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Overview of Warm Acupuncture for Chemotherapy-Induced Peripheral Neuropathy

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Abstract: *Chemotherapy-induced peripheral neuropathy (CIPN) is one of the common side effects in tumor treatment and has now become a thorny problem limiting tumor treatment. Due to the complex mechanism of CIPN, it is commonly treated clinically with symptomatic treatment, supplemented by sedation and antidepressants, with poor therapeutic effects. In this paper, we review the treatment of CIPN with warm acupuncture in order to provide reference and basis for the clinical treatment of CIPN.*

Keywords: *Warm Acupuncture, Chemotherapy-Induced Peripheral Neuropathy, Review*

1. Introduction

In the process of destroying tumor cells, chemotherapy drugs often damage normal cells indiscriminately [1], and the sensory impairment caused by damage to peripheral nerves or autonomic nerves is called "chemotherapy-induced peripheral neuropathy (CIPN). ". Chemotherapy- induced peripheral neuropathy (CIPN) is a common toxic reaction to chemotherapy drugs. The overall incidence of CIPN is reported to be greater than 60% in cancer patients, and about 30% of patients suffer from it for a long time, especially in chemotherapy drugs such as platinum, fluorouracil, microtubule protein inhibitors paclitaxel and vincristine, immunomodulator thalidomide, and proteasome inhibitor bortezomib [2], and it is mostly dose-dependent, and it is often delayed clinically by reducing the dose of chemotherapy drugs or discontinuing them CIPN, which seriously affects the efficacy of chemotherapy and patients' quality of life [3].

The typical clinical manifestations of CIPN are symmetrical burning sensation, tingling sensation, sensory loss, numbness and other symptoms in a "glove-sock" distribution at the end of the extremities, impaired fine motor movements (buttoning, earring) and sensory ataxia on examination. Motor neuropathy can also be combined with muscle weakness or (and) tremor of the muscle bundles, mainly characterized by diminished deep and ankle reflexes [4,5]. Autonomic neuropathy also often accompanies, such as abdominal pain, diarrhea/constipation, chest pain or even postural hypotension and laryngospasm. In addition, neurogenic pain is one of the common manifestations of CIPN, which is more likely to affect patients physically and psychologically compared to somatic pain and often requires analgesic and antidepressant treatment [6].CIPN symptoms may resolve after drug discontinuation and last for months or even years.

Chemotherapeutic drugs mainly damage sensory neurons on the dorsal root ganglion (DRG) of peripheral nerves by damaging them, and the incidence and extent of the disease are related to dose intensity, cumulative dose, treatment schedule, duration of administration and evaluation interval, genetic factors, and underlying diseases. The mechanisms of its development are now reported to be intricate and not yet definitive, and may be related to inflammatory stimulation, ion channel alterations, mitochondrial damage, oxidative stress, and axonal transport in neuronal cells [7].

2. The Pathogenesis Contains the Following Five Major Categories

Disruption of neuronal cell axonal transport: neuronal cells on the DRG depend on their built-in microtubule axons to transmit information and provide energy in order to survive. Similarly, microtubulin inhibitors are a type of inhibitors that affect spindle microtubule formation by inhibiting

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microtubulin polymerization, leading to vesicle accumulation, endoplasmic reticulum disruption at the synovial surface causing damage to peripheral neuronal axonal transport tracts and necrosis of DRG neuronal cells, triggering CIPN [8, 9]. Similarly, it has been shown that cisplatin inhibits DRG neuronal cellular transport [10], and Jordan P et al [11] have offered an explanation: cisplatin and DNA can form 1,2-stranded intra-adducts in the form of d(GpG) or d(ApG), which directly prevents the transcriptional process of RNA polymerase I on the DNA template strand and causes premature termination of transcription, affecting the transcriptional process in the nucleus subsequently This leads to impaired protein synthesis and axonal transport in neurons.

