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A prospective study of *Salvia miltiorrhiza* and *Rhizoma chuanxiong* preparation in the treatment of hypoparathyroidism after total thyroidectomy

XiaoYu Qian[1], Jian Tang[1], Yongquan Chu[1], Liang Chen[1], Ziqiang Chen[1] and Lin Li[2]*

[1]Department of Head and Neck Surgery, The First Hospital of Jiaxing, The Affiliated Hospital of Jiaxing University, Zhonghuan South Road, Jiaxing City Zhejiang Province, China

[2]Department of Nuclear Medicine Clinic, The First Hospital of Jiaxing, The Affiliated Hospital of Jiaxing University, Zhonghuan South Road, Jiaxing City Zhejiang Province, China

Abstract: This study aimed to investigate the clinical efficacy of *Salvia miltiorrhiza* and *Rhizoma chuanxiong* preparation on hypoparathyroidism. A total of 100 patients with hypoparathyroidism after total thyroidectomy were erolled, they were divided into the observation group (n=50), *Salvia miltiorrhiza* and *Rhizoma chuanxiong preparation* were added on the basis of traditional treatment. The control group (n=50), were treated with traditional treatment. To analyze the therapeutic effect of *Salvia miltiorrhiza* and *Rhizoma chuanxiong* preparation on hypoparathyroidism. After follow-up, the recovery time of parathyroid function in the observation group was significantly shorter than the control (P<0.05). No permanent hypoparathyroidism in the observation group and 4 cases in the control, which was statistically significant (P<0.05). The serum PTH in the observation group was significantly higher than the control on the 7th, 30th day, 3rd and 6th month. The level of serum calcium in the observation group was significantly higher than the control on the 3rd, 7th and 30th day (P<0.05). *Salvia miltiorrhiza* and *Rhizoma chuanxiong* preparation has obvious effects on the treatment of hypoparathyroidism and has low adverse reactions, which is worthy of clinical application.

Keywords: Total thyroidectomy, hypoparathyroidism, hypocalcemia, *Salvia miltiorrhiza, Rhizoma chuanxiong*

INTRODUCTION

In recent years, the incidence of thyroid carcinoma has increased rapidly, which was ranked first among female malignant tumors in China (Chen *et al*., 2016). Total thyroidectomy has become the mainstream surgical procedure for thyroid carcinoma (Haddad *et al*., 2018). The incidence of hypoparathyroidism after total thyroidectomy is as high as 7-38% (Cayo *et al*., 2012; Nawrot *et al*., 2014; Edafe *et al*., 2014), which is mainly manifested as hypocalcemia, such as local tingling and numbness in the face and limbs. In severe cases, hand and foot convulsion and laryngeal spasm may occur, seriously affecting the quality of life of the patients.

At present, the focus of research on hypoparathyroidism and hypocalcemia after total thyroidectomy is mainly focused on how to better protect the parathyroid gland during the operation, such as fine dorsal membrane anatomy (Yang *et al*., 2019), nano-carbon negative development (Xu and Gu,2017; Jha and Mishra, 2017) and so on. However, the postoperative treatment is mainly based on traditional calcium gluconate and calcitriol and few new viewpoints have been put forward. As important drugs for promoting blood circulation and removing blood stasis, *Salvia miltiorrhiza* and *Rhizoma chuanxiong* have achieved good results in coronary heart disease, angina pectoris and other diseases (Chang *et al*., 2016; Huang *et al*., 2016). In this study, *Salvia miltiorrhiza* and *Rhizoma chuanxiong* preparation was used to treat hypoparathyroidism after total thyroidectomy and to evaluate its clinical value.

MATERIALS AND METHODS

General information

Patients who underwent total thyroidectomy in the department of head and neck surgery of the first hospital of jiaxing from January 2018 to June 2019 and suffered from postoperative hypoparathyroidism were included as subjects. Inclusion Criteria: 1. Serum parathyroidhormone (PTH) < 15.0 pg/ml (reference value: 15.0-68.3 pg/ml); 2. Serum calcium < 2.11 mmol/L (reference value: 2.11-2.52 mmol/L); 3. No other diseases affecting PTH and serum calcium; 4. No bleeding tendency; 5. Patients voluntarily entered the study with informed consent. Exclusion Criteria: 1. *Salvia miltiorrhiza and Rhizoma chuanxiong preparation* allergy; 2. Tumor metastasis; 3. Severe hepatic and renal insufficiency; 4. Diabetes; 5. Severe cardiovascular and cerebrovascular diseases and hematopoietic diseases.

