Risk factors for post-thyroidectomy haemorrhage: a meta-analysis

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Abstract

Background: Post-thyroidectomy haemorrhage is a rare but potentially life-threatening and unpredictable complication of thyroid surgery. In this study, we analysed the potential risk factors for the occurrence of post-thyroidectomy haemorrhage.

Methods: The PubMed and SCIE databases were comprehensively searched for studies published before June 30, 2016. Studies on patients who underwent an open thyroidectomy with or without neck dissection were included, and RevMan 5.3 software was used to analyse the data.

Results: Twenty-five studies and 424563 patients were included in this meta-analysis, and post-thyroidectomy haemorrhage occurred in 6277 patients (incidence rate = 1.48%). The following variables were associated with an increased risk of post-thyroidectomy haemorrhage: older age (MD = 4.30, 95% CI = 3.09–5.52, P < 0.00001), male sex (OR = 1.73, 95% CI = 1.54–1.94, P < 0.00001), Graves’ disease (OR = 1.76, 95% CI = 1.44–2.15, P < 0.00001), antithrombotic agents use (OR = 1.96, 95% CI 1.55–2.49, P < 0.00001), bilateral operation (OR = 1.53, 95% CI = 1.11–2.11, P = 0.01), and previous thyroid surgery (OR = 1.62, 95% CI = 1.12–2.34, P = 0.01). Malignant tumours (OR = 1.07, 95% CI = 0.89–1.28, P = 0.46) and drainage device use (OR = 1.27, 95% CI = 0.74–2.18, P = 0.4) were not associated with post-thyroidectomy haemorrhage.

Conclusion: Our systematic review identified a number of risk factors for post-thyroidectomy haemorrhage, including older age, male sex, Graves’ disease, antithrombotic agents use, bilateral operation, neck dissection and previous thyroid surgery. Early control of modifiable risk factors could improve patient outcomes and satisfaction.

Introduction

In the past decade, the number of patients undergoing thyroid surgery has increased (1). Compared with conservative methods, thyroid surgery is a relatively safe method for treating several kinds of thyroid diseases; however, the thyroid gland is an organ with a high blood flow rate, and it is not surprising that post-thyroidectomy haemorrhage is a complication of thyroid surgery. The incidence of post-thyroidectomy haemorrhage reported in the literature varies between approximately 0.43% and 4.39% (2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26), but the major centres in developed countries commonly report the incidence of post-thyroidectomy haemorrhage as less than 2%. Post-thyroidectomy haemorrhage is a rare but potentially life-threatening complication of thyroid surgery, which is particularly important to patients with outpatient thyroid surgery (27). In severe cases, the cervical haematoma can compress the airway, and emergency surgical treatment is required (28, 29). The haemorrhage occasionally requires blood transfusions (30). Death can also occur from respiratory distress and cardiac arrest (17, 31). Given these risks, patients receiving thyroid
surgery need to be closely monitored for any signs of bleeding after surgery.

Because an increasing number of patients with thyroid nodules are being selected for outpatient thyroid surgery (1), one of the main concerns of outpatient thyroid surgery is the risk of post-thyroidectomy haemorrhage, which will increase hospital stay and medical expenses even threaten life. A better understanding of the risk factors for post-thyroidectomy haemorrhage can guide doctors in the selection of patients for outpatient thyroid surgery. To address these issues, we performed a systematic review and meta-analysis to assess the risk factors associated with post-thyroidectomy haemorrhage.

**Subjects and methods**

Our systematic review was based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (32).

**Search strategy**

PubMed and Web of Science databases were used to perform a systematic literature search of studies published through June 30, 2016 using the following key words: ‘thyroidectomy and hemorrhage’ or ‘thyroidectomy and hematoma’ or ‘thyroidectomy and bleeding’. Two authors (Liu JH and Sun W) conducted an independent selection process, and they resolved their discrepancies through discussion.

