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ORIGINAL RESEARCH

Risk factors for hypocalcemia and hypoparathyroidism following thyroidectomy: a retrospective Chinese population study

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Background: Hypocalcemia is one of the most common postoperative complications following thyroid surgery in clinical practice. The occurrence of hypocalcemia is mainly attributed to hypoparathyroidism when parathyroid glands are devascularized, injured, or dissected during the surgery. The aim of this study was to analyze the risk factors for hypocalcemia and hypoparathyroidism following thyroidectomy.

Patients and methods: A total of 278 patients who underwent thyroid surgery were analyzed retrospectively. Univariate analysis and multivariable logistic regression were performed to discover the risk factors for hypocalcemia and hypoparathyroidism.

Results: Postoperative hypocalcemia occurred in 76 (27.3%) patients and hypoparathyroidism occurred in 42 (15.1%) patients. Seven factors were significantly related to the presence of postoperative hypocalcemia, namely, age (P=0.049), gender (P=0.015), lateral lymph node dissection (P=0.017), operation type (P<0.001), preoperative parathyroid hormone (PTH) level (P=0.035), operation time (P=0.001), and applying carbon nanoparticles (CNs; P=0.007). Our result revealed that gender (P=0.014), lateral lymph node dissection (P=0.038), operation type (P<0.001), operative time (P<0.001), and applying CNs (P=0.001) had a significant correlation with postoperative hypoparathyroidism.

Conclusion: These findings were crucial for guiding surgeons to prevent the occurrence of hypocalcemia and hypoparathyroidism.

Keywords: hypocalcemia, hypoparathyroidism, thyroidectomy, risk factor

Introduction

Since the 1990s, the incidence of thyroid cancer has increased, faster than any other cancer type in the US. Over the past 3 decades, the incidence of thyroid cancer has increased 240%.[1] Currently, there are 56,780 new thyroid cancer patients in the US.[2] Although the mortality of thyroid cancer is not very high compared with other cancers, there are some subtypes of thyroid cancer that are more aggressive and needed more positive treatment.

Surgery and radioiodine therapy are the two main recommended approaches. Thyroidectomy is frequently recommended to patients with thyroid nodules, especially for those in whom thyroid cancer is suspected of carrying thyroid cancer.[3,4] The completeness of surgical resection helps to improve survival and lower recurrence; thus, most surgeons proposed total thyroidectomy over thyroid lobectomy.[5] However, compared with thyroid lobectomy, there is a higher incidence risk of complications after total thyroidectomy. Complications of these surgical procedures are numerous,

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and some of them are severe and persistent over time,[6,7] including hypoparathyroidism, hypocalcemia, vocal paralysis, and hemorrhage. Transient hypocalcemia is one of the most common postoperative complications following thyroid surgery in clinical practice.[8,9] It has been reported that the rate of postoperative transient hypocalcemia ranges from 6% to 30%,[10–12] although there is ≤2% incidence of persistent dysfunction. The nadir of hypocalcemia often appears within 48 hours after thyroidectomy.[13,14] Symptoms are severe and, requiring calcium replacement therapy.

In many cases, serum calcium levels recover spontaneously within a few months. However, in a few patients, hypoparathyroidism persists after 1 year and may be considered permanent.[15] The occurrence of permanent hypocalcemia is mainly attributed to postoperative hypoparathyroidism when parathyroid glands are devascularized, injured, or dissected during the surgery.[15,16] The hypocalcemia after surgery is related to multiple factors, including surgical technique, the definition of hypocalcemia, criteria of report series, and use of prophylactic calcium supplementation in the perioperative period.[16,17]

Postoperative hypocalcemia can not only cause clinical symptoms but can also become a major contributing factor of prolonged hospitalization time for close observation and frequent laboratory evaluations.[11,18] The aim of this study was to investigate the frequency and risk factors for postthyroidectomy hypocalcemia and hypoparathyroidism following thyroidectomy.

Patients and methods

Enrollment of patients

We performed a retrospective analysis of patients who underwent total thyroidectomy or lobectomy surgery at The First Affiliated Hospital of Wenzhou Medical University from 2012 to 2014. During surgery, all or partial thyroid tissue was removed, including the posterior capsule and pyramidal lobe, varying upon patient condition. All parathyroid glands were identified. The viable parathyroids were identified and if possible preserved on an intact vascular pedicle, and those that appeared nonviable or could not be preserved were removed, placed in cold saline, and minced into 11 mm fragments; parathyroid slivers were autotransplanted to a muscle bed in the sternocleidomastoid or the nondominant forearm.

