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Original Article

Risk factors target in patients with post-thyroidectomy bleeding

Endong Chen[1*], Yefeng Cai[1*], Quan Li[1], Pu Cheng[1], Chunjue Ni[2], Langping Jin[1], Qianqing Ji[1], Xiaohua Zhang[1], Chun Jin[1]

Departments of [1]Surgical Oncology, [2]Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China. [*]Equal contributors.

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Abstract: As the highly blood flow of thyroid gland post-thyroidectomy bleeding (PTB) is a serious and life-threatening complication. Our aim was to investigate factors that influenced bleeding after thyroidectomy. Between February 2008 and September 2012, the data of 4449 consecutive patients with thyroid diseases undergoing thyroidectomy were collected and analysed from the department of surgical oncology retrospectively. During the study period, 88 (2.0%) patients were identified to have clinically PTB. 6 risk factors were significantly related to PTB: gender (OR 3.243; 95% CI 2.078-5.061; $P < 0.001$), age (OR 1.025; 95% CI 1.006-1.043; $P = 0.009$), tumor size (OR 4.495; 95% CI 2.462-8.208; $P < 0.001$), postoperative hypertension (OR 2.195; 95% CI 1.006-1.043; $P = 0.035$), lymph node dissection (OR 3.384; 95% CI 2.146-5.339; $P < 0.001$) and Graves' disease (OR 3.744; 95% CI 1.920-7.303; $P < 0.001$). We addressed the most common explicit source of bleeding by reexploration: infrahyoid muscles (30/88), beside the laryngeal recurrent nerve (22/88), subcutaneous tissue (10/88) and superior pole (10/88). In our study, male gender, older age, tumor size > 3 cm, postoperative hypertension (SP > 150 mmHg), lymph node dissection and Graves' disease were independent risk factors for PTB. The sources of bleeding were identified more frequently in the infrahyoid muscles and beside the laryngeal recurrent nerve. It is helpful for surgeons to decide the potential bleeding points during the reexploration of PTB.

Keywords: Thyroidectomy, bleeding, risk factors

Introduction

Nowadays, thyroidectomy is a relatively safe surgical procedure for treating several diseases of the thyroid gland compared with conservative methods. The main indications for thyroidectomy are the presence of thyroid nodules, thyroid carcinoma, and multinodular goiters. It is well-known that the thyroid gland is a highly blood flow organ and is second only to the adrenal glands in terms of relative vascular perfused organ in the body [1]. Therefore, it is not surprising that post-operative bleeding is a complication of thyroid surgery. The reported incidence of post-thyroidectomy bleeding (PTB) varies between approximately 0.4 and 4.0 per cent, but in major centers among developed countries is commonly described to be approximately 1 percent [2-9]. Generally, the risk of this complication mainly depends on the extent of the operation, the conditions of patients and the experience of surgeons. Although the PTB is rare, when it occurs, it may be life-threatening and even causes severe functional impairment. Therefore, early recognition with immediate intervention is the key point to manage this complication.

Nevertheless, independent risk factors for this complication have not be clearly confirmed by previous studies, possibly because of small sample size and limited statistical power [10]. In additional, few studies focused on researching the source of bleeding after thyroidectomy. A better understanding of the independent risk factors for PTB could screen patients with high risks of PTB. Then an intensive monitor can be paid in the perioperative period of patients with high risk of PTB. Moreover, immediate intervention may be more effective when we find the possible source of PTB.

To address this issue, we conducted a retrospective study, include 4449 patients, to evaluate the independent risk factors for PTB and the source of bleeding after thyroidectomy.