**Selection criteria**

In this meta-analysis, the included studies met the following criteria: (i) a prospective or retrospective original article; (ii) English language documents; (iii) all of the patients underwent open thyroidectomy with or without lymph node dissection, (iv) all patients with post-thyroidectomy haemorrhage required reoperation, (v) the diagnosis was confirmed by intraoperative or postoperative pathology and (vi) demographics and clinical characteristics for the thyroidectomy patients were available for data extraction. Studies were eliminated from our meta-analysis using the following exclusion criteria: (i) reviews, letters to the editor, commentaries and editorials, irretrievable articles, animal studies and articles whose full text was not in the English language and (ii) patients with simple parathyroid surgery and minimally invasive thyroid surgery.

**Data extraction and quality assessment**

The two authors extracted the relevant data from the included articles according to the standardised form. Author, year of publication, country and region, research design, number of cases, incidence, potential risk factors and the corresponding data were recorded independently. The potential risk factors included the following: older age, male sex, Graves’ disease, antithrombotic agents use, bilateral operation, neck dissection, previous thyroid surgery and so forth. There were 2 investigators who evaluated the quality of studies independently using the Newcastle–Ottawa Scale (NOS) (33). The NOS was used to assess the risk of bias through three major components: (i) group selection, (ii) comparability and (iii) assessment of outcome or exposure. The total NOS scores of studies ranged from 0 to 9 (34), and studies were considered as low bias risk and high quality if they scored equal or more than 5 (35, 36).

**Statistical analysis**

Statistical analysis of the data was performed using RevMan 5.3 software. The results are presented as the mean difference IV (MD) or odds ratios (ORs) with a 95% confidence interval (CI), and a P value <0.05 was considered statistically significant, unless otherwise specified. In addition, heterogeneity was quantified using the Q test and I² statistics. When the heterogeneity test indicated no significant difference ($P>0.1$ and $I^2<50\%$), a fixed-effect model was applied; otherwise, a random-effects model was used. Begg’s funnel plot test was used to assess the possible publication bias.

