

Advances in the Intervention of *Prunella Spica* Capsules on Postoperative Recurrence of Nodular Goiter

Chuanwen SHI¹, Xiaogong YOU^{1*}, Qingyun LI¹, Honglei YANG¹, Yulin XU²

1. Taishan Vocational College of Nursing, Tai'an 271000, China; 2. Hospital of Luzhong Mining Co., Ltd., Jinan 271113, China

Abstract As important drugs for the treatment of nodular goiter (NG), *Prunella Spica* preparations are widely used clinically, and have a significant effect on NG. Various active ingredients in the preparations intervene in the formation of NG by inhibiting the proliferation of thyroid follicular cells, promoting cell apoptosis, regulating immunity, improving the microcirculation of thyroid tissue and other mechanisms, and can reduce the postoperative recurrence of NG.

Key words *Prunella Spica* capsules, Nodular goiter, Postoperative recurrence, Intervention

1 Introduction

The incidence of thyroid diseases has shown a rapid rising trend in China, from 4.5/100,000 to 12/100,000 in the past 10 years. In the clinical diagnosis of thyroid nodules (TN), nodular goiter (NG) accounts for more than 50%, and the current treatment methods are mainly surgical resection and drug therapy. The disease has a high risk of recurrence after operation, and has become a difficult problem in the clinical treatment of NG. In clinical practice, the scope of operation is often expanded to reduce the recurrence, but it is still controversial, and the clinical treatment strategy needs to be further standardized and adjusted. Traditional Chinese medicine has a reliable effect in the treatment of NG, and has advantages in prevention and treatment of postoperative recurrence. *Prunella Spica* preparations are important drugs for the treatment of NG and is widely used in clinic. On the basis of syndrome differentiation and treatment, the clinical application of *Prunella Spica* capsules has significant effect in the adjuvant treatment of NG postoperative recurrence, but relevant research and discussion are rare. The clinical research on its intervention in NG postoperative recurrence will be summarized as follows.

2 Epidemiology and pathogenesis of NG

NG, a common clinical disease, is more common in middle-aged women, and often appears in the nodular stage of diffuse nontoxic goiter. Its incidence is high in endemic areas of iodine deficient disorder (IDD). Its pathogenesis is not completely clear, and Western medicine believes that multiple factors are involved in the pathogenesis. In China, NG mostly develops from simple goiter, and it is generally believed that the pathological basis is the imbalance

of gland hyperplasia and involution. In the process of nodular formation, the thyroid follicular epithelium shows focal hyperplasia, and some tissues show degeneration. The hyperplasia and degeneration repeatedly alternate, so that nodules at different stages of development appear within the gland.

In Traditional Chinese medicine, thyroid nodules are divided into five categories, namely "five kinds of goiter". NG is a "fleshy goiter", and is related to improper diet, poor mood and personal constitution. The pathogenesis is characterized by "vitality", "depression" and "phlegm", so that phlegm is the primary pathogenesis of goiter. The formation of phlegm mostly attributes to liver depression. Western medicine believes that thyroid function is finely regulated by neuroendocrine, and mental overexcitement and depression in modern life often lead to abnormal regulation of thyroid function, resulting in the formation of pathological products such as vitality stagnation, blood stasis and phlegm turbidity in traditional Chinese medicine theory. Yin Lin *et al.*^[1] studied the relationship between pathophysiological characteristics related to thyroid nodule and anxiety and depression, and found that the maximum transverse diameter of benign nodule was positively correlated with anxiety score, again supporting the pathogenesis theory of NG emotional internal injury and liver dysfunction in Chinese medicine from the perspective of Western medicine.

3 Current situation of surgical treatment of NG

When NG produces compression symptoms and secondary hyperthyroidism, surgical resection is the main treatment means, especially for patients with multiple thyroid nodules graded as 3B and 4 TI-RADS. Surgical indications should be strictly followed, and surgical treatment should be performed as soon as possible. In order to minimize the effects of the surgery on thyroid function and tissue microenvironment, an appropriate surgical method should be adopted.

Received: May 8, 2023 Accepted: July 9, 2023

Supported by the Key Project of Teaching Reform Research of Taishan Vocational College of Nursing (202307).