Table 1. Post-operative characteristics of 4499 patients in Group I and Group II

Characteristics	Post-thyroidectomy bleeding		Test value	*P*-value
	Group I	Group II		
Total	88	4361		
Age at diagnosis (years)[a]	50.6 ± 10.6	46.5 ± 12.1	3.175	0.002*
Gender			34.808	< 0.001*
Male	39 (44.3%)	833 (19.1%)		
Female	49 (55.7%)	3528 (80.9%)		
Smoking			6.049	0.014*
Yes	17 (19.3%)	479 (11.0%)		
NO	71 (80.7%)	3882 (89.0%)		
Pathology			1.126	0.569
Benign	44 (50.0%)	2428 (55.7%)		
Microcarcinoma (≤ 1 cm)	26 (29.5%)	1146 (26.3%)		
Macrocarcinoma (> 1 cm)	18 (20.5%)	787 (18.0%)		
Graves' disease			7.049	0.008*
Yes	12 (13.6%)	284 (6.5%)		
NO	76 (86.4%)	4077 (92.5%)		
Hashimoto's thyroiditis			1.239	0.266
Yes	9 (10.2%)	311 (7.1%)		
No	79 (89.8%)	4050 (92.9%)		
Postoperative hypertension			9.924	0.002*
SP > 150 mmHg	10 (11.4%)	175 (4.0%)		
SP ≤ 150 mmHg	78 (88.6%)	4186 (96.0%)		
Tumor size			21.096	< 0.001*
> 3 cm	15 (17.0%)	228 (5.2%)		
≤ 3 cm	73 (83.0%)	4133 (94.8%)		
Operation extent			0.282	0.595
Unilateral	44 (50%)	2305 (52.9%)		
Bilateral	44 (50%)	2056 (47.1%)		
Drain			7.241	0.007*
Yes	6 (6.8%)	779 (17.9%)		
No	82 (93.2%)	3582 (82.1%)		
Total thyroidectomy			0.004	0.953
Yes	11 (12.5%)	536 (12.3%)		
No	77 (87.5%)	3825 (87.7%)		
Lymph node dissection			20.272	< 0.001*
Yes	40 (45.5%)	1068 (24.5%)		
No	48 (54.5%)	3293 (75.5%)		

Data are expressed as mean ± standard deviation and n (%). Group I: patients with PTB requiring surgical reexploration. Group II: patients with PTB but not requiring surgical reexploration or no PTB. *Statistically significant ($P < 0.05$). a: *P*-value using independent two-sample t test.

Material and methods

Patients and managements

Between February 2008 and September 2012, 4449 consecutive patients underwent thyroidectomy in our hospital. Data on each patient were collected retrospectively, including diagnosis, treatment, complications and follow-ups. During the study period, 88 (2.0%) patients were identified to have clinically significant post-thyroidectomy bleeding or hematoma after thyroidectomy (i.e., those requiring surgical reexploration; group I). Those developed hematoma but did not require surgical reexploration or had no postoperative hematoma after thyroidectomy were grouped into the non-bleeding group (group II).

The surgical procedures and postoperative managements were performed in the same operation team of the department of surgical oncology in our hospital. All the patients had no history of thyroid surgery. No patient was discharged on the same day and the postoperative observation time was 3-5 days. Thyroidectomy was performed under some experienced anesthetists who were skilled in anesthesia of thyroidectomy, available for airway management and tracheal intubation or extubation. The preoperative patients were instructed to stop anti-platelet agents at least 5 days and were asked to stop warfarin at least 4 days. Lugol solution or a saturated solution of potassium iodide was used in patients with Graves' disease for 10 days prior before surgery to decrease the vascularity of the thyroid gland. All patients received an active suction drain that was removed routinely on the third day

Table 2. Multivariate analysis (logistic regression)

Characteristic	OR	95% CI	*P*-value
Male gender	3.243	2.078-5.061	< 0.001
Older age	1.025	1.006-1.043	0.009
Tumor size (> 3 cm)	4.495	2.462-8.208	< 0.001
Postoperative hypertension (SP > 150 mmHg)	2.195	1.006-1.043	0.035
Lymph node dissection	3.384	2.146-5.339	< 0.001
Graves' disease	3.744	1.920-7.303	< 0.001

OR: odds ratio; 95% CI: 95% confidence interval.

after surgery (Suction drain was placed selectively, mostly for large-sized retrosternal goiters or those requiring concomitant neck lymph node dissections).

The retrospective review protocol was approved by the Institutional Review Board in our hospital.