**Results**

After the systematic retrieval of databases, 969 studies were initially included in this systematic review, and 1 additional record was obtained from another source (15). Because of duplication and non-English languages, 198 studies were excluded. Then, the title and abstract were scanned carefully, and another 711 reviews, case reports, letters and irrelevant studies were excluded. The full texts of the remaining 53 articles were carefully evaluated, and 25 studies that met the inclusion criteria were included in this meta-analysis. A total of 424563 patients were included in this meta-analysis, and post-thyroidectomy haemorrhage occurred in 6277 patients. The basic characteristics of the included studies are summarised in Table 1. The selection process flow chart for the studies included in the meta-analysis is shown in Fig. 1.
Table 1  The basic characteristics of the included studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Countries/regions</th>
<th>Sample size (haemorrhage/control)</th>
<th>Rate (%)</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suzuki (2)</td>
<td>2016</td>
<td>Japan</td>
<td>920/51967</td>
<td>1.77</td>
<td>7</td>
</tr>
<tr>
<td>Narayanan (3)</td>
<td>2016</td>
<td>USA</td>
<td>10/1447</td>
<td>0.69</td>
<td>7</td>
</tr>
<tr>
<td>Perera (4)</td>
<td>2016</td>
<td>USA</td>
<td>9/205</td>
<td>4.39</td>
<td>7</td>
</tr>
<tr>
<td>Pankhania (5)</td>
<td>2016</td>
<td>UK</td>
<td>27/1280</td>
<td>2.11</td>
<td>7</td>
</tr>
<tr>
<td>Oltmann (6)</td>
<td>2016</td>
<td>USA</td>
<td>20/2395</td>
<td>0.84</td>
<td>7</td>
</tr>
<tr>
<td>Sorensen (7)</td>
<td>2015</td>
<td>Denmark</td>
<td>42/1470</td>
<td>2.86</td>
<td>7</td>
</tr>
<tr>
<td>Molinari (8)</td>
<td>2015</td>
<td>Brazil</td>
<td>41/3411</td>
<td>1.20</td>
<td>7</td>
</tr>
<tr>
<td>Dehal (9)</td>
<td>2015</td>
<td>USA</td>
<td>1914/118875</td>
<td>1.61</td>
<td>7</td>
</tr>
<tr>
<td>Hardman (10)</td>
<td>2015</td>
<td>UK</td>
<td>32/1657</td>
<td>1.93</td>
<td>6</td>
</tr>
<tr>
<td>Weiss (11)</td>
<td>2014</td>
<td>USA</td>
<td>1870/150012</td>
<td>1.25</td>
<td>7</td>
</tr>
<tr>
<td>Liu (12)</td>
<td>2014</td>
<td>China</td>
<td>44/5156</td>
<td>0.85</td>
<td>6</td>
</tr>
<tr>
<td>Chen (13)</td>
<td>2014</td>
<td>China</td>
<td>88/4449</td>
<td>1.98</td>
<td>7</td>
</tr>
<tr>
<td>Dixon (14)</td>
<td>2014</td>
<td>USA</td>
<td>18/4140</td>
<td>0.43</td>
<td>7</td>
</tr>
<tr>
<td>Davidad (15)</td>
<td>2012</td>
<td>UK</td>
<td>186/15501</td>
<td>1.20</td>
<td>7</td>
</tr>
<tr>
<td>Promberger (16)</td>
<td>2012</td>
<td>Austria</td>
<td>519/30142</td>
<td>1.72</td>
<td>7</td>
</tr>
<tr>
<td>Lang (17)</td>
<td>2012</td>
<td>Hong Kong</td>
<td>22/3086</td>
<td>0.71</td>
<td>7</td>
</tr>
<tr>
<td>Calo (18)</td>
<td>2010</td>
<td>Italy</td>
<td>32/2559</td>
<td>1.25</td>
<td>7</td>
</tr>
<tr>
<td>Godballe (19)</td>
<td>2009</td>
<td>Denmark</td>
<td>230/5422</td>
<td>4.24</td>
<td>7</td>
</tr>
<tr>
<td>Lee (20)</td>
<td>2009</td>
<td>Korea</td>
<td>10/1040</td>
<td>0.96</td>
<td>7</td>
</tr>
<tr>
<td>Leyre (21)</td>
<td>2008</td>
<td>France</td>
<td>70/6814</td>
<td>1.03</td>
<td>7</td>
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<tr>
<td>Bergenfelz (22)</td>
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<td>Sweden</td>
<td>75/3587</td>
<td>2.09</td>
<td>7</td>
</tr>
<tr>
<td>Rosenbaum (23)</td>
<td>2008</td>
<td>USA</td>
<td>6/1050</td>
<td>0.57</td>
<td>7</td>
</tr>
<tr>
<td>Lefevre (24)</td>
<td>2007</td>
<td>France</td>
<td>60/5789</td>
<td>1.04</td>
<td>7</td>
</tr>
<tr>
<td>Richmond (25)</td>
<td>2007</td>
<td>Greece</td>
<td>27/2043</td>
<td>1.32</td>
<td>7</td>
</tr>
<tr>
<td>Ozlem (26)</td>
<td>2006</td>
<td>Turkey</td>
<td>5/1066</td>
<td>0.47</td>
<td>7</td>
</tr>
</tbody>
</table>

Age

A random-effects model was used to analyse this risk factor ($P = 0.03$, $I^2 = 59\%$). Age was described as a risk factor for post-thyroidectomy haemorrhage in 6 studies (4, 6, 7, 11, 13, 21). There was a significant difference between the haemorrhage and no-haemorrhage groups (MD = 4.30, 95% CI = 3.09–5.52, $P < 0.00001$) (Fig. 2A).

Gender

The data were analysed by a random-effects model ($P = 0.08$, $I^2 = 36\%$). The incidence of post-thyroidectomy haemorrhage was 2.11% in males and 1.29% in females. Male patients with thyroidectomy had a significantly higher incidence of post-thyroidectomy haemorrhage (OR = 1.73, 95% CI = 1.54–1.94, $P < 0.00001$) (Fig. 2B).

