocin, excessive uterine flexion or retroflexion, low immune function and other factors[8].In addition, studies by Hu Z et al. believe that menarche occurs before the age of 12 or menstrual disorder, underweight, irregular diet and bad mood are all risk factors for PD[9]. The modern drug treatment of PD mainly uses non steroidal anti-inflammatory drugs (NSAIDs) and hormone symptomatic treatment to decrease the production of prostaglandins and leukotrienes, which can relieve pain. However, NSAIDs are not difficult to cause adverse reactions such as dizziness, headache, drowsiness, insomnia and other central nervous system, gastrointestinal tract, liver and kidney function damage, and even withdrawal symptoms and drug resistance[10]. The long-term use of hormonal drugs such as contraceptives can inhibit ovulation and cause trouble to the reproductive needs of women of childbearing age. Some women will also have side effects such as shortened menstrual periods, reduced menstrual volume, and even amenorrhea[11-12]. Overall, the advantage of oral western medicine in the treatment of PD is the fact that it can relieve pain quickly, but there are definite contraindications and side effects, and the condition is easy to repeat.

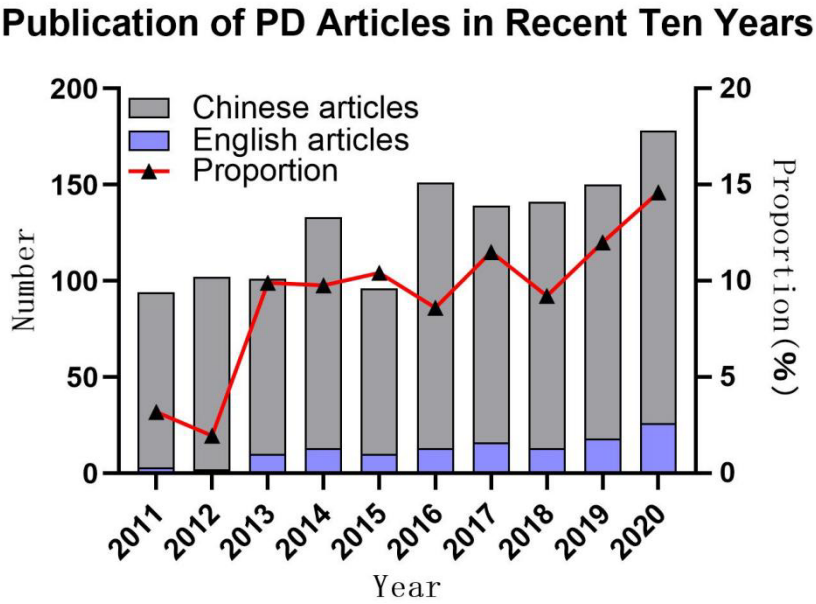

Fig.1 Publication of Pd Articles in Recent Ten Years

TCM has paid attention to PD as early as 610 AD. and it was not until the Qing Dynasty that “dysmenorrhea” was clearly proposed as the name of the disease and has been used until now[13].Since the Qin and Han Dynasties, TCM has gradually recognized the etiology and mechanism of PD, and its theories and methods for the treatment of PD are integrated. PD falls within the category of women's menstrual diseases. TCM believes that menstruation is related to the operation of viscera such as kidney, liver and spleen, the circulation of Chong, Ren, Du and belt, and the reproductive axis of kidney-Tiangui-Chong Ren-uterus. The spleen governs the blood, the liver stores blood, the kidneys store essence, and essence can transform blood. The liver, spleen and kidney function operates normally, the blood is injected into the body, the blood sea overflows on time, and the menstruation can arrive on time. When kidney, liver, and spleen function problems or meridian stagnation, qi and blood flow abnormally, it can be expected to result in PD. The etiology of PD is mainly due to stagnant movement or nor full of Qi and blood. Visceral dysfunction, leading to qi stagnation, cold coagulation, blood stasis, poor circulation of qi and blood, stagnation of body fluid, steaming and burning of damp heat to turn into phlegm, stasis blocking the uterus, and

obstruction leads to pain; Liver and kidney deficiency, Qi and blood weakness, Chong Ren and the uterus are lost in nurturing, it will be painful if it is not prosperous for a long time[14].In addition to the oral medicine, TCM often combines characteristic external treatment methods to alleviate and strive to eliminate the pain of PD patients. Commonly used external treatment methods in TCM include acupuncture, massage, moxibustion, scraping, herbal medicine application, ear acupoint pressing and so on.