* Corresponding author. E-mail: chuanwen2018@163.com

3.1 Choice of surgical methods and recurrence The relationship between the recurrence of NG and the scope of surgical resection has been a hot topic in thyroid surgery. At present, there are still differences on the choice of surgical methods for NG. Some doctors believe that it is appropriate to remove nodules and relieve symptoms through the surgery. However, due to the post-operative pituitary feedback mechanism, thyroid stimulating hormone (TSH) secretion is increased, which increases the chances of residual and contralateral thyroid tissue hyperplasia, resulting in an increased risk of postoperative recurrence. Some physicians believe that NG has a high recurrence rate, and re-operation after recurrence will increase the incidence of parathyroid gland and recurrent laryngeal nerve injury, so they advocate total or near-total thyroidectomy, but it has a greater impact on thyroid function. Jin Lailun *et al.* [2] found that the recurrence rate of the affected side was 93.33% in NG patients with simple nodule removal, suggesting that the recurrence was related to the growth of residual small nodules, and was essentially a "false recurrence". Therefore, lobectomy of the affected side is recommended for NG patients.

From the perspective of traditional Chinese medicine, it is not advisable to reduce the recurrence of NG by simply expanding the scope of surgical resection, and it is not in line with the theory and treatment principles of traditional Chinese medicine. Clinically, it is appropriate to take individualized operation according to the location, size, quantity, hyperplasia, and compression symptoms of nodules and the experience of the surgeon. It is recommended to stratify the recurrence risk of patients before surgery to maximize the protection of normal thyroid function on the basis of eradicating the lesion.

3.2 Tissue microenvironment characteristics of postoperative thyroid The tissue microenvironment of NG changes immediately after surgery, and postoperative recurrence is still difficult to avoid because the pathogenic factors have not been eliminated. As the soil where nodules occur, tissue microenvironment is an important factor for NG recurrence. Among them, there are many researches on the regulation of thyroid microenvironment by TSH, and TSH is regulated by hypothalamic-adenohypophyseal-thyroid axis, neurotensin, emotion and many other factors. The disorder of TSH regulation can cause biological effects of glandular cells and lymphocytes, and they interact with each other in the tissue environment and reshape the glands, resulting in cell hyperplasia. Under the action of chronic stimulation and inflammatory factors, macrophages and fibrocytes initiate the repair process and form nodules of different sizes again. Studies have shown that during postoperative biopsy of recurrent nodules, the activities of respiratory enzymes SDH and NADPH-d in glandular cells are changed, leading to impairment of cell oxygen utilization, suggesting that changes in postoperative tissue microenvironment may be a key factor of NG recurrence^[3].

3.3 Chinese medicine intervention in NG perioperative period

3.3.1 Overview of NG treatment by traditional Chinese medi-

cine. There is a lot of experience in NG treatment by traditional Chinese medicine. Acupuncture, external treatment and other methods have been used, and the results are very effective. There is no shortage of clinical reports on the treatment of NG based on syndrome differentiation, and more than 10 kinds of drugs are commonly used. The treatment is based on syndrome differentiation, and expectum, vitality-regulating and heat-clearing agents are mainly adopted. Traditional Chinese medicine with functions of promoting blood circulation and removing blood stasis, resolving hard lump, dispersing the liver and rectifying vitality are mainly adopted. The commonly used representative formulations are Haizao Yuhu Decoction, Sihai Shuyu Pill, Jiawei Xiaoyao Powder, Neixiao Luoli Pill, Xihaicao Granule, *etc.* Zhao Yong *et al.* [4] studied the rule of medicine used in the treatment of NG by traditional Chinese medicine. Among the 145 drugs of 103 prescriptions, they found that *Prunella Spica* was used the most frequently (74 times), and doctors of all dynasties used *Prunella Spica* more frequently to treat goitre.

3.3.2 Traditional Chinese medicine treatment to reduce postoperative recurrence. Traditional Chinese medicine thinks that the operation consumes vitality and blood, is easy to cause patients' vitality and blood deficiency in a period of time after the operation, so patients should take a positive and cautious attitude to the operation. More attention should be paid to syndrome differentiation in postoperative adjuvant treatment. Because the pathogenesis and pathological changes are different at different stages of the disease, and different prescriptions should be administered according to different clinical times. After NG surgery, the syndrome of blood stasis and vitality stagnation is obvious, and there is local inflammatory reaction. The interlocking of vitality, phlegm and blood stasis is the pathogenesis of this stage, thereby increasing the possibility of postoperative recurrence. Therefore, after visible phlegm is removed by the operation, it is appropriate to use drugs to relieve liver depression and clear phlegm stasis to prevent recurrence as soon as possible. In Western medicine, the endocrine treatment method of taking thyroxine tablets after surgery is more prone to subclinical hyperthyroidism and cardiovascular complications, and the auxiliary Chinese medicine treatment can significantly reduce the side effects of endocrine drug treatment, and can achieve the effect of removing blood stasis and eliminating goitre, and curing both symptoms and causes.