Graves’ disease

We used a random-effects model for data analysis ($P = 0.06$, $I^2 = 44\%$). Eleven studies were included in the analysis. The incidence of post-thyroidectomy haemorrhage was significantly increased in patients with Graves’ disease (OR = 1.76, 95% CI = 1.44–2.15, $P < 0.00001$) (Fig. 2C).

Antithrombotic agents use

Patients who used oral or injectable antithrombotic agents, regardless of dosage, were included in this meta-analysis. A fixed-effects model was applied to this data analysis ($P = 0.1$, $I^2 = 46\%$), and 6 studies about antithrombotic agents use were included.

Figure 1  Flow chart of the meta-analysis.
After the analysis, we concluded that the use of antithrombotic agents for thyroidectomy patients, regardless of dosage, was associated with post-thyroidectomy haemorrhage (OR = 1.96, 95% CI = 1.55–2.49, P < 0.00001) (Fig. 3A).

**Operation extent**

Operation type data were analysed by a fixed-effects model (P = 0.21, I² = 26%). Unilateral (lobectomy and unilateral partial thyroidectomy) and bilateral (bilateral, unilateral subtotal thyroidectomy) were compared.

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Figure 2

Meta-analysis results for the occurrence of post-thyroidectomy haemorrhage between the two groups. (A) Age; (B) gender; (C) Graves’ disease.
total and completion thyroidectomy) operations were evaluated in 9 studies. Compared with unilateral thyroid surgery, bilateral operations showed a higher propensity to post-thyroidectomy haemorrhage in thyroidectomy patients (OR = 1.71, 95% CI = 1.50–1.96, \( P < 0.00001 \)) (Fig. 3B).

**Previous thyroid surgery**

A random-effects model was used due to the heterogeneity of the data (\( P = 0.003, F^2 = 65\% \)). A total of 9 papers were included in this analysis. Patients who previously suffered a thyroid operation exhibited a high propensity for post-thyroidectomy haemorrhage (OR = 1.62, 95% CI = 1.12–2.34, \( P = 0.01 \)) (Fig. 3C).

**Neck dissection**

Due to the high heterogeneity, a random-effects model was used to analyse the data (\( P = 0.05, F^2 = 57\% \)). Five studies about the relationship between post-thyroidectomy haemorrhage and neck dissection were investigated (8, 10, 13, 14, 20). Thyroidectomy patients with neck dissection exhibited an increased risk of post-thyroidectomy haemorrhage (OR = 1.53, 95% CI = 1.11–2.11, \( P = 0.01 \)) (Fig. 4A).

**Pathological diagnosis**

As the data showed a high heterogeneity, a random-effects model was used for this analysis (\( P = 0.0002, F^2 = 68\% \)).
Thirteen studies were included, and the risk of post-thyroidectomy was not associated with malignant and benign thyroid disease (OR = 1.07, 95% CI = 0.89–1.28, P = 0.46) (Fig. 4B).

Drainage device use

We used a fixed-effects model to analyse the data involving the use of a drainage device ($I^2 = 0\%$, $P = 0.49$). In this analysis, 4 retrospective studies were included (3, 8, 12, 26), and studies with selected conditions for drainage device use were excluded. The analysis showed that post-thyroidectomy haemorrhage was not associated with the use of a drainage device (OR = 1.27, 95% CI = 0.74–2.18, $P = 0.40$) (Fig. 4C).

