Efficacy and safety of negative pressure versus natural drainage after thyroid surgery
A systematic review and meta-analysis

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Abstract
Background: To evaluate whether negative pressure drainage has advantage over natural drainage in effectiveness and safety for patients with thyroid disease after thyroid surgery.

Method: We performed extensive literature search and followed the standards described in preferred reporting items for systematic review and meta-analysis (PRISMA) statement to conduct this systematic review. Risk of bias was assessed using the Cochrane Risk of bias tool. We used Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate the quality of evidence body.

Results: Total 1195 participants with thyroid disease from 13 studies were included. For patients underwent thyroidectomy without neck dissection, negative pressure drainage group has a lower risk of seroma and wound infection. The duration of tube placement was shorter in negative pressure drainage group, which produced more fluid than natural drainage in the first 24-hour period. The effect of negative pressure drainage on reoperative rates, mortality, and length of hospitalization remains unclear.

Conclusions: For patients underwent thyroidectomy with neck dissection, the difference between negative and natural pressure drainage groups remains uncertain due to sparse data. The quality of evidence for the above findings is low. The risk of bias for the studies is also serious. Therefore, more randomized or non-randomized controlled trials with larger sample sizes are required.

Abbreviations: CBM = China Biology Medicine, CD = thyroid surgery with central neck dissection, CI = confidence interval, CNKI = China Knowledge Resource Integrated Database, GRADE = Grading of Recommendations Assessment, Development and Evaluation, LD = thyroid surgery with lateral neck dissection, MD = mean differences, PRISMA = preferred reporting items for systematic review and meta-analysis, RCT = randomized controlled trials, RR = risk ratio.

Keywords: neck dissection, negative pressure drainage, thyroid disease, thyroid surgery

1. Introduction
It is a common belief that following thyroid surgery, the remaining dead space must be obliterated and any blood collections should be drained.[1] The postoperative hemorrhage after thyroid surgery is also life-threatening; therefore drainage can help doctors to recognize bleeding at the very early stage. For patients undergoing thyroidectomy with neck dissections, the dead space after surgery is considered larger with more exudate accumulation. The accumulated exudate dissociates the flaps, subsequently prolonging the period of wound healing and increasing the risk of local infection. Drainage can promote wound healing. Especially, the negative pressure drainage causes suction within the emptied thyroid area, which ensures the elimination of any collection of blood and fluid. This type of drainage leads to re-positioning of the flaps and improved recovery of patients. One study stated that the natural drainage may induce the accumulation of fluid in the incision area which delays germination of skin flaps and prolongs the duration of wound healing.[2] Some studies found favorable effect of negative pressure drainage over natural drainage, such as higher rate of stage I wound and less seroma.[3,4] However, other studies[5-6] demonstrated negative pressure drainage may not bring benefits for patients as significantly higher amount of fluid was drained in the negative pressure drainage group. It has been demonstrated...
that the amount of liquid in the drainage bag can affect the length of hospitalization. Therefore, negative pressure drainage may lead to longer hospitalization than natural drainage group.

The current clinical guidelines did not address this controversial issue. Although numerous systematic reviews\(^7\)–\(^9\) compared the different effect between drainage and no drainage, the preference between negative pressure drainage and natural drainage remains unknown. In this study, we systematically searched relevant prospective controlled trials on this topic to evaluate the efficacy and safety of negative pressure drainage versus natural drainage for patients with thyroid disease after surgery.

2. Materials and methods

2.1. Ethics statement

This work was based on previous published studies. Therefore, no ethical approval or patient consent was necessary.

2.2. Criteria for including studies

We included studies that meet the following criteria: randomized controlled trials (RCTs) or non-randomized controlled trial; participants with thyroid disease and received thyroid surgery; trials compared negative pressure drainage with natural drainage.

2.3. Types of outcome measures

2.3.1. Primary outcomes.

1. Adverse events: incidence of any adverse events or specific adverse events such as respiratory distress, wound infection, pain, hemotoma, seroma, and so on.
2. Rates of reoperation.
3. Mortality.

2.3.2. Secondary outcomes.

1. Wound healing.
2. Length of hospitalization.
3. The daily or total volume of drainage.
4. Duration of drain placement.

2.4. Data source and study selection

We searched relevant trials by October 1\(^{st}\), 2017 in the following databases: PubMed, The Cochrane Library, EMBASE via Ovid SP, Medline via Ovid SP, China Biology Medicine (CBM), wanfang and China Knowledge Resource Integrated Database (CNKI). Search strategy we developed in Cochrane library was presented in Supplemental Table 1, http://links.lww.com/MD/C357. Two authors screened the study independently. Titles and abstracts were firstly inspected, then full texts of potentially relevant publications were obtained and screened. Any discrepancy was resolved by discussion between the 2 reviewers.