Parameters analyzed

The main observations were bleeding after thyroidectomy and source of bleeding. The bleeding after thyroidectomy was defined as a hematoma in a patient who developed respiratory compromise and required emergent surgical evacuation of the hematoma. The source of bleeding was confirmed by reexploration in operation room.

The following variables selected from perioperative characteristics were used to analyze risk factors of PTB: age at diagnosis, gender, smoking, pathology, Graves' disease, postoperative hypertension, tumor size, operation extent, drain, total thyroidectomy and lymph node dissection.

The potential risk factors for PTH were compared between groups I and II (show in **Table 1**).

Statistical analysis

The frequency distribution of PTB in two groups of clinical and pathologic characteristics was compared by χ^2 test or Fisher's exact test. Continuous variables like age at diagnosis were compared by independent two-sample t test. Logistic regression analysis was fitted to data to assess independent risk factors of bleeding with all variables above. All statistical tests received the same level of significance with *P*-value < 0.05.

Results

Patient population

In our study, a total of 4449 patients who underwent thyroidectomy in the First Affiliated Hospital of Wenzhou Medical University from 2008 to 2012 were included. Of those, 872 were females and 3577 were males. Age at diagnosis in Group I was 50.6 ± 10.6 and Group II was 46.5 ± 12.1 (years) retrospectively.

Univariate analysis: **Table 1** demonstrated the relationship between risk factors and PTB. 8 risk factors were significantly related to PTB: age at diagnosis (years) ($P = 0.002$), gender ($P < 0.001$), smoking ($P = 0.014$), Graves' disease ($P = 0.008$), postoperative hypertension ($P = 0.001$), drain ($P = 0.007$), tumor size (> 3 cm) ($P < 0.001$) and Lymph node dissection ($P < 0.001$). The factors of pathology, Hashimoto's thyroiditis, operative extent and total thyroidectomy have no statistical significance.

Multivariate logistic regression: A multivariate analysis was performed to determine whether these parameters were independent risk factors for PTB. Male gender (OR 3.243; 95% CI 2.078-5.061; $P < 0.001$), older age (OR 1.025; 95% CI 1.006-1.043; $P = 0.009$), tumor size (> 3 cm) (OR 4.495; 95% CI 2.462-8.208; $P < 0.001$), postoperative hypertension (SP > 150 mmHg) (OR 2.195; 95% CI 1.006-1.043; $P = 0.035$), lymph node dissection (OR 3.384; 95% CI 2.146-5.339; $P < 0.001$) and Graves' disease (OR 3.744; 95% CI 1.920-7.303; $P < 0.001$) turned out to be independent risk factors for PTB (**Table 2**).

The source of bleeding

As shown in **Table 3**, for 84 patients (95.5%), we addressed the explicit source of bleeding by reexploration: infrahyoid muscles (30/88), beside the laryngeal recurrent nerve (22/88), subcutaneous tissue (10/88), superior pole (10/88), residual thyroid tissue (8/88), beside the vena jugularis interna (4/88). In the remaining 4 patients (4.5%), we could not confirm the source of the bleeding.

Table 3. Sources of bleeding

Sources of bleeding	Number	Percent (%)
Infrahyoid muscles	30	34.10
Beside the laryngeal recurrent nerve	22	25.00
Subcutaneous tissue	10	11.40
Upper pole of thyroid	10	11.40
Residual thyroid tissue	8	9.09
Beside the vena jugularis interna	4	4.55
Unknown	4	4.55
Total	88	

Table 4. Bleeding sources in infrahyoid muscles

Bleeding sources in infrahyoid muscles	Number	Percent (%)
Pre-thyroid muscles	22	73.33
Sternocleidomastoid	4	13.30
Platysma	2	6.67
Strap muscles	2	6.67
Total	30	

The source of bleeding in infrahyoid muscles was shown in **Table 4**.

Discussion

Bleeding after thyroidectomy is an infrequent, but a potentially fatal complication. The common symptoms of bleeding are neck swelling, central neck pressure, choking sensation, and severe dyspnea. Other relatively uncommon symptoms include dysphagia, wound drainage or difficulty with phonation [5]. Early recognition with immediate intervention is the key point to the management of this complication. Therefore, it is imperative to identify possible risk factors of PTB and common bleeding source.