This study obtained ethical approval from the Institutional Review Board of First Affiliated Hospital of Wenzhou Medical University (approval no. 2012-57). In addition, the medical directors' offices of the hospital granted permission to use the patients' data for this study. All data had no personal identifiers and were kept confidential and therefore did not require informed consent.

A total number of 278 consecutive patients were finally enrolled with criteria as follows. The serum calcium and parathyroid hormone (PTH) level of patients were tested preoperatively and 48 hours after the operation, respectively. In our hospital, we routinely tested the preoperative PTH in order to exclude postoperative hypocalcemia and hypoparathyroidism. All patients were routinely supplemented with calcium through intravenous injection, and dose adjustment of calcium and appropriate amounts of vitamin D was managed based on clinical symptoms. In all, patients with symptoms of hypocalcemia or hypoparathyroidism occured for a period of 1 month after the surgery is usually temporary. If the symptoms were not alleviated after 6 months postoperatively, hypocalcemia or hypoparathyroidism symptoms could be seen as permanent. Hypocalcemia and hypoparathyroidism were diagnosed according to the American Thyroid Surgery Society 2009 guideline.[19]

There was a significant association between preoperative PTH and postoperative hypocalcemia and hypoparathyroidism.

Patients were finally enrolled with exclusion criteria as follows:

1. Patients had hypocalcemia or abnormal parathyroid function before the surgery.
2. Patients had a history of thyroid or neck surgery. All patients were operated on by Xiao-hua Zhang, Cheng-ze Chen, and Ying-hao Wang.

Collection of clinicopathological parameters and study protocol

Demographic, pathologic, and laboratory data of all enrolled patients were collected from electronic medical records. Clinicopathological data collected encompassed age, gender, and preoperative and postoperative corrected serum calcium and PTH levels. In addition, information on the type of operation, operative time, and intraoperative management of the parathyroid gland was obtained from the surgical records. Patients were defined as having hypocalcemia if the serum calcium value was <2.0 mmol/L 48 hours after an operation or related symptoms were present, and oral treatment with calcium and calcitriol was started if the serum calcium level dropped below this value. This selective therapeutic strategy allows for patients to be discharged home early on the next day and minimizes overtreatment of the normocalcemic patients.

Among patients with hypocalcemia, we further defined them as with hypoparathyroidism, once the postoperative serum PTH value was <15 pg/mL.

Application of carbon nanoparticle (CN) suspension injection

CN suspension injection was applied in the form of a standard CN suspension injection (1 mL: 50 mg). The suspension does not enter the blood circulation and has no toxic side effects on the human body.[20] The suspension comprises nanosized carbon particles with an average diameter of 150 nm. The cell gap between capillary endothelial cells is 20–50 nm, and the capillary lymphatic endothelial cell gap is 120–500 nm with a hypoplasia of the basement membrane. Therefore, CN is unable to enter the blood vessels when it is injected into the thyroid tissue, and it will rapidly enter lymphatic vessels or the lymphatic capillaries through macrophage phagocytosis and be retained in the lymph nodes. The thyroid and lymph in their drainage areas are stained black in surgery.[20] However, the parathyroid glands do not stain black, and hence, the black-stained thyroid and lymph nodes can be identified and are distinguished clearly. After cutting along the white cervical line, the thyroid gland can be identified carefully eliminating the false fibrous capsule from the thyroid gland and revealing the gland near the isthmus. Unnecessary freed gland can cause damage to the surrounding lymphatic network and influence the effects of CNs after injection. The integrity of the fibrous capsule of thyroid glands must be maintained. Damage of the fibrous capsule of thyroid glands can cause a leakage of CN suspension, resulting in the entire operative field stained black, which will render it impossible to distinguish the parathyroid gland and increase surgical risk. One injection of 0.1 mL CN suspension injection was administered with a fine needle in the lower one-third of the ventral surface to each of the bilateral glands, and the injection depth was roughly within the upper third of the glands. Too deep or shallow an injection can also cause the extravasation of CN suspension, which can result in a black-stained surgical field and increase the risk of surgery. All of the abovementioned factors are essential to take into consideration when performing the injection. Thus, the injection requires extra care. The needle must avoid the tumor, and the surgeon must proceed to inject slowly if no blood is found upon pump back during injection of the suspension. After injecting the needle, pressure must be applied for 1–2 minutes with a gauze and this allows the full staining of the suspension injection in the thyroid gland, parathyroid glands and lymph nodes.