According to opinion No. 760 issued by ACOG Committee in 2018, for the effective treatment of PD, hyperthermia, acupuncture and other methods can also be selected to assist in alleviating PD, indicating that external treatment has a certain effect on the treatment of PD [15]. Compared with the contraindications and side effects of some Western medicines, the external treatment methods of TCM are rich and diverse, with the advantages of high safety, small adverse reactions, low price and high efficiency, which is worthy of popularization and use.

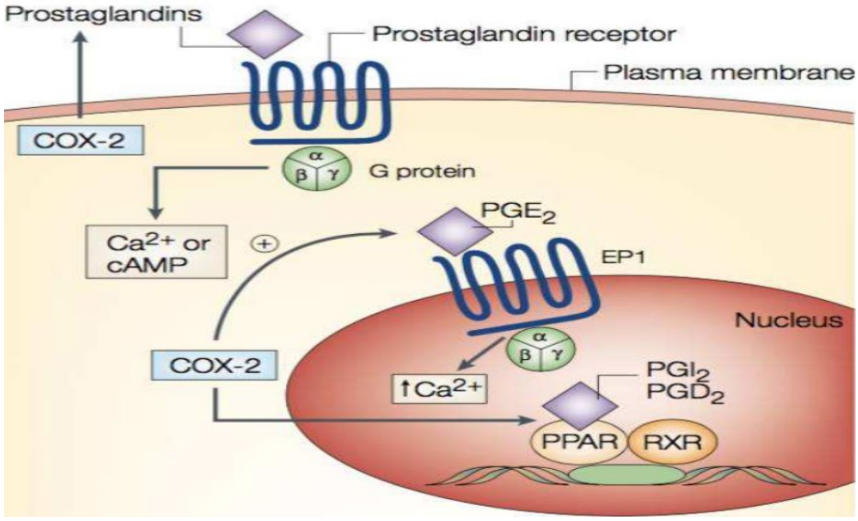

Fig. 2 Pge2 and Its Receptor Related Signaling Pathways (the Picture Comes from the Network and is Only Used to Represent the Relationship Diagram.)

3. TCM External Therapy of Pd

3.1 Acupuncture and Moxibustion Therapy

Under the guidance of the theory of TCM, acupuncture can dredge the meridians, activate the circulation of blood and Qi, harmonize the Yin and Yang of viscera, so as to achieve the purpose of preventing and treating diseases by stimulating specific acupoints with specific needles[16]. Moxibustion refers to a stimulation therapy of fumigating and burning acupoints on the body surface with the help of the heat ignited by moxas. It holds the functions of warming meridians, promoting qi and blood circulation, removing cold and expelling dampness. A number of domestic and foreign studies on basic research and clinical trials of acupuncture points analgesic mechanism have shown that acupuncture points could achieve analgesic effect by increasing pain threshold or activating substances such as 5-hydroxytryptamine and opioid peptides in the brain[17-18].

Acupuncture and moxibustion therapy have a long history and rich experience in the treatment of PD. Studies have demonstrated that acupuncture can reduce the level of PGF2αto relieve the spasm of uterine smooth muscle, so as to alleviate the pain of patients[19-21]. Studies by Gong CR, Yu SY and others have shown that the acupoints selected for acupuncture and moxibustion in the treatment of PD are mainly concentrated on the Ren meridian. Common acupoints are related to Guanyuan, Sanyinjiao, Zhongji, Shenque, etc., among which Guanyuan acupoint was selected with the highest frequency[22-23]. Stimulation of Guanyuan point can dilate local blood vessels, promote local uterine microcirculation, inhibit the synthesis of prostaglandins, reduce the release of PGF2α, and relieve uterine smooth muscle contraction, thus achieving the effect of pain relief [24-25]. After 4 months of treatment of 60 young PD patients with warming Shenque combined with acupuncture Guanyuan and Sanyinjiao, Liao BD found that the pain severity scores, total frequency and pain VAS scores of

PD patients were all lower than before treatment, indicating that acupuncture points can effectively alleviate PD symptoms[26].