4 Application of *Prunella Spica* capsules in the treatment of NG

4.1 Analysis of pharmacology and medicinal properties of *Prunella Spica* capsules *Prunella Spica* is the dry ear of *Labiatae* plant *Prunella vulgaris* L. It is an important medicine for the treatment of NG. It is pungent and bitter in taste and cold in nature. It is mainly used to clear the liver and relieve the fire, diffuse knots and reduce swelling. *Prunella Spica* preparations com-

monly used in clinical practice include decoction paste, oral liquid, capsules, and tablets, and are made mainly by water extraction. The main components are triterpenoids, sterols, flavonoids and sugars, of which *Prunella Spica* polysaccharide is the main active component. Modern pharmacological studies have shown that the polysaccharide has the functions of anti-inflammation, anti-proliferation, anti-fibrosis, induction of tumor cell apoptosis, inhibition of granulation tissue proliferation, regulation of endocrine and improvement of microcirculation^[5].

Prunella Spica capsules extracted and concentrated by modern technology were included in the 2015 edition of *Chinese Pharmacopoeia*, and have the effect of clearing fire, dispersing knot and reducing swelling. The *Guide to Clinical Application of Proprietary Chinese Medicine* recommends that *Prunella Spica* capsules can be used for the treatment of thyroid diseases^[6].

4.2 Research status of *Prunella Spica* capsules used to reduce NG recurrence after the operation Surgery causes inevitable damage to thyroid tissue and blood vessels, so postoperative obstruction of blood flow is very common, and due to vitality stagnation and blood stasis, it is easy to lead to accumulation of dampness and phlegm, blood stasis block, Yin deficiency and blood stasis. *P. vulgaris* L. is named according to its characteristic of withering in summer. It has the effect of clearing liver heat, regulating liver qi, dispelling liver depression, tonifying liver blood, dispersing knot and eliminating goitre, detoxifying and detumefying, and so it can be used to prevent postoperative recurrence of NG. Modern medicine summarizes the mechanism of NG treatment by *Prunella Spica* in three aspects.

4.2.1 Inhibiting the proliferation of thyroid follicular cells and promoting cell apoptosis. Liu Jingru *et al.*^[7] studied 136 cases of NG, and found that after the treatment by thyroxine and *Prunella Spica* capsules, the maximum diameter of thyroid gland and thyroid nodules could be significantly reduced; the capsules inhibited tumor-associated fibroblasts (CAFs) by inhibiting the expression of basic fibroblast growth factor (bFGF). A number of studies have confirmed that the *Prunella Spica* used to cure thyroid diseases in different functional states can further shrink the volume of enlarged thyroid with the recovery of thyroid function, and *Prunella Spica* capsules can inhibit the secretion of hyaluronic acid, reduce edema, and inhibit the expression of adhesion molecule (ICAM-1)^[8]. Modern pharmacological studies have also shown that *Prunella Spica* is rich in bioactive substances and has anti-proliferation and pro-apoptosis effects on tumor cells. *In vitro* experiments have shown that it can down-regulate the expression of Bcl-2 and promote the apoptosis of thyroid hyperplasia cells^[9].

4.2.2 Regulating immunity. *Prunella Spica* can not only enhance immunity, but also inhibit immunity, that is, it has a bidirectional regulatory effect. Xiang Juan *et al.*^[10] found that the number of peritoneal macrophages of the mice administered with *Prunella Spica* increased, and the phagocytosis ability enhanced; the IgG content in serum also increased, suggesting that *Prunella*

Spica could enhance the immunity on the whole. Xiong Yi *et al.*^[11] found that the ethanol extract of *Prunella Spica* can significantly inhibit the diffusion of lipopolysaccharide (LPS)-mediated splenic cells in immune mice, indicating that the extract can inhibit cellular and humoral immune responses in the mice.