Discussion

In the past decade, the increasing prevalence of thyroid nodules allowed rapid development of thyroid diagnosis and treatment techniques. Ultrasound and fine needle aspiration biopsy have become the most important methods to diagnose and surveil thyroid nodules. Radioactive iodine therapy is a reliable method for treating goitre with iodine intake (37). Radiofrequency ablation has also become an alternative treatment for benign thyroid nodules. Though the development of these methods provides patients with options for the treatment of thyroid disease, thyroid surgery is still unavoidable for a number of patients. It is no wonder that thyroid operations are also increasingly performed with the increasing prevalence of thyroid disease (38).
Thyroidectomy and neck dissection are the most commonly performed neck surgeries. With the application of energy-based devices and novel haemostatic in thyroid surgery, the increase in safety over the past few decades, but several postoperative complications, including post-thyroidectomy haemorrhage and recurrent laryngeal nerve palsy and hypoparathyroidism, still occur. Among these, post-thyroidectomy haemorrhage is an uncommon but potentially life-threatening complication and requires urgent treatment due to the risk of major airway compression.

It is also important to study the risk factors of post-thyroidectomy haemorrhage as more patients have been undergoing thyroidectomy as an outpatient procedure (1). A number of studies have described the risk factors of post-thyroidectomy haemorrhage. However, the results are inconsistent. Therefore, this meta-analysis of the related research was necessary. The pooled outcomes of all items in this meta-analysis are showed in Table 2.

The data from our analysis showed very large differences in the incidence of post-thyroidectomy haemorrhage among the literature (range 0.43-4.39%) (Table 1), and the total incidence rate was 1.48% (6277/424,563) (2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26). In addition, we found that most of the studies reported an incidence rate less than 2% (20/25).

Because of the timely and effective treatment, only 2 patients died of post-thyroidectomy haemorrhage in this meta-analysis (17). Analysing the delay between surgery and haemorrhage requiring re-surgery, post-thyroidectomy haemorrhage occurred in 30-80.6% (3, 16) patients within 6 h and 65-97.6% (6, 16) patients within 24 h. Although the risk of bleeding is greatest within 6 h after surgery, the risk of haemorrhage requiring re-surgery can remain for more than 24 h. Therefore, it is important to determine the risk of haematoma formation and select appropriate patients for outpatient surgery.

We found that there was a difference in the incidence of post-thyroidectomy haemorrhage in different regions (Table 1), which means that a regional analysis of the risk factors for postoperative haemorrhage cannot be directly used in other regions.

Several studies have reported that older age is a risk factor for post-thyroidectomy haemorrhage. Consistent with these results, we found that the age of the haemorrhage group was older than the age of the no-haemorrhage group (MD = 4.30, 95% CI = 3.09-5.52, P < 0.00001). However, the age threshold reported in previous studies is inconsistent, and we did not identify a specific age as the most dangerous threshold. We believe that it is not possible to improve risk factors for the elderly, but we can provide more intensive care for patients of older age during the operation and perioperative period.

In our study, approximately 3.92 times more female patients underwent surgery for thyroid disease compared to male patients (223,297/58,413). However, males exhibited a 1.73-fold increased risk of post-thyroidectomy haemorrhage compared to females (OR = 1.73, 95% CI = 1.54-1.94, P < 0.00001), and the reason for the difference is unclear. As male was one of the risk factors of thyroid carcinoma (39), and lymph node metastasis was more likely to happen in male (40), which means that male thyroid surgery may be more complex. Some studies also suggest that male muscles are stronger and their contractions at awakening provoke the slipping of ligatures or the reopening of previously ligated vessels, thus causing haemorrhage. Moreover, males are more likely to have hypertension and bad habits such as smoking and drinking (18, 41). Because the diagnostic criteria of hypertension differ among the related studies, and there is no description of smoking and alcohol abuse, we are unable to analyse whether hypertension, smoking or alcohol abuse could be risk factors for postoperative bleeding.