2.5. Data extraction and management

A data extraction form was pre-designed for data collection. The form was piloted and revised. Any disagreement was resolved by discussion and consensus. The following items were collected:

1. Study characteristics: first author, year of publication, settings, patients characteristics (such as diagnose, surgery type, total number of participants, drop-outs), drainage procedure.
2. Study design (method of randomization, blinding, assessment of selective reporting; incomplete data, and funding sources).
3. Outcomes (time point of measurement, definition of outcomes, and numeric data).

2.6. Assessment of risk of bias in included studies

We made risk of bias judgment based on methods described in Chapter 9 in the Cochrane Handbook.\(^10\) We assessed 7 domains of risk of bias for each included study: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessor, incomplete data, selective reporting, and other bias.

2.7. Data synthesis

Revman 5.3 (Cochrane Collaboration) was used to input and combine the data. For dichotomous outcome data, we used risk ratios (RR) and its 95% confidence interval (CI) to measure the treatment effect. For continuous outcome data, we used the effect measure of mean differences (MD) and its 95% confidence interval (CI). We selected random-effect model to combine the data. We applied Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rate the quality of evidence for each outcome. Grade pro 3.6 (Cochrane Collaboration) was used to generate a summary of findings table.

2.8. Assessment of heterogeneity

Heterogeneity in pooled results is usually resulted from clinical and methodological heterogeneity. An \(I^2\) estimate \(\leq 50\%\) accompanied by a statistically significant Chi\(^2\) statistic (\(P<.1\)) was interpreted as evidence of substantial levels of heterogeneity.\(^10\) Where heterogeneity was suspected, we explored the sources of heterogeneity from the above 2 aspects. If any source was identified, we planned to conduct post-hoc subgroup analysis. If the source was not identified, we combined the data in a random-effect model and downgraded the quality of evidence for one level. Subgroup analysis was conducted based on different types of thyroidectomy (thyroidectomy with central neck dissection, thyroidectomy with lateral neck dissection and that without neck dissection).

2.9. Assessment of reporting biases

We used funnel plot to test the publication bias when the included study in one meta-analysis was >10.\(^10\)

3. Results

3.1. Literature screening

The literature search produced 1248 references. After removing the duplicates, 925 references were screened and 859 references were excluded through viewing the titles and abstracts. Fifty three out of 66 full reports were excluded after eligibility check. Two studies were not eligible due to inappropriate disease conditions. Fifty one studies were excluded due to ineligible comparisons, for instance, comparison of 2 different types of negative pressure drainage, comparison of drainage versus no drainage, and...
comparison of drainage versus fibrin sealant (Supplemental Figure 1, http://links.lww.com/MD/C357). Finally, 13 studies were included in this review.

3.2. Study characteristics
Thirteen studies with 1195 participants with thyroid carcinoma were included. The included participants were diagnosed with thyroid cancer, hyperthyroidism, goiter, or thyroid adenoma. The age of participants ranged from 12 to 81 years old. The average age of the populations in each study ranged from 37.9 years old to 53 years old. As reported by 5 studies, women were the predominant population (76.3%). The included studies were conducted in China (n=62), Mexico (n=100), Korea (n=62), Germany (n=80), and Catania (n=141). All studies compared negative drainage with natural drainage. The details of study characteristics and inclusion and exclusion criteria of each study were presented in Supplemental Table 2, http://links.lww.com/MD/C357.

3.3. Risk of bias
Of the 13 included studies, 2 studies reporting adequate method of randomization were rated as low risk. The randomization was using random number table (20%). Another 8 studies did not state the randomization. Three studies were non-randomized controlled trial. Only 2 studies reported the usage of concealed envelopes to conceal the allocation. Other studies did not report any information about allocation concealment. Three studies were non-RCT, therefore, the allocation concealment was not applied. One study reported that a single blind method was used. The other studies did not report whether a blinding procedure were conducted. However, we considered that even the participants and outcome assessors were not blinded, it was unlikely for them to influence the outcome assessment due to the objective measurements. Another concern influencing the overall quality of included studies was selective reporting. The protocol of included studies was not available to view, so it’s unclear whether there is selective reporting. The drop-out rates were not a concern as all participants completed the trials (Fig. 1).