The main component of *Prunella Spica* capsules, *Prunella Spica* polysaccharide, has obvious effects on scavenging free radicals and anti-oxidation. Xiang Juan *et al.*^[10] found that *Prunella Spica* polysaccharide can effectively remove NO₂- free radicals, and has strong reducing ability and chelating ability to iron ion. Flavonoids, another active component of *Prunella Spica*, can significantly remove free radicals and has oxidation resistance.

4.2.3 Regulating thyroid function by improving thyroid tissue microcirculation. *Prunella Spica* can promote nodular shrinkage by improving the thyroid microenvironment. It can prevent atherosclerosis, and reduce blood lipids and blood viscosity. Tang Yonghe *et al.*^[5] found that the curative effect of blood stasis syndrome of NG by *Prunella Spica* was good. Besides, the treatment of NG by *Prunella Spica* capsules and levothyroxine tablets had good clinical efficacy, and they can improve clinical symptoms and regulate the levels of FT3, FT4, TSH and IGF-1, with good safety^[9].

5 Conclusions

To sum up, *Prunella Spica* is an important medicine for the treatment of "goiter" in traditional Chinese medicine, and it is cheap and effective. *Prunella Spica* capsules mainly made of this drug has a significant effect on NG. Various effective components in them can interfere with the formation of NG by inhibiting the proliferation of thyroid follicular cells, promoting cell apoptosis, regulating immunity, improving thyroid tissue microcirculation and other mechanisms, and can reduce postoperative recurrence. At present, studies on the application of *Prunella Spica* capsules in the intervention of postoperative recurrence of NG mostly stay in the stage of clinical observation, and there is a lack of clinical and animal experimental studies and research on the mechanism of action, which affects the clinical application. Therefore, it is necessary to use modern research technology to further improve the research on the postoperative recurrence of NG treated with *Prunella Spica* capsules, so as to promote the rationality and effectiveness of clinical use of *Prunella Spica* capsules.

References

- [1] YIN L, HUO SN, YU MA, *et al.* Relationship between pathophysiological characteristics of thyroid nodules and anxiety and depression[J]. Chinese Mental Health Journal, 2010, 23(9): 690–694. (in Chinese).
- [2] WANG JJ, ZHAO ZH, FU ZD, *et al.* Problems in thyroid nodule operation in primary hospitals and investigation of postoperative standard detection and drug use[J]. Chinese Journal For Clinicians, 20, 48(12): 1467–1469. (in Chinese).
- [3] CHEN LJ. Research progress in the pathogenesis of nodular goiter[J]. The Medical Forum, 2019, 24(22): 3241–3243. (in Chinese).

- [4] ZHAO Y, XU WH, CHEN RQ. Selection of common proprietary Chinese medicine for the treatment of thyroid nodules[J]. Chinese Traditional Patent Medicine, 2014, 36(6): 1334–1336. (in Chinese).
- [5] TANG YH, LIANG YY, WANG HY, *et al.* Clinical application and pharmacological action of *Prunella chinensis* in treating thyroid diseases [J]. Journal of China–Japan Friendship Hospital, 2019, 34(3): 176–178. (in Chinese).
- [6] WANG EM, QI RG, HAN LL, *et al.* Clinical Study on Xiakucao capsules in the adjuvant treatment of Hashimoto's thyroiditis[J]. New Chinese Medicine, 2019, 52(19): 91–94. (in Chinese).
- [7] LIU JR, WANG Q. Effect of *Prunella* capsule on autoantibody and Th17 cells in Hashimoto thyroiditis patients[J]. Chinese Journal of Gerontology, 2012, 32(24): 5413–5415. (in Chinese).
- [8] FU XD, ZHANG XF, MA LZ, *et al.* Effect of aqueous extract of *Prunel-*

la vulgaris on experimental autoimmune thyroiditis in rats[J]. Zhejiang Medical Journal, 2019, 49(9): 893–897. (in Chinese).