Statistical analysis

Measurement data on normal distribution are expressed as the mean ± standard deviation (SD) and were compared with the two-sample *t*-test. Categorical data are expressed as a percentage and were compared with chi-square test or Fisher's exact test, as appropriate. Logistic regression analysis was also performed to estimate the odds ratios (ORs) of certain parameters. A P value of <0.05 was considered as statistically significant. Statistical analysis was performed with SPSS software version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

A total of 278 patients who underwent thyroid operations were included in the study, including 218 women and 60 men. Table 1 lists the baseline clinicopathological characteristics

Table 1 Baseline characteristics of enrolled patients

Variables	n (%)
Age (years), mean ± SD	48±11
Gender	
Female	218 (78.42)
Male	60 (21.58)
Pathology	
Benign	81 (29.14)
Malignant	197 (70.86)
Central lymph node dissection	
No	100 (35.97)
Yes	178 (64.03)
Lateral lymph node dissection	
No	240 (86.33)
Yes	38 (13.67)
Parathyroid inadvertent dissection	
No	247 (88.85)
Yes	31 (11.15)
Operation	
Lobectomy	137 (49.28)
Lobectomy plus isthmusectomy	62 (22.30)
Near-total thyroidectomy	30 (10.79)
Total thyroidectomy	49 (17.63)
Postoperative hypocalcemia	
No	202 (72.66)
Yes	76 (27.34)
Postoperative hypoparathyroidism	
No	236 (84.89)
Yes	42 (15.11)
No. of patients with parathyroid autotransplantation	52 (18.71)
One parathyroid gland	48 (17.27)
Two parathyroid glands	4 (1.44)
Inadvertent removal of the parathyroid glands	31 (11.15)
One parathyroid gland in specimen	30 (10.79)
Two parathyroid glands in specimen	1 (0.36)

Abbreviation: SD, standard deviation.

of enrolled patients. Postoperative hypocalcemia occurred in 76 (27.3%) patients, and hypoparathyroidism occurred in 42 (15.1%) patients. Table 2 lists the usage status of CN suspension injection in different operations.

Table 2 Usage status of CN suspension injection in different operations

Operation	CN suspension injection, n (%)	
	Yes (n=95)	No (n=183)
Lobectomy	45 (47.37)	92 (50.27)
Lobectomy plus isthmusectomy	13 (13.68)	49 (26.78)
Near-total thyroidectomy	6 (6.32)	24 (13.11)
Total thyroidectomy	31 (32.63)	18 (9.84)

Abbreviation: CN, carbon nanoparticle.

Risk factors for postoperative hypocalcemia

To discover potential risk factors for postoperative hypocalcemia, the patients were divided into two groups. Table 3 lists the differences in clinicopathological characteristics between the two groups. Among these, eight factors were significantly related to the presence of postoperative hypocalcemia, namely, age (P=0.049), gender (P=0.015), lateral lymph node dissection (P=0.017), operation type (P<0.001), preoperative PTH level (P=0.035), operation time (P=0.001), parathyroid autotransplantation (P=0.002), and applying CNs (P=0.007). However, pathology, central lymph node dissection, parathyroid inadvertent dissection, number of

Table 3 Univariate analysis for risk factors for postoperative hypocalcemia and hypoparathyroidism