Dysmenorrhea rats have obvious uterine microcirculation disorders and circulatory related substances. Acupuncture can improve uterine microcirculation during PD. The mechanism may be related to plasma thromboxane B2 and 6-keto-prostaglandin F1αlevel regulation is involved[27]. Guanyuan and Sanyinjiao were selected to moxibustion the PD model of rats induced by oxytocin. It was determined that moxibustion can antagonize the PD symptoms of rats induced by oxytocin. Its anti-PD effect may be related to improving blood rheology and lowering the content of PGF2αin uterine[28]. In the meta-analysis of the clinical efficacy of acupuncture versus ibuprofen in the treatment of PD, a total of 897 subjects were included in 23 RCT experiments, and the total effective rate, VAS score, and dysmenorrhea symptom score were analyzed. The results showed that the efficacy of acupuncture in the treatment of PD was preferable to ibuprofen[29]. Another study showed that compared with the control group, the level of PGE2 increased and PGF2 αdecreased in PD patients after receiving acupuncture at Shenque, Sanyinjiao, Zusanli, Hegu and Neiguan points, indicating that acupuncture and moxibustion is effective in the treatment of PD[30].

3.2 Massage and Scraping Therapy

As mentioned earlier, the occurrence of PD is also related to the position and tilt angle of the uterus. The normal position of the uterus depends on the support of the uterine ligaments and pelvic floor muscles and fascia. For example, under the influence of long-term adverse posture, the related fascia and muscle structure will change, which will lead to the change of uterine position[31-32]. Yuval Y believes that dysmenorrhea is related to the trigger point of myofascial pain in the muscles[33]. The results showed that there were more myofascial pain trigger points in rectus abdominous, quadratus psoas and paravertebral muscles in menstrual women.

TCM massage acts on the acupuncture points or painful areas of the patient's body surface. Which can relax the tendons and activate the meridians, unblock the qi and blood, and achieve the effects of detumescence and pain relief. Studies have shown that massage on the waist and abdomen can regulate muscles and bones, dredge the meridians, improve pelvic blood circulation, accelerate tissue repair, and reduce serum PGF2αlevels, so as to achieve the purpose of analgesia[34-35].A clinical case-control study showed that compared with patients taking ibuprofen, the menstrual serum PGF2αof PD patients was significantly reduced and PGE2 increased after Tuina treatment. Massage can improve the blood flow characteristics of the uterine artery with high resistance and low speed, thereby regulating abnormal PGF2 αand PGE2 level to exert analgesic effect[36]. Another study showed that massage combined with acupuncture can significantly increase the level of PGF2αin the PD patient's serum, and significantly reduce the level ofβ-EP[37]. The researchers used a double-blind, placebo-controlled method to randomly massage the abdomen and lumbosacral part of 65 PD patients with enzyme ginger oil and placebo. The test results showed that the dysmenorrhea symptom score and NRS pain score of the two groups were lower than those before treatment[38].

Scraping is to friction the skin surface with instruments such as horn and jade to stimulate the subcutaneous capillaries, so that to expand or rupture, resulting in flushing millet particles and papule like spots, as well as local heat and pain plaques. According to the research, the symptoms of PD patients treated with scraping and cupping were significantly relieved, and the effective rate of treatment reached 97.26%, while the effective rate of conventional western medicine treatment group was only 80.82%[39]. Physiotherapy such as scraping causes local slight damage to the body, which can promote blood circulation and cell metabolism, stimulate the body's own repair mechanism, enhance immunity, and thus promote disease recovery[40-41]. Therefore, TCM massage, scraping and other therapies can significantly improve the pain symptoms of PD by stimulating blood circulation in local tissues of PD patients, which is a feasible and relatively safe treatment for PD patients.

3.3 Acupoint Application Therapy

Acupoint application therapy is based on the meridian theory of TCM and uses drugs with

different effects to apply acupoints to stimulate local tissue microcirculation and promote the effectiveness of drugs. Modern pharmacological studies have found that the cuticle of the skin at acupoints is thinner, lower than the resistance of surrounding skin, which has external sensitivity and amplification effect on drugs[42]. Acupoint application stimulates the acupoints on the skin surface, quickly transmits the efficacy to the viscera through the meridians, giving play to the overall regulatory role of the body, avoiding liver and gastrointestinal damage that may occur by oral administration, and reducing the toxic and side effects of drugs[43]. TCM believes that the external application of herbal medicine to acupoints can achieve the purpose of promoting blood circulation and removing blood stasis and alleviate the pain of PD patients[44]. Clinically, oral administration of herbal combined with acupoint application is often used to enhance drug targeting and stimulation and improve curative effect[45].