Altered ion channels: The stability of ion channels is important for maintaining the vital activities of the body. Vincristine and platinum drugs often target ion channels and cause clinical reactions such as pain and allergy.Starobova H [12] and Andersson [13] et al. found that by interfering with the calcium transporter on the mitochondria, Vincristine makes Ca2+ difficult to be taken up and transported by the mitochondria and accumulates in the cytoplasm, causing Ca2+ to be active and affecting its influx into the extracellular This leads to increased neurotransmitter secretion and damage to glial cells can cause CIPN. Krishnan et al [14] showed that oxaliplatin leads to increased Na+ outflow and decreased inward flow in dorsal root central neuron cells, increased negative membrane potential and weakened action potential, leading to peripheral nerve hypersensitivity and hyperexcitability, mediating acute peripheral neurotoxicity of oxaliplatin.

Mitochondrial dysfunction: normally active mitochondria are able to maintain the basic function and metabolism of neurons. Peripheral nerve damage and myelin mitochondria maintain the function of distal nerves, skin innervated by epidermal nerve fibers, and other areas require the budding or regenerative action of nerve axon collaterals, a process dependent on neurotrophic factors that consume large amounts of ATP derived from mitochondria to maintain the continuous growth of peripheral nerve axons and nerve fibers and to keep them resilient [15, 16]. Paclitaxel, as an inhibitor of anti-microtubule assembly, has been shown to cause impairment of mitochondrial function in sensory neurons, as evidenced by diminished mitochondrial respiratory function and reduced ATP production [17]. A study showed that cisplatin can damage mitochondria by binding nuclear DNA, inducing mitochondrial membrane depolarization and an increase in mitochondrial p53, causing behavioral abnormalities in CIPN [18].

Inflammatory stimulation: chemotherapy activates a large number of macrophages around peripheral nerves, Schwann cells and dorsal root ganglia, and macrophage infiltration leads to the release of cytokines (TNF-α, TL-1β, IL-6 and IL-8), inflammatory chemokines (human CC chemokine ligand 2 and CXC family), growth factors and inflammatory mediators (bradykinin, prostaglandins, serotonin and NO), causing peripheral pain sensitization [19]. In an animal model of CIPN [20], a high expression of transcriptional activator 3, a marker of nerve damage, was found around activated macrophages. In addition Langerhans Cells (LCs) act as antigen-refractory cells with a role in promoting inflammatory factor synthesis. A growing body of evidence [21, 22] suggests that vincristine and paclitaxel activate LCs to release specific antibodies to NO acting on peripheral nerve cell membranes, macrophage aggregation, activation of glial cells, and action on the terminal nociceptive receptors of C-fibers triggering CIPN.

Oxidative stress: An imbalance between the production of reactive oxygen/nitrogen radicals (ROS/RNS) in an organism and the antioxidant protection system can activate oxidative stress [23]. Chemotherapeutic agents mostly mediate peripheral nerve injury through increased ROS production due to mitochondrial damage, which activates oxidative stress. For example, platinum inhibits mitochondrial DNA replication in DRG neurons, which increases ROS production and damages peripheral nerves [24]. Kim et al[25] conducted in vitro experiments and detected that low expression of Keap1 caused upregulation of Nrf2 and peroxiredoxin reductase 1 (Prx1), thus exerting a scavenging effect on oxygen radicals in vivo, which could further reduce the development of peripheral neuropathy.

Western medicine has previously entered a large number of drugs into clinical studies to observe the effect of prevention and treatment of CIPN, including ion channel modulators, neuroprotective agents, neurotransmitter receptor inhibitors, antioxidants, etc., so far no positive results have been achieved. The current clinical management of CIPN is often empirical in terms of drug use, and the evaluation of clinical treatment effects is mixed [26]. The general measures and pharmacological treatments are discussed separately[27].