	Postoperative hypocalcemia		χ^2/t	P-value	Postoperative hypoparathyroidism		χ^2/t	P-value
	No	Yes			No	Yes		
Number	202	76			236	42		
Age (years), mean ± SD	47±11	50±12	1.976	0.049	47±11	48±12	0.535	0.592
Gender			5.864	0.015			6.095	0.014
Female	151	67			179	39		
Male	51	9			57	3		
Pathology			1.506	0.239			1.424	0.272
Benign	63	18			164	33		
Malignant	139	58			72	9		
Central lymph node dissection			2.240	0.161			2.055	0.167
No	78	22			89	11		
Yes	124	54			147	31		
Lateral lymph node dissection			6.708	0.017			4.311	0.038
No	181	59			208	32		
Yes	21	17			28	10		
Parathyroid inadvertent dissection			1.165	0.290			2.246	0.134
No	182	65			213	34		
Yes	20	11			23	8		
Operation			24.664	0.000			69.078	0.000
Lobectomy	112	25			133	4		
Lobectomy plus isthmusectomy	49	13			58	4		
Near-total thyroidectomy	17	13			23	7		
Total thyroidectomy	24	25			22	27		
Preoperative serum calcium level, mean ± SD	2.31±0.11	2.29±0.10	1.384	0.167	2.30±0.11	2.32±0.10	1.100	0.272
Preoperative PTH level, mean ± SD	34.34±10.21	38.02±18.42	2.109	0.035	35.49±10.96	34.53±21.48	0.438	0.661
Operative time (minutes), mean ± SD	66±27	79±39	3.144	0.001	66±25	93±48	5.452	0.000
CNs			8.096	0.007			11.604	0.001
Injected	59	36			71	24		
Non-injected	143	40			169	18		
Parathyroid autotransplantation			9.198	0.002			42.3	0.000
No	173	53			207	19		
Yes	29	23			29	23		
Inadvertent removal of the parathyroid glands			1.165	0.28			N	0.106
No	182	65			213	34		
Yes	20	11			23	8		

Note: N indicates this group is not suitable for chi-square test but fisher exact test.
Abbreviations: SD, standard deviation; PTH, parathyroid hormone; CN, carbon nanoparticle.

identified parathyroid glands, and preoperative serum calcium levels were not significantly correlated with the presence of postoperative hypocalcemia ($P>0.05$). Multivariate analyses showed that age ($P=0.038$), lateral lymph node dissection ($P=0.050$), operation type ($P<0.001$), and applying CNs ($P=0.036$) were independent predictors for postoperative hypocalcemia (Table 4).

Risk factors for postoperative hypoparathyroidism

Next, we detected potential risk factors for postoperative hypoparathyroidism. Our results revealed that gender ($P=0.014$), lateral lymph node dissection ($P=0.038$), operation type ($P<0.001$), operative time ($P<0.001$), parathyroid autotransplantation ($P<0.001$), and applying CNs ($P=0.001$) had a significant correlation with postoperative hypoparathyroidism (Table 3). Multivariate analysis showed that operation type ($P<0.001$), gender ($P=0.026$), and preoperative PTH level ($P=0.006$) were independent predictors for postoperative hypoparathyroidism (Table 5).

Discussion

Hypocalcemia and hypoparathyroidism are a frequent complication of thyroidectomy with the growing incidence of thyroid disease.[21,22] The increased incidence of hypocalcemia in post-thyroidectomy patients may be attributed to hemodilution. Earlier studies also provide various other factors such as age, basic pathology, and duration of surgery as reasons for increased incidence of hypocalcemia.[23] When all glands are compromised by injury of the vascular pedicle, resection or unintended surgical manipulation and sudden significant fall in levels of PTH occur, leading to more intense and faster hypocalcemia, hence causing the symptoms. With partial preservation of the function of the parathyroid glands, the PTH decrease is less significant, remaining so until there is retrieval or repair of the remaining glands of the ischemic parathyroid cells. In such cases, the calcium concentration falls more slowly and with less intensity, lesser possible to cause clinical symptoms. Searching for parathyroid glands may, theoretically, increase the risk of them being injured, being a contributing factor to hypocalcemia.[24,25]

Hypocalcemia occurs secondary to hypoparathyroidism due to trauma, devascularization, or removal of the parathyroid glands that leads to prolonged hospitalization, increased medical cost, and patient discomfort.[26,27] Therefore, it is necessary to find risk factors for hypocalcemia and hypoparathyroidism following thyroidectomy and to help guide clinical practice.