In our series, the overall rate of bleeding was 2%. This rate appeared to be consistent with most other single institution study. Furthermore, we found that male gender, older age, tumor size > 3 cm, postoperative hypertension (SP > 150 mmHg), lymph node dissection and Graves' disease were independent risk factors for PTB on multivariate analysis.

Previous literatures, male gender was associated with a higher risk of bleeding [5, 9, 11]. In our study, we confirmed male gender has higher risk for PTB, compared to female. However, the reason for this difference is obscure: perhaps the male muscles are stronger and their contractions at awakening provoke slipping of ligatures or reopening of previously ligated vessels causing hematomas; besides male gender is more frequently associated to hypertension and smoking. Smokers have a recognized increased bleeding tendency [11, 12]. However, smoking is not an independent risk factor in our study.

Previous studies had reported that older age was an risk factor for PTB [4, 6, 9]. Be consistent with this consequence, we also demonstrated that older age increased the risk of hemorrhage after thyroidectomy. But, we did not identify the most dangerous threshold of age. We believed that, improving the risk factor of older age being impossible, we should take more intensive care for the patient with older age after thyroidectomy.

Lang et al. [7] determined dominant nodule with 3 cm as a cutoff and found those with size of dominant nodule > 3 cm had an OR of 4.54 (95 % CI, 1.22-16.92; p = 0.024) or approximately 4.5 times higher risk for hemorrhage after thyroidectomy than that of size ≤ 3 cm. The results of our study suggested that nodule size (> 3 cm) was an independent risk factor for bleeding. We postulate that the larger nodule size tended to larger extent dissection and raw surfaces, which may have resulted in increased rate of PTB. Therefore, more attentions should be paid to the patients with nodule size > 3 cm after thyroidentomy.

Calò et al. [11] suggested that the most bleeding after thyroidectomy was probably due to higher systolic blood pressures postoperatively. While, Burkey et al. [5] identified 42 cases of hemorrhage (0.03 percent of the serie), from 13817 operations, were found higher systolic blood pressures postoperatively was not an risk factor. We considered this study is not strictly comparable to others, because they used a systolic blood pressure threshold of 170 mmHg. Morton et al. [13] demomstrated that the factor of higher systolic blood pressures postoperatively in excess of 150 mmHg was associated with an increased risk of hemorrhage after thyroid surgery. Similarly, in our facility, we also found that the higher systolic blood pressures postoperatively (using the

blood pressure threshold of 150 mmHg), dentified by regression analysis, was the major significant factor for PTB. For this reason, a close attention must be paid in the postoperative period of patients with higher systolic blood pressures (> 150 mmHg) postoperatively, especially if an anti-hypertensive therapy has been stopped preoperatively on request of the anaesthetist, and prompt treatments of all manifestations of hypertension with appropriate drugs are recommended.

To our knowledge, Graves' disease can increase the vascularity of the thyroid and make thyroidectomy more difficult as increased intraoperative bleeding [3]. Campbell et al. [10] conducted a retrospective, multi-Center and case-control study identifying 207 patients, Graves' disease was an independent risk for PTB. Contrarily in other studies, the association between Graves' disease and PTB failed to reach statistical significance [8, 9]. While, in our study, we confirmed that Graves' disease was an independent risk in multivariate analysis. The reason of the different consequences may be the varying use of preoperative iodine (Lugol's solution) among surgeons. Iodine has been shown to reduce blood flow within the thyroid gland and may decrease the bleeding after thyroidectomy. On the other hand, almost hyperthyroidism can be seen in patients with Graves' disease. Many literatures demonstrated that a statistically significant higher prevalence of hyperthyroidism in patients requiring re-intervention for hematoma [3, 12, 14, 15]. Therefore, although our study did not evaluate the use of iodine, we believed that Graves' disease was significant risk factor for PTB. Close attention should be paid for postoperative patients with Graves' disease.

