Review

Total Thyroidectomy versus Bilateral Subtotal Thyroidectomy for Bilateral Multinodular Nontoxic Goiter: A Meta-Analysis

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Key Words

Total thyroidectomy · Bilateral subtotal thyroidectomy · Bilateral multinodular nontoxic goiter · Meta-analysis

Abstract

Aim: The aim of this meta-analysis is to assess and validate the feasibility and safety of total thyroidectomy (TT) when compared to bilateral subtotal thyroidectomy (BST) for bilateral multinodular nontoxic goiter (BMNG). **Materials and Methods:** PubMed, Web of Knowledge, and Ovid's database were searched for studies published in English language between January 1990 and December 2014. A meta-analysis was performed to compare the complications and recurrences of TT versus BST. The search terms used were 'total thyroidectomy', 'bilateral subtotal thyroidectomy', 'multinodular nontoxic goiter' and 'randomized clinical trial'. The reference lists of relevant studies were checked manually to locate any missing studies. **Results:** Four trials with a total of 1,078 patients were analyzed. Although the incidence of transient hypoparathyroidism was higher in TT than in BST (OR = 2.59, 95% CI [1.58–4.24], $p = 0.0002$), TT was associated with a significantly lower incidence of recurrence (OR = 0.04, 95% CI [0.01, 0.17], $p < 0.0001$). There were no statistically significant differences for the presence of transient/permanent recurrent laryngeal nerve palsy and permanent hypoparathyroidism between the two groups. **Conclusion:** TT is a feasible and safe procedure for patients with BMNG. Although TT involves a significantly higher risk of postoperative transient hypoparathyroidism, it has a lower recurrence rate than BST.

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The surgical procedure for bilateral multinodular nontoxic goiter (BMNG) remains controversial. Delbridge [1] reported that subtotal thyroidectomy for benign thyroid disease has been performed for more than a century and that it may reduce the associated risk of postoperative hypocalcemia and recurrent laryngeal nerve (RLN) palsy. However, it usually leads to high recurrence for BMNG patients in the long-term follow-up. Most surgeons still argue whether the potential risk of total thyroidectomy (TT) outweighs the potential benefits [2–5]. The management for BMNG intends to treat goiters that need surgical treatment and to reduce the risk of complications and recurrence [6–8]. In recent decades, TT has become a preferred surgical procedure for BMNG for the majority of surgeons [9] because it eliminates the risk of recurrence and there is no need reoperation for incidental differentiated thyroid cancer. However, this radical procedure may increase the risk of iatrogenic injury [4]. Some authors also discussed whether postoperative thyroid-stimulating hormone (TSH) suppression can prevent recurrence, but the conclusion was uncertain [10].

Up to the present time, no meta-analysis of randomized clinical trials has been performed to compare and summarize the results of TT with those of bilateral subtotal thyroidectomy (BST). The aim of this study is to assess and validate the safety and feasibility of TT when compared to BST and to verify other potential benefits and drawbacks for BMNG.

Materials and Methods

Search Strategy

PubMed, Web of Knowledge, and Ovid's database were searched for studies in English language published between January 1990 and December 2014. The search terms used were 'total thyroidectomy', 'bilateral subtotal thyroidectomy', 'multinodular nontoxic goiter' and 'randomized clinical trial'. The reference lists of relevant studies were checked manually to locate any missing studies.

Study Selection

The identified studies were assessed for eligibility for inclusion in the review by scrutinizing their titles, abstracts and keywords. Studies were restricted to those published in English. Clinical studies concerning comparisons of any aspects between TT and BST for MNG were also included.

Data Extraction

Two coauthors (Yujie Li and X.Z.) independently selected studies for inclusion and exclusion and reached consensus when they did not agree initially. The following variables were recorded: authors, journal and year of publication, number of patients, age, transient RLN palsy, permanent RLN palsy, transient hypoparathyroidism, permanent hypoparathyroidism and recurrence. If necessary, the corresponding authors of the studies were contacted to obtain supplementary information.

Quality Assessment

The quality of the trials was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 [11]. It contained the following aspects: randomization, allocation concealment, blinding, description of withdrawals, and selective outcome reporting.

Trials which did not cover the outcomes of completely randomized patients were regarded as suffering from bias because of incomplete outcome data and were thus excluded from further analysis.

Statistical Analysis

A formal meta-analysis was carried out for all included studies comparing the results of TT and BST for BMNG. The outcomes in our study were transient RLN palsy, permanent RLN palsy, transient hypoparathyroidism, permanent hypoparathyroidism and recurrence. A fixed-effects model was used to calculate a pooled odds ratio (OR) with its 95% confidence interval (CI). Heterogeneity was explored using I^2 statistics, a measure of how much the variance between studies, rather than chance, can be attributed to inter-study differences. $I^2 > 50\%$ was regarded to indicate strong heterogeneity. The Cochrane Collaboration's Review Manager Software (RevMan version 5.0) was utilized for data analysis.

Fig. 1. Flowchart of the results of the literature search.