General measures: (1) strengthen nursing care, health education, bed rest, and ask patients to pay attention to warmth and avoid contact with cold objects, metal objects, and cold air; (2) eat a light diet

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and avoid spicy stimulation; (3) reduce skin friction on the extremities and do not apply irritating liquids or ointments; (4) use central venous infusion and avoid infusion of chemotherapeutic drugs from peripheral veins; (5) extend the time of sedative drug administration; (6) If CIPN occurs, according to the individual situation, the drug is immediately stopped, the drug dose is reduced or the duration of chemotherapy is extended, and after symptomatic treatment, chemotherapy is restarted after adjustment and recovery, i.e. "stop-and-go" reduction strategy [28].

Pharmacological treatment:The following are the main ones that are currently used clinically:

(1) Ion-channel modulators: e.g. calcium-magnesium combination, pregabalin, gabapentin, etc. As an ion channel modulator, calcium-magnesium combination against oxaliplatin-induced CIPN may be related to the oxalate base chelating Ca2+ in the pathogenesis of CIPN, thus calcium-magnesium combination has been tried for the prevention and treatment of CIPN. (2) Neuroprotective agents: Acetyl L-carnitine (ALC) and methylcobalamin are commonly used in clinical practice. As a natural compound involved in the acetylation of microtubulin, acetyl-L-carnitine has an important role in neuroprotection. Methylcobalamin is an endogenous coenzyme B12 that is distributed in large quantities within nerves and is important for nucleic acid synthesis in nerve cells, as well as repairing nerve cells, improving nerve conduction speed and improving the effects of symptoms such as limb pain and numbness. (3) Antioxidants: Amphotericin, reduced glutathione (GSH) and Vitamins B and group E are the main ones. Amphotericin is a broad-spectrum selective cytoprotective agent with potent free radical scavenging and antioxidant effects. Studies have shown that it can significantly reduce the incidence of CIPN without affecting the efficiency of chemotherapy, but it can increase the chance of nausea and vomiting and induce hypotension in patients; similarly, GSH is a free radical scavenger in the body, which can repair peripheral nerve cells and restore cell function, and has a better effect on nerve conduction velocity than traditional B vitamins [29]. (4) The two main groups are tricyclic antidepressants (TCAs) and antiepileptic drugs (AEDs), namely nortriptyline, amitriptyline and duloxetine. AEDs include gabapentin, pregabalin and carbamazepine. Pregabalin is commonly used for peripheral neuralgia as well as for the treatment of epilepsy. To date, the effectiveness of various types of clinical drug use has not been fully validated because the mechanism of action of CIPN has not been well studied, and authoritative organizations, including the American Society of Clinical Oncology (ASCO), do not recommend any method of providing prevention of CIPN [30].

With the increasing understanding of the symptoms of post-chemotherapy neurotoxicity, and combining Chinese and Western medical theories, it is classified as "blood paralysis" in Chinese medicine, whose main pathogenesis is deficiency of qi and blood, stagnation of qi and blood stasis, and deregulation of ying and gui, resulting in the loss of moistening of the limbs, which leads to symptoms such as numbness of the limbs. Warm acupuncture has shown great advantages in reducing the incidence of peripheral nerve pain, numbness, and other sensory abnormalities caused by chemotherapy, making up for the shortcomings of Western medical treatment.

Peripheral neuropathy is not clearly recorded in ancient medical literature, but the description of symptoms such as numbness, abnormal sensation and even pain in the limbs is similar to that of "blood paralysis", so peripheral neurotoxic lesions are classified as "blood paralysis". The term "blood paralysis" first appeared in "The Nine Needles": "When evil enters the yin, it is blood paralysis". The first time the term "blood paralysis" appeared was in "The Nine Needles": "When evil enters Yin, it is blood paralysis". As a complete name for the disease, it appeared in Zhang Zhongjing's "The Essential Guide to the Golden Kui", and in "The Essential Guide to the Golden Kui - Blood Paralysis and Void Labor Disease", it was pointed out that "blood paralysis ..... is cured when the pulse is weak and astringent, at the inch, and the small tightness on the gate. The blood paralysis yin and yang with micro, inch mouth on the micro, ulnar small tight, external evidence of the body is not benevolent, such as wind paralysis, Huangqi Gui Zhi Wuwu Tang is the main ".