Table 4 Multivariable logistic regression for risk factors for postoperative hypocalcemia

Variables	Coefficient	Standard error	Wald value	*P*-value	OR	95% CI	
						Lower	Upper
Age (years)	0.028	0.013	4.298	0.038	1.028	1.002	1.055
Lateral lymph node dissection							
Yes versus no	0.759	0.388	3.832	0.050	2.137	0.999	4.570
Operation				0.000			
Lobectomy plus isthmusectomy versus lobectomy	0.161	0.392	0.168	0.682	1.174	0.545	2.531
Near-total thyroidectomy versus lobectomy	1.388	0.441	9.904	0.002	4.005	1.688	9.503
Total thyroidectomy versus lobectomy	1.310	0.378	12.035	0.001	3.708	1.768	7.774
CNs							
Injected versus non-injected	0.644	0.308	4.375	0.036	1.904	1.041	3.480

Abbreviations: OR, odds ratio; CN, carbon nanoparticle.

Table 5 Multivariable logistic regression for risk factors for postoperative hypoparathyroidism

Variables	Coefficient	Standard error	Wald value	*P*-value	OR	95% CI	
						Lower	Upper
Gender							
Male versus female	–1.583	0.709	4.988	0.026	0.205	0.051	0.824
Preoperative PTH level	–0.066	0.024	7.528	0.006	0.936	0.894	0.981
Operation				0.000			
Lobectomy plus isthmusectomy versus lobectomy	0.619	0.735	0.709	0.400	1.857	0.440	7.844
Near-total thyroidectomy versus lobectomy	2.352	0.688	11.676	0.001	10.502	2.726	40.466
Total thyroidectomy versus lobectomy	3.799	0.609	38.946	0.000	44.647	13.541	147.207

Abbreviations: OR, odds ratio; PTH, parathyroid hormone.

In this study, we performed a retrospective analysis of 278 patients and used statistical tools to analyze clinical data. Collectively, our results demonstrate that gender, lateral lymph node dissection, operation type, operation time, and use of CNs were related to the occurrence of hypocalcemia and hypoparathyroidism.

In 2012, "Management Guidelines of Thyroid Nodules and Differentiated Thyroid Cancer" was made by Chinese Society of Endocrinology, Chinese Society of Surgery, China, Anti-Cancer Association of Head and Neck Specialized Committee, and Chinese Society of Nuclear Medicine depending on management guidelines made by American Thyroid Association (ATA), European Society for Medical Oncology (ESMO), and American Association of Clinical Endocrinologists (AACE). In this guideline, it recommended prophylactic central lymph nodes dissection with the preservation of recurrent laryngeal nerve and parathyroid glands. According to this guideline, whether to perform dissection of central lymph nodes depends on pathologic characteristics and surgeon skills, rather than surgery type. Surgery type is more dependent on tumor size, single or multiple nodules, invasion of adjacent tissues, lymphatic metastasis, metastasis, radiation in childhood, family history of thyroid cancer or subtype, and so on. In addition, whether to perform lateral lymph node dissection depends on patients with lateral lymph node metastasis or part of patients with central lymph node metastasis.

Patients with evidence of nodal disease require therapeutic neck dissection. When disease is restricted to the central compartment, clearance of levels VI and VII is suggested. Therapeutic central-compartment neck dissection for patients with clinically involved central nodes should undergo total thyroidectomy to provide clearance of disease from the central neck. The recurrent laryngeal nerves should be carefully dissected and preserved, and the parathyroid glands should be identified and preserved along with their blood supply. When the parathyroid glands are devascularized, they may require autotransplantation in the sternocleidomastoid muscle. In patients with proven lateral neck disease, therapeutic neck dissection is indicated and can be done in a rather selective manner. Rates of metastasis in levels I, IIb, and Va are low, and are in the absence of proven disease, these levels can be spared to avoid morbidity, especially to the marginal mandibular and spinal accessory nerves. The lateral neck dissection should normally entail levels IIa through Vb and can be done simply by continuing the thyroidectomy, central neck dissection incision laterally within the same skin crease. In thyroid cancer, special attention should be paid to nodal tissue posterior to the great vessels in level IV, as this is a common site for recurrent nodal disease. Besides, lymph mode metastases are often found very low in the base of the neck, and dissecting this area may increase the risk for substantial vascular and lymphatic injury.[28]

We found that female patients were vulnerable to postoperative hypoparathyroidism. Serum calcium is regulated by 1,25-dihydroxyvitamin D or calcitriol through bone resorption, PTH through calcium reabsorption of renal tubules, and calcitriol through calcium intestinal absorption.[29] This phenomenon may be attributed to the dropping hormone levels in menopausal women.[30,31] Previous studies also showed that intrathyroidal parathyroid glands were more frequent in women owing to the high occurrence rates of parathyroid injury and hypocalcemia.[32–34]