Hu adopted a prospective randomized crossover double-blind clinical trial, in which 30 PD patients in the two groups were randomly treated by applying drugs and placebo to Guanyuan and Shenque point respectively on the basis of ibuprofen sustained release capsule, and the results showed that the pain symptoms of PD patients who received acupoint application were significantly relieved[46]. Studies have suggested that after acupoint application treatment, serum PGE2 of PD patients increased, PGF2αdecreased, and pain score decreased significantly[47]. Based on the idea of "prevention of disease" in TCM, clinical studies have found that external application at Guanyuan point to prevent PD before menstruation has significant clinical efficacy[48]. Acupoint application therapy is simple and easy to learn, widely obtained materials, inexpensive and simple drugs, with remarkable curative effect. It is suitable for clinical promotion and easy to be accepted by patients.

4. Other Therapies

After acupoint catgut embedding intervention in PD rats, uterine PGE2 and serum IL-2 content increased, PGF2αcontent decreased, and the analgesic effect was significant. The mechanism of which may be related to the regulation of neuro-endocrine-immune network[49-50]. Tang w suggested that the analgesic effect of catgut embedding at acupoints may be related to the down-regulation of p-NF-κB expression and coX-2 and PGF2αlevels[51]. In addition to acupoint catgut embedding, different therapies such as Chinese herbal hot embalming therapy, acupoint injection and ear point pressing beans can effectively relieve the symptoms of PD patients.According to the study, the visual analog score of PD patients decreased after treatment with Chinese herbal hot embalming, and the effect was significant[52]. Tang WJ's experiment found that the mechanism of Sanyinjiao and Guanyuan acupoint catgut embedding in the treatment of PD rats may be through the inhibition of NF-κB activation, reduce the level of COX-2 protein and effectively regulate uterine PGF2αof PD rats and synthesis, thereby improving the pain symptoms of PD rats[53].

Acupoint injection is based on the principle of acupoint application, combining the dual effects of drugs and acupoint stimulation, which can not only quickly dredge meridians, stimulate qi, relieve pain, but also enhance the effect of drugs, and achieve better analgesic effect in a short time. Xu QF injected extractant of salia miltiorrhiza at sanyinjiao acupoint to treat PD patients for 3 menstrual cycles, and the follow-up showed that the pain score of PD patients decreased in nearly 3 menstrual cycles after drug withdrawal, indicating that point injection therapy has outstanding clinical efficacy in the treatment of PD, and has good long-term effect[54]. Lu CX randomly divided 90 PD patients into ear acupuncture group, auricular point pressing group, and comfort control group. The study results showed that the clinical symptoms of the three groups were improved, ear acupuncture and auricular point pressing could adjust the levels of serum PGF2αand PGE2 in patients, and ear acupuncture had obvious advantages[55].

Because the position of the rectum and uterus is similar in anatomy, TCM believes that Chinese herbal extracts can be perfused into the rectum to relieve PD pain. Sun SH treated PD with Chinese herbal decoction enema combined with moxibustion. The total effective rate of the treatment group was 95%, which proved that pelvic microcirculation was improved, pain center was inhibited, and drugs were well absorbed without adverse reactions[56].

5. Conclusion

PD is a common disease in women of childbearing age. Lower abdominal pain and other accompanying symptoms seriously affect patients' daily life and work. At present, modern medicine mainly uses oral painkillers and contraceptives to temporarily relieve PD pain symptoms, but there are many side effects and the long-term efficacy is not exact. TCM has unique views on PD treatment. The external treatment of TCM has the characteristics of simplicity, convenience, simplicity and ease, with few adverse reactions, easy acceptance and strong patient compliance[57]. The appropriate application of TCM external treatment in the adjuvant treatment of PD patients will help to improve the quality of life and work efficiency of patients, and reduce the related medical expenses.

TCM external treatment for PD has broad prospects in clinical practice, but there are still some deficiencies:(1) Lack of unified and standardized syndrome differentiation, basis and treatment plan; (2)Lack of multi center, large sample clinical randomized controlled study, few related basic and clinical evidence studies; (3)There are few foreign literatures, most of which show the treatment of TCM external treatment in China, and lack of research data from other countries. In view of the above deficiencies, scientific research programs should be designed in the future to provide high-level evidence-based medical evidence for the application of TCM external treatment, so as to form a unified, more convenient and effective PD treatment program and promote its use.

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