TCM treatment emphasizes the principle of holistic concept and evidence-based treatment, which should not be neglected. At the same time, it should master the law of transmission and change, be dynamic and flexible, and take into account the strategy of "treating the untreated". Medical doctors of all generations have explained the causes of tumor from internal, external and non-internal causes. For example, The Treatise on the Origin of Diseases says: "Accumulation is caused by disharmony of yin and yang, weakness of the internal organs, and wind and evil in the internal organs", emphasizing the internal causes of disease; The Spiritual Pivot says: "The eight winds in the four seasons are in the meridians and veins, causing tumor disease", emphasizing the external causes of disease. On the basis of the "Three Causes Theory", we can learn from the modern tumor etiology and pay attention to the theory of disease caused by deficiency. Chemotherapeutic drugs are very poisonous products, which enter the blood and the ligaments and are prone to depletion of qi and blood. Blood can carry qi,

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nourish qi, blood is sufficient qi flourishing, blood deficiency is qi failure, blood deficiency qi is also lost, blood stasis is not smooth, then qi stagnation is not. Blood is the main moistening, blood is sufficient, nourishing and moisturizing effect is normal, then the performance of the muscle is full and strong, the skin is lustrous, tendons and bones are strong, feeling and movement flexible. Su Wen - Five Organs Generation says: "The liver receives blood and can see, the foot receives blood and can walk, the palm receives blood and can hold, the fingers receive blood and can take." If the blood is deficient, the nourishing and moisturizing effect is weakened, then the numbness of the limbs, inflexible movement, yellowish face, pale lips and nails, withered skin and hair, wasted muscles, and atrophied tendons and bones may appear. Tumor disease is long, chemotherapy consumes qi and blood for a long time, aggravating the internal deficiency, which is aggravated by qi deficiency over time and yin and blood deficiency. Qi deficiency is unable to transport blood, resulting in blood stagnation in the veins and collaterals, which causes pain and pins and needles; Qi deficiency is unable to produce new blood, resulting in loss of moistening of the skin, hair and muscles, resulting in abnormal sensation and numbness. In summary, CIPN is caused by single or multiple factors of "deficiency" or "stasis" or "toxicity" at the same time, with Qi and blood deficiency as the primary cause and drug toxicity and blood stasis as the primary cause. The pathogenesis is (Yang) Qi deficiency (Yin) blood stasis and meridian paralysis. The pathological nature of the disease is mainly internal deficiency at the beginning. The location of the disease is initially in the muscle surface and meridians, but for a long time it penetrates deep into the bone marrow and the five organs. The principle of treatment is to benefit the temperature and meridians, and to harmonize the blood to clear the paralysis.

In the Jin-Yuan period, the acupuncturist Dou Hanqing's "Piao-Yu Fu": "Cold and heat paralysis, open the four gates only." The "Acupuncture and Moxibustion Dacheng" has "four points, that is, the two Hegu, two Taichong is also." Hegu is the original point of the Hand Yangming Large Intestine meridian, good at regulating Qi, and belongs to the meridian of more Qi and blood, favoring to replenish Qi and activate Blood; Taichong is the original point of the Foot Convulsive Yin Liver meridian, which is good at regulating Blood, and belongs to the meridian of less Qi and more Blood, favoring to replenish Blood and regulate Blood[31]. The two points, one above and one below, one Yang and one Yin, one Qi and one Blood, are mutually dependent and useful, and their elevation is coordinated so that Yin and Yang can be connected smoothly; the simultaneous use of the two points has the effect of regulating Qi and Blood, invigorating Blood and removing blood stasis, and unblocking the meridians, and together with the moxa stick, they can fully achieve the effects of tonifying Qi and invigorating Blood, warming the meridians and opening the channels [32]. In the "Thousand Gold Wing Formula", it is said that "all diseases are caused by congestion of qi and blood, which cannot be promoted; acupuncture to open and guide, moxibustion to warm and pass." Warm acupuncture is based on acupuncture by heating the needle handle so that the warm stimulation of moxa fire is transmitted through the needle body to the deep acupuncture points, which can improve local microcirculation to move qi and activate blood; the power of warmth can unblock the blockage of meridians, so that the evil qi has no place to stay [33]. The warm acupuncture can make the heat source along the needle body into the body, and this warm effect can anti-inflammatory, promote blood circulation, and reduce nerve excitability.