It is known to all that the extent of thyroidectomy has a great influence on the complications, including PTB. Nevertheless, previous studies fail to certify neck lymph dissection (NLD) performed was associated with PTB [6, 10]. In present study, we demonstrated the risk of NLD was an independent predictor for PTB, with an odds ratio of 3.384. This finding may be explained that the patients who need NLD had malignant pathological diagnosis and necessarily underwent a large thyroid tissue removal, which led to a larger dead space and allowed a hematoma to form easily. Moreover, NLD need greater extent of dissection and more likely to damage the surrounding tissue, such as infrahyoid muscles or jugular vein. Therefore, meticulous hemostasis during operation and close attention after thyroidectomy should be required when performing NLD.

The use of a drain was not an independent risk factor for PTB. Generally, drains have long been used empirically in thyroid surgery to prevent postoperative hematoma formation. However, in theory, there is a risk of disrupting previously ligated vessels with the placement (or more likely removal) of a closed suction drain. Furthermore, negative pressure in the wound could promote bleeding from disrupted vessels in the operative bed. Previous studies demonstrated that the use of a drain has no significant reduction on the occurrence of bleeding in thyroid surgery [16, 17]. In addition, many reports suggested drains should not be used as a preventive measure [5, 18-20].

The second part of our analysis focused on the source of bleeding. In our present study, the sources of bleeding were identified in 84 patients (95.5%) and unknown in 4 patients (4.5%).

Infrahyoid muscles were the most common bleeding source and were confirmed in 30 patients: pre-thyroid muscles (22/88), sternocleidomastoid (4/88), platysma (2/88) and strap muscles (2/88) (**Table 4**). Be consistent with Spinelli et al [21], the pre-thyroid muscles were the common bleeding sources, in our study. Muscle blood supply is relatively abundant. If this place was not taken suture to hemostasis but electrocoagulation, heavy neck exercise after thyroidectomy may lead to bleeding because of a blood clot removal. However, due to the muscle bleeding not fast and blood clot formation early, symptoms of respiratory distress often were delayed or not serious. We recommend the suture for hemostasis was necessary when breaking down infrahyoid muscles or extensive errhysis on infrahyoid muscles. Moreover, it is important to ask patients to avoid heavy neck exercise after thyroidectomy.

The bleeding source was found beside the laryngeal recurrent nerve in the majority of patients (22/88). This situation often occurs when performing the central lymph node dissection in thyroid carcinoma. Due to this bleeding source is adjacent to the trachea, PTB could

lead to serious and emergency airway compression. It can be explained that this placement has a highly blood supply of adipose tissue in central compartment and recurrent laryngeal nerve. Therefore, to avoid damaging recurrent laryngeal nerve, the surgeons often hemostasis incompletely maybe result in postoperative hemorrhage.

In our study, 10 (10/88) patients' bleeding sources were identified in upper pole of thyroid and all were arterial bleeding. These sources of bleeding frequently occurred in the case of suddenly violent cough, sneeze or vomit, especially during the procedure of extubation. Because arterial bleeding was fast and large volume, the patient would have neck swelling, pain, and even dyspnea. The cause mainly was of ligating vessels untightly. Generally, it results from chunk ligation, instead of each branch ligation for upper pole of the thyroid vessels. In our experience, chunk ligation always associate with expose inadequately, dissect incompletely and ligate with part of cricothyroid during the surgery. When a patient occurred suddenly violent cough, sneeze or vomit, the upper pole would lift with thyroid cartilage, generating forces between the upper pole and cricothyroid, making the part cricothyroid evulsion, loosing bleeding ligation, and lead to the bleeding after operation. Therefore, firm and careful attention is required to ligate the upper pole of thyroid.

The source of bleeding was confirmed from subcutaneous tissue in 10 patients (10/88). The reasons can be explained that incomplete hemostasis or suture on the subcutaneous tissue during the operation. The violent cough or vomit and unexpected hypertension were also responsible for the subcutaneous tissue bleeding. Patients with subcutaneous tissue bleeding almost had neck swelling and ecchymosis in the early time. Therefore, if one patient appears above symptoms in the early time, close attention and timely intervention will be necessary. According to our experience, completely hemostasis and suture were the crucial step to prevent subcutaneous tissue bleeding.