Table 2 Pooled outcomes of all the subgroups.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>No. of studies</th>
<th>Statistical model</th>
<th>MD/OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>6</td>
<td>Random-effects</td>
<td>4.30</td>
<td>(3.09, 5.52)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Gender</td>
<td>15</td>
<td>Random-effects</td>
<td>1.73</td>
<td>(1.54, 1.94)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>11</td>
<td>Random-effects</td>
<td>1.76</td>
<td>(1.44, 2.15)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Antithrombotic agents</td>
<td>6</td>
<td>Fixed-effects</td>
<td>1.96</td>
<td>(1.55, 2.49)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Operation extent</td>
<td>9</td>
<td>Fixed-effects</td>
<td>1.71</td>
<td>(1.50, 1.96)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Previous thyroid surgery</td>
<td>9</td>
<td>Random-effects</td>
<td>1.62</td>
<td>(1.12, 2.34)</td>
<td>0.01</td>
</tr>
<tr>
<td>Neck dissection</td>
<td>5</td>
<td>Random-effects</td>
<td>1.53</td>
<td>(1.11, 2.11)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pathological diagnosis</td>
<td>13</td>
<td>Random-effects</td>
<td>1.07</td>
<td>(0.89, 1.28)</td>
<td>0.46</td>
</tr>
<tr>
<td>Drainage device use</td>
<td>4</td>
<td>Fixed-effects</td>
<td>1.27</td>
<td>(0.74, 2.18)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval; MD, mean difference; OR, odds ratios.

To determine the risk of haematoma formation and select appropriate patients for outpatient surgery, we believe that it is not possible to improve risk factors for the elderly, but we can provide more intensive care for patients of older age during the operation and perioperative period.
The thyroid glands of patients with Graves’ disease are richly vascular (37). This may make thyroid surgery more difficult, due to increased intraoperative bleeding, which may hinder the surgical field of vision, leading to an increased incidence of complications. Previous studies have identified a significant increase in the risk of parathyroid and recurrent laryngeal nerve injury in patients with Graves’ disease. In a previous study, Promberger found no association between Graves’ disease and post-thyroidectomy haemorrhage (16). This conclusion may be a result of the large variation in the rate of haemorrhage between surgeons, which may have overshadowed the contribution of Graves’ disease. Inorganic iodide (potassium iodide, saturated solution of potassium iodide and Lugol’s solution) can reduce thyroid hormone release and thyroid vascularity, which in turn decreases intraoperative blood loss. Therefore, preoperative inorganic iodide before surgery was recommended for most surgical patients with Graves’ disease (37). Most of the studies included in our analysis did not evaluate the use of iodine and the varying use of preoperative inorganic iodide among surgeons also influences the accurate definition of Graves’ disease as a risk factor for post-thyroidectomy haemorrhage (42). Ignore the use of inorganic iodide, we found that Graves’ disease had a 1.73-fold increase in the risk of post-thyroidectomy haemorrhage (OR=1.76, 95% CI=1.44–2.15, $P<0.00001$). Therefore, postoperative patients with Graves’ disease should be monitored closely regardless of the use of iodine before surgery. Additionally, to decrease intraoperative haemorrhage, pretreatment with inorganic iodide should be considered in patients with Graves’ disease (37, 43). Radioactive iodine therapy is one of the effective methods for the treatment of Graves’ disease, but the included studies, except 1 study (19), had not considered the influence of the history of radioactive iodine therapy before operation. The only 1 study found that the history of radioiodine treatment did not increase the incidence of postoperative haemorrhage, though it was confirmed that the history of neck radioiodine treatment may bring difficulties to thyroid surgery (44). More researches are needed to determine whether radioiodine therapy will increase the risk of post-thyroidectomy haemorrhage.