Table 1. Overview of the reviewed studies

First author [Ref.], year	Country	Patients, n	Sex (male/female)	Patient source	Mean age, years	Levothyroxine therapy	Study design
Barczyński [12], 2010	Poland	381	TT: 17/174 BST: 16/174	Jagiellonian University College of Medicine	TT: 46.5 BST: 47.2	TT: mean 100.59 µg/day BST: mean 77.16 µg/day	RCT
Giles [7], 2004	Turkey	218	TT: 15/94 BST: 17/92	Istanbul Medical Faculty	TT: 50.3 BST: 45.7	–	RCT
Yang [13], 2009	China	346	TT: 36/129 BST: 42/139	Ruijin Hospital	–	TT: 50–75 µg/day BST: 75–125 µg/day	RCT
Pappalardo [14], 1998	Italy	141	TT: 20/49 BST: 21/51	University hospital	TT: 48.0 BST: 50.0	1.5–2.25 µg/kg, subsequently adjusted depending on TSH	RCT

RCT = Randomized clinical trial.

Results

Study Selection

We identified 213 potentially relevant articles (fig. 1). After exclusion of duplicate references, nonrelevant literature, and articles that did not meet the inclusion criteria, 17 candidate articles were considered for the meta-analysis. After careful review of the full text of these articles, 4 studies were included. The study characteristics are summarized in tables 1 and 2.

Patient demographics for the 4 studies are presented in table 1. All papers were randomized clinical trials. The publication dates ranged from 1990 to 2014. Study sizes ranged from 141 to 381 patients.

Outcome Measures

A total of 528 patients who underwent TT and 550 patients who underwent BST were analyzed. In the included studies, more than 2 g of normal remnant thyroid tissue on both sides of the neck was left in the BST group. The criteria for the recurrences are summarized in table 2.

Table 2. Overview of the reviewed studies

First author [Ref.], year	Inclusion criteria	Exclusion criteria	Criteria used for recurrences	Median follow-up, months
Barczyński [12], 2010	A bilateral nontoxic MNG with the posterior aspects of both thyroid lobes appearing normal on ultrasound of the neck	MNG involving the posterior aspect/s of thyroid lobe/s, suspicion of thyroid cancer, previous thyroid surgery, thyroiditis, subclinical or clinically overt hypothyroidism or hyperthyroidism, pregnancy or lactation, and age <18 or >65 years	Presence of hypoechoic or hyperechoic nodular pattern at least 5 mm in diameter, identification of perinodular hypoechogenic or hyperechogenic halo, and presence of an anechoic lesion with a reinforced posterior wall	60
Giles [7], 2004	Bilateral multinodular goiter, euthyroid and no history of hyperthyroidism, radiation exposure, or familial thyroid cancer	Preoperative or perioperative suspicion of malignancy	–	–
Yang [13], 2009	Bilateral multinodular goiter	History of thyroidectomy	De novo nodules more than 3 mm in remnant thyroid by ultrasonography	TT: 36 BST: 39
Pappalardo [14], 1998	Unilateral and bilateral multinodular euthyroid goiters	Graves' disease, Plummer disease, thyroiditis, hyperfunctioning single adenoma, or cancer	Physical examination or ultrasound scan showed nodular involvement or an enlargement of the residual thyroid remnant	174

Transient RLN palsy was observed in 4 studies. The BST group had less transient RLN palsy, but no significant difference was found (OR = 1.68, 95% CI [0.75, 3.74], $p = 0.21$; fig. 2). The prevalence of permanent RLN palsy was 0.77% in the TT group versus 0.76% in the BST group without a significant difference (OR = 1.01, 95% CI [0.17–5.92], $p = 0.99$; fig. 2). All 4 studies assessed patients for transient hypoparathyroidism. The prevalence of transient hypoparathyroidism was 11.0% in the TT group versus 4.9% in the BST group, and this difference was statistically significant (OR = 2.59, 95% CI [1.58–4.24], $p = 0.0002$; fig. 2). The prevalence of permanent hypoparathyroidism was 0.6% in the TT group versus 0.2% in the BST group, and no significant difference was observed (OR = 2.42, 95% CI [0.35–16.64], $p = 0.37$; fig. 2). Recurrence was assessed in 3 of the 4 studies. The recurrence rate in BST was approximately 10% and significantly higher than that in TT (OR = 0.04, 95% CI [0.01, 0.17], $p < 0.0001$; fig. 3). The incidence of thyroid cancer was lower in the BST group, but no significant difference was found (OR = 1.35, 95% CI [0.79–2.30], $p = 0.27$; fig. 4).

Discussion

There are several surgical procedures for BMNG, including subtotal thyroidectomy, near-total thyroidectomy, and TT. The postoperative complications (transient/permanent hypocalcemia and transient/permanent RLN palsy) and recurrences are regarded as the assessment of the balance between TT and ST.