3.4. Effects of measurements

3.4.1. Adverse events: The adverse events reported by these original studies included seroma (6.3%), hematoma (0.6%), hemorrhage (3.8%), transient vocal cord palsy (1.6%), transient hypocalcemia (8.1%), wound infection (3.8%), lymph leakage (4.8%), and skin flap necrosis (4.2%). However the incidence of most adverse events, excluding seroma and transient hypocalcemia, was very low. Results from meta-analysis supported a lower risk of seroma in negative pressure drainage group than that in natural drainage group (10 RCTs, n=840, RR 0.29, 95% CI 0.12–0.72, I² = 32%, low quality of evidence, Fig. 2). A lower risk of wound infection was also observed in negative pressure drainage group (5 RCTs, n=558, RR 0.18, 95%CI 0.06–0.57, I² = 0%, low quality of evidence, Fig. 3). The above findings were derived from patients receiving thyroidectomy with or without neck dissection. Subgroup analysis was conducted according to different types of surgeries. A clear difference was observed between groups that received thyroidectomy without neck dissection (Figs. 2 and 3). For those received thyroidectomy with lateral or central neck dissection, due to the insufficient data, the result did not show significant difference between groups. There was no difference between negative pressure drainage group and natural drainage group for other adverse events (Supplemental Figure 2, http://links.lww.com/MD/C357).

3.4.2. Rates of reoperation. No case with reoperation was reported.

3.4.3. Mortality. No mortality case was reported.

3.5. Secondary outcomes

3.5.1. Wound healing. Three studies reported the period-I wound incision healing. Pooled data are in favor of negative pressure drainage group with higher wound healing rate than natural drainage group (3 RCTs, n=142, RR 1.14, 95% CI 1.02–1.27, I² = 1%, low quality of evidence, Fig. 4). This outcome was measured in patients received thyroidectomy with lateral neck dissection or unclear type of thyroid surgery. Subgroup analysis based on different types of thyroid surgeries showed no difference between groups (Fig. 4).

Two studies reported the rate of prolonged wound healing. Result showed that there was a tendency of lower risk of prolonged wound healing in the negative drainage group. However, no clear statistical difference was found between negative pressure and natural drainage group (2 RCTs, n=90, RR 0.14, 95% CI 0.02–1.12, I² = 0%, very low quality of evidence, Supplemental Figure 3, http://links.lww.com/MD/C357). This outcome was measured in patients received unclear
3.5.2. Length of hospitalization. Three studies [4,6,18] had measured the length of hospital stay. Data were not pooled due to insufficient outcome data reporting. For patients received thyroidectomy with central neck dissection, longer hospitalization was observed in negative pressure group [6]. However, for patients underwent thyroidectomy without neck dissection, no difference between groups was found [4,18].

3.5.3. The daily volume of drainage. Three studies measured the daily volume of drainage. Negative drainage resulted in more fluid than natural drainage at the first 24 hours (3 RCTs, n = 363, MD 14.02 mL, 95% CI 8.25 mL, 19.8 mL, 95% confidence interval) and at the third 24 hours (1 RCT, n = 160, MD –7.0 mL, 95% confidence interval). For the volume of drainage at the second 24 hours, one study found more fluid in the negative pressure group [6]. The reason for this controversial results remains unclear. The above findings were derived from patient underwent thyroidectomy without neck dissection.

For the total drainage volume, 3 studies found more fluid in the negative pressure group [4-6], while one study did not found difference between groups. [18] Data were not pooled due to significant heterogeneity (Supplemental Figure 4, http://links.lww.com/MD/C357).

Figure 2. Negative pressure drainage versus natural drainage: adverse events—seroma. Notes: “T” represents thyroid surgery without neck dissection; “CD” represents thyroid surgery with central neck dissection; “LD” represents thyroid surgery with lateral neck dissection.

Figure 3. Negative pressure drainage versus natural drainage: adverse events—infection. Notes: “T” represents thyroid surgery without neck dissection; “CD” represents thyroid surgery with central neck dissection; “LD” represents thyroid surgery with lateral neck dissection.
3.5.4. Duration of drain placement. Meta-analysis showed that the duration of tube placement was shorter in negative pressure drainage group than that in the natural drainage group (5 RCTs, n = 545, MD = –1.06 days, 95% CI = –1.57 days to –0.55 days, I² = 98%, Fig. 6, low quality of evidence). Subgroup analysis found this difference in both patients who underwent thyroidectomy and thyroidectomy with lateral neck dissection. We presented the detailed assessment of the quality of evidence in Supplemental Table 3, http://links.lww.com/MD/C357.