Antithrombotic agents included antiplatelet agents (aspirin, cilostazol, ticlopidine, clopidogrel, sarpogrelate, beraprost and icosapentate) and anticoagulant agents (warfarin, dabigatran, edoxaban, rivaroxaban and apixaban) (2). Antiplatelet therapy is often used to prevent in-stent thrombosis in patients who have previously received percutaneous coronary or other vascular interventions and the recurrence of cerebral thrombosis. These patients are problematic for many surgical procedures. Compared with antiplatelet therapy, anticoagulant therapy poses a larger problem (45, 46). Through an analysis of relevant studies, patients who used oral or injectable antithrombotic agents, regardless of dosage, were included in this meta-analysis. We demonstrated post-thyroidectomy haemorrhage rates of 2.48% for patients receiving antithrombotic therapies, which is significantly higher than the overall rate of 1.34% (OR=1.96, 95% CI=1.55–2.49, $P<0.00001$). This conclusion is consistent with an increase in the incidence of postoperative haemorrhage in other surgical procedures (45, 46, 47, 48). Despite the infrequent use, anticoagulants have a close correlation with increased rates of postoperative haemorrhage in both parathyroid and thyroid surgery, even if the usage is stopped 5–7 days before operation (6). What we have to say is that the use of injectable anticoagulant agents can make thyroid hematoma formation increased more than 20 times (6). Due to these reasons, the risk of postoperative haemorrhage and the risk of thrombosis events should be comprehensively evaluated in patients receiving antithrombotic therapy, especially injectable anticoagulants, and an appropriate antithrombotic therapy plan should be developed during the perioperative period. New oral anticoagulants (such as dabigatran, edoxaban, rivaroxaban, apixaban etc.) are increasingly used in clinical applications due to their lesser side effects (49). All the included studies in this analysis are retrospective studies, and the use of new oral anticoagulants was not evaluated in most included studies, except 2 articles published in 2016 (6, 12). Although only these 2 studies suggest new oral anticoagulants still increase the probability of bleeding, more studies are needed to clarify their impact on the risk of post-thyroidectomy haemorrhage.

In our analysis, patients with post-thyroidectomy haemorrhage were more likely to have had a bilateral thyroidectomy. Approximately 55% of patients underwent bilateral thyroid surgery in our study, and they exhibited a 1.73-fold increased risk of post-thyroidectomy haemorrhage compared with patients with unilateral thyroid surgery (OR=1.71, 95% CI=1.50–1.96, $P<0.00001$). Bilateral thyroidectomy resulted in a larger wound and more tissue injury compared to unilateral thyroidectomy. The larger wound and injury greatly increase the probability of haemorrhage after operation. In Promberger’s study, 10 of 519 patients demonstrated signs of bleeding after 24 h, and all of them had bilateral thyroid procedures (16). Thus, patients with bilateral
thyroid surgery need a larger monitoring period, and there is a great risk in the outpatient operation of bilateral thyroid surgery.

The proportions of patients who received neck dissection are different in medical institutions, and the proportions of the 5 included studies in our analysis range from 6.90% to 34.17% (7, 9, 12, 13, 19). We found that neck dissection is another risk factor for postoperative hematoma formation (OR=1.53, 95% CI=1.11–2.11, P=0.01). Unlike simple thyroidectomy, neck dissection requires a larger range of anatomy and a greater risk of injury to the surrounding tissues, including cervical muscles, subfascial veins and subcutaneous tissue. Neck dissection also leads to a larger dead space and allows for the easy formation of a haematoma (13). Cervical muscles are important location of the source of bleeding (12, 16), in the process of the operation, muscles and other tissues need to be stretched to obtain a good surgical vision and operating space when performing deep lymph nodes dissection. This may cause muscle vessel injury and lead to imperceptible haemorrhage. Accordingly, meticulous haemostasis during surgery and close monitoring after operations are necessary when performing neck dissection.

Previous thyroid surgery was another risk factor identified in our study with an OR of 1.62 (95% CI=1.12–2.34, P=0.01). An explanation for this risk factor is that scar tissue present in the reoperated field will arise as a result of strong adhesions and a distorted anatomy and may increase the difficulty of dissection (50). The scar tissue formed in a previous operation will also prevent the dead space after thyroidectomy to collapse so that smaller vessels can vasoconstrict. These factors may contribute to the risk of post-thyroidectomy haemorrhage (17).