According to the wishes of the patients, a total of 50 patients, including 19 males and 31 females, were treated with Salvia miltiorrhiza and *Rhizoma chuanxiong* preparation as the observation group. The mean age was 49.68±10.44 years. The control group received traditional treatment, with a total of 50 cases, including 21 males and

**Corresponding author:* e-mail: 742925695@qq.com

29 females, with an average age of 48.45±12.29 years. There were no statistically significant differences between the two groups in general information (age, gender, tumor distribution, number of lesions, preoperative serum PTH and serum calcium) (P>0.05), as shown in table 1.This study was approved by the medical ethics committee of the first hospital of jiaxing and all patients signed the informed consent.

Therapeutic method

The control group was treated with traditional treatment: 10% calcium gluconate injection (Jinan Huarun Shuanghe limin Pharmaceutical Co.Ltd. Chinese medicine H37021227), 2 g per day, intravenous drip; calcitriol (Qingdao Haier Zhengda Pharmaceutical Co. Ltd. Chinese medicine H20030490), 0.5μg per day, oral, for 1 week. On the basis of traditional treatment, the observation group was given *Salvia miltiorrhiza chuanxiong preparation* 10ml plus normal saline 100ml intravenous drip on the first day after operation, once a day for one week.

Observation Indicators

Serum PTH<15.0 pg/ml was diagnosed as hypoparathyroidism, permanent hypoparathyroidism was diagnosed if lasts more than 6 months, and serum calcium <2.11mmol/L was diagnosed as hypocalcemia (Gao *et al*., 2015). The recovery time of parathyroid function, the incidence of permanent hypoparathyroidism, the levels of serum PTH and calcium on the 1st, 3rd, 7th and 30th day after operation and 3rd and 6th month after operation were compared between the two groups.

STATISTICAL ANALYSIS

Under SPSS 26.0 statistical software, measurement data were expressed as mean ± standard deviation, t-test is for inter-group comparison; count data by percentage, inter-group comparison by χ2 Test; P<0. 05 was statistically significant.

RESULTS

The recovery time of parathyroid function and the incidence of permanent hypoparathyroidism

During the 6-month follow-up, there was no permanent hypoparathyroidism in the observation group and 4 cases in the control group, with an incidence of 8%. The difference between the two groups was statistically significant (χ^2=4.167 P=0.041). The recovery time of parathyroid function was 3.32±1.34 weeks in the observation group and 5.31±1.63 weeks in the control group. There was significant difference between the two groups (t=8.156 P=0.000).As shown in table 2 and fig. 1.

Postoperative serum PTH follow-up

Within 6 months after operation, the level of serum PTH in the observation group recovered rapidly to the normal level, while that in the control group recovered slowly to the normal level. On the 1st and 3rd day after operation, the serum PTH levels in the observation group were 4.47±2.59pg/ml and 7.64±1.76pg/ml, respectively, compared with those in the control group (4.74 ±3.01 pg/ml, 5.94±2.39 pg/ml), the difference was not statistically significant (t=0.215,P= 0.832, t=1.813, P=0.087). On the 7th, 30th day, 3rd and 6th month after operation, the serum PTH levels in the observation group (10.65±2.36 pg/ml, 21.03±5.56 pg/ml, 27.95±8.87pg/ml, 36.96±8.59pg/ml) were significantly higher than those in the control group (7.42±2.65 pg/ml, 13.20±3.26 pg/ml 7.69±3.05pg/ml , 25.09±6.37pg/ml), The difference was statistically significant (t=17.763 P=0.010, t=3.843 P=0.001, t=3.458 P=0.003,t=3.512 P=0.002). As shown in fig. 2.

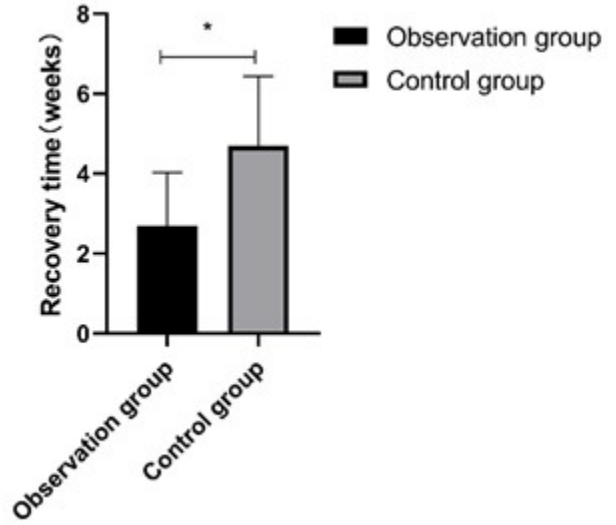

Fig. 1: Comparison of parathyroid function recovery time between the two groups. *P<0.05.