Acupuncture, as is the gem of our medical treatment methods, has gradually gained attention in recent years and is used to improve CIPN with outstanding efficacy. And warm acupuncture is through the moxibustion fire corresponding heat to the human body acupuncture points to form a certain warm stimulation, the way has the function of activating blood, expelling cold, reducing swelling, warming the meridian, etc., may mobilize the body function for its own regulation, no side effects, and safe action. Acupuncture can microscopically and bidirectionally regulate the ion concentration in nerve cells, affect the transport of ion channels, enhance the antioxidant capacity of neurons, remove excess free radicals inside and outside the cells, restore normal cellular functioning, and improve peripheral neuropathy [34]. Cui Deli et al [35] divided 62 patients with CIPN into treatment group and control group by random grouping, 31 cases in each group, all of them were treated with chemotherapy with olisaplatin, and reduced glutathione was used to alleviate the presence of toxic side effects, during the experimental comparison, the treatment group used warm acupuncture in the interval of chemotherapy, mainly taking Quchi, Waiguan and Houxi points on the upper limbs, and mainly taking Yinlingquan, Foot Sanli and In the treatment group, warm acupuncture was used during the interval of chemotherapy, mainly at Quchi and Houxi points on the upper extremity and Yinlingquan, Foot Sanli and Yanglingquan on the lower extremity. Tian Yanping et al [36] treated 76 patients with CIPN with warm acupuncture, and conventional acupuncture treatment was performed at several acupoints such as Wai Guan, Qu Chi, and Tai Chong, and the duration of needle retention was 30 min. During the needle retention period, moxibustion was applied to the stems of six acupoints such as He Gu and Foot San Li

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to improve the neutralization effect of yin and yang and reduce pain, which significantly reduced the neurotoxic grading and improved the quality of life of patients.

The Suwen - Regulating the Classic: "Qi and blood, like warm but hate cold, cold is weeping and not working, warm is eliminating and going." Therefore, if you want to have a smooth flow of qi and blood, the temperature factor is not to be ignored. Warm acupuncture is a treatment method that combines acupuncture, moxibustion and specific acupoint stimulation. Clinical studies and animal experiments have confirmed that warm acupuncture is more effective than acupuncture alone, and warm acupuncture is the effect of acupuncture and temperature factor 1+1>2[37] .

3. Conclusions

In conclusion, moxibustion focuses on the heat conduction of meridian qi, while acupuncture focuses on the conduction of meridian qi. Warm acupuncture combines the effects of acupuncture and moxibustion in one, forming a high-temperature zone in the body and conducting it along the meridian, promoting vasodilation and other series of responses on the meridian high-temperature line, improving microcirculation, and reducing peripheral neurotoxicity. Clinical studies and animal experiments have confirmed that warm acupuncture is more effective than acupuncture alone, which is a synergistic effect of acupuncture and temperature factors. Warm acupuncture is a synergistic effect of acupuncture and temperature, which can reduce the excitability of neurons, improve blood circulation, enhance the local tissue metabolism and overall immune function, and relieve CIPN. It can effectively relieve the symptoms of chemotherapy-induced peripheral neuropathy, such as numbness, pain, weakness, etc., and ensure the smooth implementation of chemotherapy in the near term and improve the quality of life in the long term.

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