Eight (8/88) patients' bleeding sources were found in residual thyroid tissue. This situation mainly occurred after the subtotal thyroidectomy surgery, especially hyperthyroidism surgery [12, 22]. Moreover, in one large multicentre Italian study including 14,934 patients, Rosato et al. [2] found residual thyroid tissue was association with postoperative hematoma formation. Generally, the main reason is the surface of residual thyroid tissue was sutured unfirmly. We recommend complete hemostasis of the cut surface in the residual thyroid tissue with using suture ligation to prevent a hematoma.

We identified the source of PTB beside the vena jugularis interna in 4 patients. Moreover, these 4 patients all understood lateral compartment lymph node dissection. The main reason was the damage to the internal jugular vein during the lateral compartment lymph node dissection and a blood clot or ligation off because of the increase jugular venous pressure after thyroidectomy. Therefore, greater attention and meticulous hemostasis are required when we must expose the jugularis interna, especially the lateral compartment lymph node dissection.

The observation for up to 24 h is recommended for the majority of patients undergoing thyroidectomy [7, 9]. Lee et al. [19] recommended the PTB should be divided into the superficial strap muscles and the deep. Ecchymosis was prominent symptom in superficial strap muscles bleeding. While, the early and seriously life-threatening airway obstruction occurred in the deep strap muscles bleeding and discoloration of the mucosa was an important sign of the deep hemorrhage. Besides, surgeons should pay more emphasis on the importance of subtle early signs of hypoxia such as sweating, tachycardia, irritability and confusion rather than neck swelling, drainage and other obvious signs of airway obstruction to avoid delays in reintervention [23].

At the time of surgical re-intervention, it is crucial to identify the source of bleeding early and exactly. We recommend that infrahyoid muscles should be explored prior when the bleeding sources in the superficial strap muscles and the region of beside the laryngeal recurrent nerve ought to be explored firstly when in deep. Furthermore, attention should be paid to parathyroid glands vulnerable to injury or removal during the process of irrigation, suction and clot evacuation. It is worth noting that the recurrent laryngeal nerve must be demonstrated prior to clipping or ligation of any structures. Blind clamping of vessels within the haematoma is to be avoided, and we suggest the use of water to assist in identification of any bleeding points.

However, there are several potential limitations in this study. Firstly, the group I only included patients who developed PTB that required surgical reexploration. The previous studies suggested that 46% of hematomas may be managed non-operatively [7]. Whether our findings can be extrapolated to patients who develop hematomas that can be managed non-operatively is unclear. Secondly, the neck lymph dissection in our study defined as the central and/or lateral compartment lymph dissection. At present, there no research about PTB in the central and/or lateral compartment lymph dissection. Besides, due to some patients' pathological data incompletely, we can't do further research on the association between PTB and NLD. Thirdly, this study was conducted in a retrospective investigation. However, owing to the low incidence of PTB, the prospective study is very difficult to carry out. The last, single center study is not accurate enough. Generally, multicenter study could find more credible independent risk factors for PTB. Hence, We are trying to cooperate with more hospitals to develop multi-center study about PTB. Despite these limitations, we believe that our central findings of the study are valid.

In summary, postoperative hematoma remains a rare but potentially life-threatening complication. Early recognition with immediate intervention is the key to the management of this complication. In our study, male gender, older age, tumor size > 3 cm, postoperative hypertension (SP > 150 mmHg), lymph node dissection and Graves' disease are independent risk factors for PTB. Meticulous hemostasis and close attention should be paid for these patients with these risk factors. The sources of bleeding are identified more frequently in the Infrahyoid muscles and beside the laryngeal recurrent nerve. We recommend that infrahyoid muscles should be explored prior when the bleeding sources in the superficial strap muscles and the region of beside the laryngeal recurrent nerve ought to be explored firstly when in deep during the surgery of reexploration.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Chun Jin, Department of Surgical Oncology, The First Affiliated Hospital of Wenzhou Medical University, ShangCai Village, Ouhai District, Wenzhou, Zhejiang, People's Republic of China. Tel: +86-0577-55579461; Fax: +86-0577-55579461; E-mail: jc_oncology@126.com

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