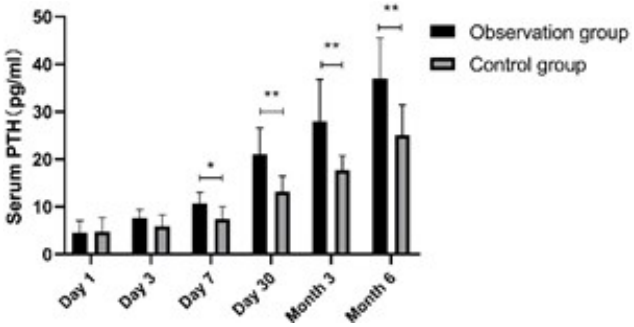

Fig. 2: Changes of serum PTH in the two groups at 6 months after operation.*P<0.05; **P<0.01.

Postoperative serum calcium follow-up

Within 6 months after operation, the level of serum calcium in the observation group returned to normal faster than that in the control group. The level of serum calcium in the observation group on the 3rd, 7th and 30th day after operation (1.99±0.10mmol/L, 2.12±0.08mmol/L, 2.24± 0.12mmol/L) was significantly higher than that in the

control group (1.85±0.09mmol/L, 1.99±0.05mmol/L, 2.09±0.16mmol/l) and the difference was statistically significant (t=3.303, *P*=0.004, t=4.392 *P*= 0.001, t=2.325 *P*=0.032). On the 1st day, 3rd month and 6th month after operation, there was no significant difference in serum calcium level between the observation group (1.83±0.12 mmol/L, 2.32±0.11mmol/L, 2.37±0.11mmol/L) and the control group (1.81±0.10mmol/L, 2.28±0.14mmol/L, 2.32±0.15mmol/L). There was no significant difference between the two groups (t=0.461 *P*=0.650, t=0.834 *P*=0.415, t=0.988 *P*=0.336. As shown in fig. 3.

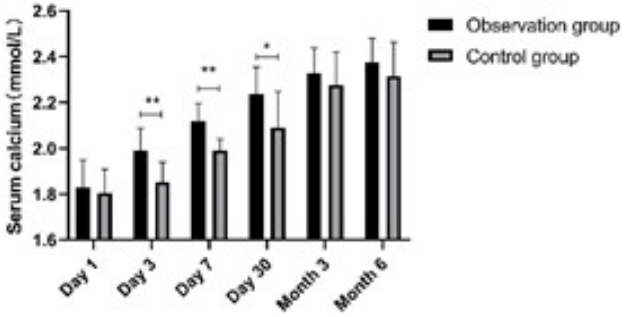

Fig. 3: Changes of serum calcium in the two groups at 6 months after operation. **P*<0.05; ***P*<0.01.

Adverse reactions

In the observation group, nausea and vomiting occurred in 2 cases, arrhythmia in 1 case and electrolyte disturbance in 1 case. In the control group, nausea and vomiting occurred in 3 cases, arrhythmia in 1 case and electrolyte disturbance in 2 cases. All patients were improved after symptomatic treatment.

DISCUSSION

Hypoparathyroidism is the most common complication after total thyroidectomy, which can be divided into temporary hypoparathyroidism and permanent hypoparathyroidism according to whether the postoperative function can return to normal. Hypoparathyroidism following total thyroidectomy is an important complication occurring on a temporary basis in up to 50% of cases and on a permanent basis in 1.5-4% (Serpell, 2018). This is an important complication because it has a significant negative impact on the quality of life of patients, such as drug burden, follow-up needs, economic burden and potential consequences, such as renal insufficiency, nervous system abnormalities and so on (Underbjerg *et al*., 2014; Leidig-Bruckner *et al*., 2016). The main cause of hypoparathyroidism after total thyroidectomy is the direct injury of parathyroid gland during operation, including accidental resection, contusion, thermal radiation, and the disturbance of parathyroid blood circulation caused by various reasons. The operation-related factors that increase the incidence of postoperative hypoparathyroidism include the scope of surgical resection, central lymph node dissection, reoperation and so on (El and Abouqal, 2014). With the transition of the concept of thyroid surgery from "protection of recurrent laryngeal nerve" to "protection of parathyroid function", new progress has been made in clinical research on the protection of parathyroid function, such as fine dissection of the terminal branches of inferior thyroid artery along the thyroid capsule, in situ preservation of parathyroid gland and its blood supply (Lorente-Poch, 2015), auto transplantation of parathyroid gland (Ji, 2017), protection of parathyroid gland with various stains (Long, 2017) and so on. However, these studies focus on intraoperative treatment, and there is a lack of innovation and in-depth research on postoperative treatment.