In the past several years, a lot of data has been published indicating the equal incidence of both transient/permanent RLN palsy and transient/permanent hypocalcemia for subtotal thyroidectomy and TT [3, 15, 16]. According to the research of Randolph [17], the incidence of transient/permanent RLN palsy was 0–6% and <1%, respectively. The incidence of

Fig. 2. Forest plot of the comparison of transient RLN, permanent RLN, transient hypoparathyroidism, and permanent hypoparathyroidism for TT versus BST.

Fig. 3. Forest plot of the comparison of recurrence for TT versus BST.

Fig. 4. Forest plot of the comparison of thyroid cancer incidence for TT versus BST.

transient/permanent hypocalcemia was 0.3–49% and 0–13%, respectively. Thirteen studies [3, 7, 14, 16, 18–26] were summarized by Agarwal and Aggarwal [9]: only 1 study [26] reported that the permanent RLN palsy rate was significantly higher, and merely 2 studies [22, 26] showed that the permanent hypocalcemia rate was significantly higher. Other studies did not find any significant difference in the incidence of permanent hypocalcemia and permanent RLN palsy after TT and BST.

In all 4 included studies, the incidence of transient/permanent RLN and transient/permanent hypocalcemia was similar to that reported by Randolph [17]. Our meta-analysis showed that TT was of similar risk of complications compared with BST except for transient hypoparathyroidism. Patients with transient hypoparathyroidism can receive calcium substitution after surgery.

The rates of recurrence are considered as long-term therapeutic effect for BMNG. In some studies, the rates of recurrence of BMNG after BST ranged from 1.2% in a retrospective study [3] to 50% in another retrospective study [27], and the risk for recurrence was significantly higher in the BST group than in the TT group. Delbridge et al. [28] reviewed that subtotal

thyroidectomy for multinodular goiter led to a second operation because of recurrence in 13–20% of patients, reaching a peak incidence 13 years after the primary operation. For these patients, the second operations are usually associated with higher complications in contrast with primary surgery [28, 29].

Incidental thyroid cancers have been detected in 3–16.6% of apparently benign goiters after TT or BST in various studies [5, 9, 28, 30, 31]. About two thirds of cancers are micro-papillary or microinvasive follicular cancers [3, 19, 27, 32–35]. Though the treatment of microcarcinomas is still a matter of discussion, some microcarcinomas may have a negative outcome, including distant metastasis and patient death [36–39]. Pellegriti et al. [40] detected local regional metastasis in one fourth of 299 carcinoma patients with tumors smaller than 1.5 cm. The other third of cancers are follicular cancers and multicentric or large papillary cancers; such patients need further surgical treatment after subtotal thyroidectomy.

In our meta-analysis, the incidence of thyroid cancer was comparable between TT and BST (fig. 4). According to 3 included studies [12–14], the mean recurrence rate in BST was 10.0% (44/441), and TT fared significantly better than BST in terms of the frequency of recurrence. Therefore, TT was considered to be a valuable option for BMNG.

Furthermore, 3 included studies [12–14] reported levothyroxine requirements following thyroidectomy. Biological hypothyroidism occurred on average 5.6 months after surgery [41]. On monitoring thyroid function, patients with hypothyroidism received levothyroxine substitution following the operation. For those who received TT, the goal of therapy was euthyroidism, and the correct maintenance dose allowed TSH to be in the normal range. Thus, the quality of life was affected by levothyroxine reposition [42].

Several authors have hypothesized that postoperative levothyroxine therapy could hinder MNG recurrence by retractive control of the production of TSH. However, this hypothesis is controversial. Moalem et al. [10] assessed that approximately 50% of studies on the subject support this hypothesis, but with sometimes questionable methodology. Some studies indicated that substitutive levothyroxine therapy does not have any influence on nodular recurrence [41, 43, 44].

In case of unilateral disease, some studies recommended unilateral resection in both adults and children [45, 46]. For unilateral resection, transient hypocalcemia was reported in 0–18% of patients, voice hoarseness in 1–6%, and hematoma in 0–1%; moreover, transient hypoparathyroidism is uncommon [10, 16, 47, 48]. In addition, the large majority of patients with unilateral resection avoided lifelong thyroid replacement therapy [49], while this treatment was needed in all patients after bilateral resection to prevent hypothyroidism. So, we recommend that patients with unilateral, benign MNG be treated with unilateral resection.

In summary, our meta-analysis reviewed much of the literature published to date and demonstrated that TT has rates of complications similar to BST except for transient hypoparathyroidism. Patients with transient hypoparathyroidism can receive calcium substitution after surgery. However, the present study has some limitations. First, selection bias is the domain that could lead to a biased estimate of the procedural effects in this analysis. Second, there is no standard definition for recurrent goiter in the literature.

Conclusions

While TT obviates the need for completion thyroidectomy in incidentally found thyroid cancer and there is no difference in the rate of RLN palsy between the two methods, TT has a significantly lower rate of recurrence than BST. It may be presumptuous to suggest that TT is the right choice for all patients with BMNG. Further prospective randomized studies with long-term follow-up are required to validate the results of this meta-analysis.

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