In fact, vitamin D level may be a really important preoperative risk factor in predicting the postoperative hypocalcemia. Griffin et al[35] found that vitamin D does not play a significant role in the occurrence of postoperative hypocalcemia. This result is in accordance with other studies.[36,37] Recently, Danan and Shonka[26] demonstrated that vitamin D level is a significant predictor of postoperative hypocalcemia in patients in whom ≥3 parathyroid glands were identified. However, in our retrospective study, we did not have the data for preoperative vitamin D levels. We believe that this complicated risk factor needs further investigation.

In our analysis, we found that parathyroid autotransplantation is a risk factor for postoperative hypoparathyroidism. Many analyses have demonstrated that parathyroid autotransplantation plays an important role in avoiding permanent hypoparathyroidism and should be a routine surgery.[38–40] After autotransplantation, grafted parathyroid required time to regain its function.[41] We also demonstrated that parathyroid autotransplantation increases the risk of postoperative hypoparathyroidism.

It is well known that different types of thyroid disease need appropriate excision extension, which affects operation time. The extent of thyroidectomy, which depends on the pathology and operation method, is significantly related to the frequency of postoperative hypoparathyroidism.[42] Certainly, isolation of the recurrent laryngeal nerve during surgery can attribute to venous congestion and edema. Besides, ligation of thyroid blood vessels also disrupts the stasis of blood supply. Edema and blood supply stasis have a negative influence on parathyroid function and may induce a transient hypoparathyroidism lasting for ≥1 week after surgery.[43] In our study, the surgical method played a dominant role in causing postoperative hypoparathyroidism.

The near-total thyroidectomy and total thyroidectomy were independent risk factors attributing to hypothyroidism (P=0.001, OR=10.502, 95% CI: 2.726–40.466; P<0.001, OR=44.647, 95% CI: 13.541–147.207). Similarly, Nawrot et al[44] have demonstrated that hypoparathyroidism was more frequently seen after total thyroidectomy (20.2%) than near-total thyroidectomy (6.7%) or subtotal thyroidectomy (4.1%). González-Botas and Piedrahita[45] and Merchavy et al[46] have reported that postoperative hypocalcemia was less common in patients with completion thyroidectomy than in patients who underwent total thyroidectomy.

Shen et al[47] have demonstrated that the incidence of hypoparathyroidism was statistically significant between patients who underwent thyroidectomy with or without neck lymph node dissection. Similarly, we found that patients with lateral lymph node dissected showed a higher incidence of hypocalcemia and hypoparathyroidism than those without receiving lateral lymph node dissection (P=0.017; P=0.038). Actually, parathyroid blood vessels are thin, fragile, and terminal; parathyroid blood supply is easily affected or disrupted, which may result in the high occurrence of hypocalcemia after lateral lymph node dissection.[48]

CN suspension injection is applied for helping identify lymph nodes in lymph node dissection, including breast cancer and gastrointestinal cancer.[49–51] Because the components for CN suspension injections are nanocarbon granules, these have diameters of 150 nm and they can enter lymphatic capillaries (diameters of 500 nm) rather than blood vessel capillaries (diameters of 30–50 nm) and immediately enter into drainage lymph nodes.[52] Furthermore, recent studies have shown that CN suspension injection can aid in identifying parathyroid glands, which may provide a new strategy for identification and protection during parathyroid surgery.[52,53]

Results

Our results have shown, with the aid of CN suspension, that incidence of hypocalcemia and hypoparathyroidism is lower, which implies that CNs could help to distinguish the parathyroid glands from thyroid tissue. This result is in accordance with previous research.[54,55]

Conclusion

Postoperative hypocalcemia and hypoparathyroidism incidence were significantly related to the extent of thyroidectomy, gender, lateral lymph node dissection, operative time, and use of CNs. These findings were crucial for guiding surgeons to prevent the occurrence of hypocalcemia and hypoparathyroidism.

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The data sets supporting the conclusions of this article are included within this article. Raw data are available on the main electronic data storage system of First Affiliated Hospital of Wenzhou Medical University, and access can be provided upon request to the authors.

Disclosure

The authors report no conflicts of interest in this work.

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