- [9] TU XQ, ZHANG JJ, PENG XB, *et al.* Study of mechanism of *Prunella vulgaris* decoction on thyroid cancer based on network pharmacology and molecular docking technology[J]. Lingnan Modern Clinics in Surgery, 2019, 20(5): 567–572. (in Chinese).
- [10] WANG BQ, XIANG J, WANG Y, *et al.* Improvement effect and its mechanism of *Prunella vulgaris* polysaccharides on Graves' disease mice [J]. Guangxi Medical Journal, 2019, 42(14): 1850–1854. (in Chinese).
- [11] XIONG X, ZHAO M, TAN JB, *et al.* Effects and mechanism of *Spica Prunellae* on proliferation and apoptosis of human medullary thyroid carcinoma TT cells[J]. China Journal of Traditional Chinese Medicine and Pharmacy, 2018, 33(8): 3379–3384. (in Chinese).

(From page 118)

- [27] RAO DS. Clinical observation on the treatment of 357 cases of venomous snake bites by "Wuyishan snake medicine" [J]. Fujian Medical Journal, 1982(1): 4–6. (in Chinese).
- [28] RAO DS, ZHAO JC. Clinical observation on the treatment of 81 cases of five-step snake bites by "Wuyishan snake medicine" [J]. Fujian Medical Journal, 1983(2): 32–33. (in Chinese).
- [29] LU SG. The identification meeting of Wuyishan snake medicine was held in Fujian Province[J]. Chinese Traditional and Herbal Drugs, 1981(10): 54. (in Chinese).
- [30] Cultural and Historical Data Committee of Fuzhou Municipal Committee of Fujian Province, Chinese People's Political Consultative Conference. Collection of Fuzhou cultural and historical data (No.21): Cultural part [M]. Cultural and Historical Data Committee of Fuzhou City Committee of Fujian Province, Chinese People's Political Consultative Conference, 2002: 427–428. (in Chinese).
- [31] Editorial Department of Fujian Medical Journal. Technical appraisal meeting of "Xiongshan snake medicine" [J]. Fujian Medical Journal, 1983(5): 76. (in Chinese).
- [32] WU QC, ZHAO JC. Clinical observation of 414 cases of venomous snake bites treated by Xiongshan snake medicine[J]. Fujian Medical Journal, 1984(2): 3–5. (in Chinese).
- [33] LIN QH. The identification meeting of Xiongshan snake medicine was held in Zhenghe County, Fujian Province[J]. Chinese Pharmaceutical Journal, 1984(2): 52. (in Chinese).
- [34] Writing Group of "Prevention and Cure of Venomous Snakes and Snake Bites in Fujian Province". Prevention and cure of venomous snakes and snake bites in Fujian Province[M]. Quanzhou: Printing Plant of Jin-

jiang Area in Fujian, 1978: 37–41. (in Chinese).

- [35] ZHAO YD. Venom and antivenoms of venomous snakes in China[J]. Journal of Guangzhou Medical University, 1982(1): 61–72. (in Chinese).
- [36] ZHAO JC, RAO DS. Report of 111 cases of five-step snake bites treated by integrated Chinese and Western medicine[J]. Journal of Traditional Chinese Medicine, 1981(6): 35–37. (in Chinese).
- [37] JAO DS. Nursing of patients bitten by five-step snakes[J]. Fujian Journal of Medicine, 1984(5): 51–52. (in Chinese).
- [38] LIN ZM, LI JL. A snake school has been set up in the Wuyi Mountain, and provides more than 400 snake doctors; Students set up more than 300 snake bite medical stations and snake farms[N]. People's Daily, 1987-08-10(3). (in Chinese).
- [39] XUE TY, GUAN JX, ZHAO YD. Protective effect of refined anticobra venom on animals with cobra venom poisoning[J]. Journal of Guangzhou Medical College, 1982(2): 30–36. (in Chinese).
- [40] ZHANG Z. Clinical application of refined anticobra venom[J]. Journal of Guangzhou Medical College, 1983(1): 38. (in Chinese).
- [41] YU PN. Report on the preparatory work of Snake Bite Group of Emergency Medicine Professional Committee of Chinese Society of Integrated Traditional and Western Medicine[J]. Wuzhou: National Snake Bite Academic Exchange Association, 1987: 1. (in Chinese).
- [42] LAN H, CHEN YC. Venomous snakes and treatment of snake bites in China[M]. Shanghai: Shanghai Science and Technology Press, 2008: 22–39. (in Chinese).
- [43] LIU FJ, JIN YL. Research on antivenomous Chinese herbs in recent years[J]. Chinese Traditional and Herbal Drugs, 1989, 20(5): 44–46. (in Chinese).