Unlike previous studies suggest that post-thyroidectomy haemorrhage increased in patients with malignant pathology (2, 13, 19, 21) or benign pathology (11, 12, 15, 18). We were surprised to find that there was no association between the pathological diagnosis and post-thyroidectomy haemorrhage (OR=1.07, 95% CI=0.89–1.28, P=0.46). This result may be related to the surgical procedure, depending on the preoperative diagnosis and intraoperative frozen section diagnosis, and the final pathological diagnosis, which may differ from the previous diagnosis in some patients. In the included studies, there were differences in the composition of the patients with different pathological diagnoses and the inclusion of Graves’ disease as a benign lesion. These differences will influence the results.

The results indicated that there is no evidence to advocate for the use of drains in routine thyroid surgery to reduce the risk of post-thyroidectomy haemorrhage. This outcome was consistent with the findings of a previous meta-analysis (51, 52, 53). Particularly in Woods’ meta-analysis, the use of drains may increase postoperative pain and the length of hospital stay and wound infection rates in patients with routine thyroid or parathyroid surgery (53). Though the use of drainage is not conducive to preventing the occurrence of post-thyroidectomy haemorrhage, there is still a certain degree of uncertainty in the use of a drainage device for complex thyroid surgery, such as giant thyroid surgery and neck dissection.

In addition to the items analysed in this meta-analysis, Hashimoto’s thyroiditis, smoking status, alcohol abuse, hypertension, thyroid weight, chronic obstructive pulmonary disease, use of novel haemostatic, postoperative vomiting and even obesity are also reported relevant to post-thyroidectomy haemorrhage in few studies. However, it is a pity that the inconsistencies of diagnostic criteria and research methods as well as too few studies let us unable assessed these items in our meta-analysis. The surgical experience of experts and surgeons in training seems to affect the occurrence of postoperative complications of thyroid operation; however, in several related studies, we found that thyroid surgery performed by residents in training under supervision has similar complication rates as thyroid surgery performed by experts (54, 55, 56, 57). In conclusion, there are some other possible risk factors for post-thyroidectomy haemorrhage, and to confirm these possibilities, more researches are needed.

Limitations

There are several limitations to this study. First, although 25 papers were included in our meta-analysis, they were all retrospective studies. And 18 of the 25 included studies were from United States or European countries, only 5 studies are issued from Asia, 1 from Brazil and 1 from Turkey, this may cause bias. Second, the types of patients that underwent thyroidectomy for thyroid lesions were inconsistent, including total thyroidectomy, subtotal thyroidectomy and lobectomy plus isthmus. Third, this meta-analysis included several large studies, and these trials may lead to a bias in assessing the outcome of our study. Fourth, the varying use of preoperative inorganic iodide among surgeons might cause bias in analysing Graves’ disease. Fifth, the differences in the study population and aims of the included studies might lead to selective bias. Sixth, the studies included in our meta-analysis did not describe the details of the operative
procedure and the application of new technology, such as novel haemostatic devices and haemostatic agents, which might affect the occurrence of haematoma. Seventh, due to the inconsistencies of diagnostic criteria and research methods as well as too few studies, we failed to analyse some other possible risk factors, such as Hashimoto's thyroiditis, smoking status, alcohol abuse, hypertension, thyroid weight etc.

**Conclusion**

In conclusion, post-thyroidectomy haemorrhage is an uncommon but potentially life-threatening complication of thyroid surgery. Because it is difficult to predict and develops rapidly, post-thyroidectomy haemorrhage should be taken seriously, especially among patients with outpatient thyroid surgery. Our meta-analysis identified the following significant risk factors for post-thyroidectomy haemorrhage: older age, male sex, Graves’ disease, antithrombotic agents use, bilateral operation, neck dissection and previous thyroid surgery. The pathological diagnosis and the use of drainage were not related to the occurrence of post-thyroidectomy haemorrhage.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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**Author contribution statement**

Conceived and designed the experiments: H Z, W S, X B L, W W D, Z H W, T Z and J H L. Performed the experiments: J H L and W S. Analysed the data: J H L, W S and H Z. Contributed reagents/materials/analysis tools: J H L and S W. Wrote the paper: J H L.

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