4. Discussion
This systematic review aims to explore whether there is difference between negative pressure drainage and natural drainage in patients who received any type of thyroid surgery. Results from meta-analysis showed that negative drainage may lower risk of seroma to an average of 29% of the natural drainage group and lower the risk of wound infection to an average of 18% of the natural drainage group. Whether negative pressure drainage can lower the incidence of other adverse events, such as hematoma, hemorrhage, transient vocal cord palsy, transient hypocalcemia, skin flap necrosis, and lymph leakage remains unclear due to sparse data and poor quality of evidence. Negative drainage may also promote the wound healing. However, the quality of evidence is low as the data were insufficient and risk of selection bias of included studies was serious. Compared with natural drainage, negative pressure drainage may also increase the daily volume of fluid collection at first 24-hour drainage (average 14.02 mL more) but decrease the daily volume of fluid at third 24-hour drainage. The negative pressure drainage seems also reduced the duration of drain placement comparing to natural drainage (average 1.57 days less). The quality of evidence is low or very low due to high risk of selection bias, insufficient sample size, or significant statistical heterogeneity. Whether negative pressure drainage prolonged or reduced hospitalization is controversial. No mortality or reoperation cases were reported by included studies. Most of the included studies investigated patients who received total/subtotal thyroidectomy, hemi- or bilateral thyroidectomy without neck dissection. Very few studies investigated the use of these 2 interventions after thyroidectomy with central neck dissection. Therefore, the above findings were limited to patients received thyroidectomy without neck dissection. For patients who underwent thyroidectomy with neck dissection, whether negative pressure drainage has beneficial effect over natural drainage remains unclear due to sparse data.

Overall, the selection bias is serious as in most studies (11/13), the author did not use randomization or state the method of randomization. The potential bias of selective reporting may also confound the true effect measurement. The GRADE assessment
shows that most results are derived from low quality of evidence, indicating that our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. The quality was downgraded due to the small sample size, low incidence of events, or serious risk of selection bias.

Several previous systematic reviews addressed whether clinicians should use drainage after thyroidectomy.\cite{7,8,19} The results from these systematic reviews demonstrated that drainage did not bring benefits for postoperation patients (such as lowering adverse events). Inversely, it prolonged hospitalization and increased the risks of infection compared with no drainage. However, the findings were based on sparse data, and the estimate of effects was underpowered, which makes this effect uncertain. One recently published RCT\cite{20} involving 215 participants, also claimed that drainage is unnecessary after thyroid surgery. Although the authors found lower risk of wound infection and transient hypoparathyroidism in the non-drainage group, the beneficial or harmful effect of non-drainage on other aspects remains unclear such as incidence of hematoma, seroma, bleeding requires reoperation and permanent transient hypoparathyroidism. One important reason is that the author calculated sample size based on a 5% difference on adverse events between groups, however, the actual incidence of some adverse events were very low (for instance, 2.77%), and a 5% difference between groups was not possible to reach. So the study was still underpowered to test difference for other outcomes. In general, the above studies only included patients with benign thyroid disease who underwent thyroidectomy and excluded patients who underwent neck dissection. So the findings cannot apply to patients receiving all types of thyroid surgery. One RCT\cite{21} included participants undergoing thyroidectomy with central neck dissection, and found that drainage did not bring beneficial effects than non-drainage. Despite this finding, drainage has been commonly used in clinic for this population.

It is believed that the dead space after neck dissection is larger resulting in more fluid to accumulate. Hence, the fluid should be drained. The Cochrane review published in 2007\cite{9} aimed to identify any RCTs exploring this question. No other systematic reviews had ever compared negative pressure drainage with natural drainage in patients after thyroid surgery. The effect of negative pressure drainage on the length of hospitalization is controversial. The effect of negative pressure drainage on other adverse events, reoperation, and mortality remains unclear due to insufficient data. For patients with thyroid disease who requires thyroidectomy with neck dissection, the difference between negative and natural pressure drainage remains uncertain due to sparse data.

### 5. Conclusion

#### 5.1. Implication for clinicians

For patients with thyroid disease who underwent thyroidectomy without neck dissection, compared with natural drainage, negative pressure drainage may lower risk of seroma and wound infection, and reduce duration of drain placement. However, it may increase the volume of drainage at the first 24-hour drainage. The effect of negative pressure drainage on the length of hospitalization is controversial. The effect of negative pressure drainage on other adverse events, reoperation, and mortality remains unclear due to insufficient data. For patients with thyroid disease who requires thyroidectomy with neck dissection, the difference between negative and natural pressure drainage remains uncertain due to sparse data.

#### 5.2. Implication for research

Our analysis showed that the current evidence comparing the advantage of these 2 drainage applications is still limited. More randomized or non-randomized controlled trials with larger sample size are required. More studies are needed to compare the 2 types of drainage in patients receiving neck dissection. It’s also important to assess the difference of these 2 interventions on length of hospitalization.

### Author contributions

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