Salvia miltiorrhiza is an eminent herbal medicine, which is widely used in Asian countries to treat cardiovascular diseases, including coronary heart disease, myocardial infarction, angina pectoris and atherosclerosis (Fang *et al*., 2018; Chen and Xu, 2014; Zhu *et al*., 2017). Therefore, *Salvia miltiorrhiza* represents a traditional Chinese medicine (TCM) that has a relatively high safety profile. To date, the chemical constituents of *Salvia miltiorrhiza* have been well identified, including more than 30 lipophilic compounds (*tanshinone I–VI, cryptotanshinone, isotanshinone I–II, Danshenol A,* etc) and more than 50 hydrophilic compounds (*Danshensu, salvianolic acid A, salvianolic acid B, protocatechuic aldehyde,* etc) (Zhao *et al*., 2017). Various components may function in concert, targeting different tissues and signal pathways to realize the vascular protective effect of *Salvia miltiorrhiza* in human and experimental animals. It is reported in the literature (Huang *et al*., 2016; Wu *et al*., 2014) that the main mechanisms of *Salvia miltiorrhiza* in the treatment of cardiovascular diseases are anti-inflammation, anti-platelet aggregation, anti-thrombosis and so on. *Rhizoma chuanxiong* is one of the most important and commonly used drugs for promoting blood circulation and removing blood stasis in traditional Chinese medicine. So far, more than 170 chemical constituents such as phthalic acid, terpenes and their enols, alkaloids, polysaccharides, organic acids and esters have been isolated. Previous studies have reported (Chen *et al*., 2018), these main compounds can dilate blood vessels, improve cerebral circulation, inhibit platelet aggregation, prevent liver lipid accumulation and exert antioxidant activity. *Salvia miltiorrhiza* and *Rhizoma chuanxiong* preparation is compatible with *Salvia miltiorrhiza* and *Rhizoma chuanxiong*. From the theory of traditional Chinese medicine, the compatibility of *Salvia miltiorrhiza* as the king and *chuanxiong* as the agent helps to better exert its effects of improving circulation, inhibiting thrombosis and anti-inflammatory.

In this study, *Salvia miltiorrhiza* and *Rhizoma chuanxiong* preparation was used in the treatment of hypoparathyroidism after total thyroidectomy, drawing

lessons from its successful experience in cardio-cerebrovascular diseases (Feng *et al*., 2016; Zhang *et al*., 2017). The results showed that the recovery time of parathyroid function in the observation group was significantly shorter than that in the control group (P<0.05). There was no permanent hypoparathyroidism in the observation group and 4 cases in the control group, the difference was statistically significant (P<0.05). The serum PTH level in the observation group was significantly higher than that in the control group on the 7th, 30th day and 3rd, 6th month after operation (P<0.05).

Table 1: Comparison of general conditions between the two groups

Clinical features	Observation Group (n=50)	Control Group (n=50)	χ2/t	P-Value
Age (Y)	49.68±10.44	48.45±12.29	0.357	0.723
Gender				
Male	19	21	0.167	0.683
Female	31	29		
Tumor Distribution			0.623	0.732
Left Lobe	3	5		
Right Lobe	5	4		
Bilateral Lobes	42	41		
Lesions number			0.965	0.617
2	20	23		
3	17	18		
≧4	13	9		
Preoperative PTH (pg/ml)	50.35±9.75	49.98± 10.14	0.083	0.935
Preoperative serum calcium (mmol/L)	2.35±0.13	2.33±0.09	0.381	0.707

Table 2: Comparison of parathyroid function recovery time and incidence of permanent hypoparathyroidism between the two groups.

	Observation Group	Control Group	χ^2/t	P-Value
Parathyroid function recovery time (weeks)	3.32±1.34	5.31±1.63	8.156	0.000
Permanent hypoparathyroidism			4.167	0.041
Yes	0	4		
No	50	46		

The level of serum calcium in the observation group was significantly higher than that in the control group on the 3rd, 7th and 30th day after operation (P<0.05). The mechanism may be related to the improvement of local microcirculation, inhibition of postoperative micro-vascular thrombosis and reduction of inflammatory reaction in the operative area by *Salvia miltiorrhiza and Rhizoma chuanxiong preparation*.

A very small number of patients were intolerant to *Salvia miltiorrhiza* and *Rhizoma chuanxiong* preparation, resulting in vomiting, electrolyte imbalance and arrhythmia. In this study, nausea and vomiting, electrolyte disturbance and arrhythmia occurred in both the observation group and the control group, which were improved after symptomatic treatment. This may be related to the change of blood pressure after the application of *Salvia miltiorrhiza* and *Rhizoma chuanxiong* preparation, but the number of cases is small, which needs to be further analyzed after the increase of cases.

CONCLUSION

In conclusion, *Salvia miltiorrhiza and Rhizoma chuanxiong preparation* has obvious therapeutic effect on hypoparathyroidism after total thyroidectomy, it can effectively shorten the recovery time of parathyroid function, reduce the occurrence of permanent hypoparathyroidism and improve the quality of life of patients and has fewer adverse reactions, so it is worthy of clinical promotion and application. The next research should focus on its specific mechanism, and further explore the therapeutic effect of *Salvia miltiorrhiza and Rhizoma chuanxiong preparation* on hypoparathyroidism after total thyroidectomy.

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