The effect of fibrin glue on the quantity of drainage after thyroidectomy: a randomized controlled pilot trial

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INTRODUCTION

A seroma is a collection of inflammatory exudates in response to surgical trauma in the acute phase of wound healing [1]. Since it is the body’s natural response after surgery to fill the space with exudates, the incidence of seroma has been variously reported, depending on the site and extent of surgery. In the case of thyroid surgery, the incidence of seroma after conventional technique for thyroidectomy has been reported to be approximately 14%, which causes swallowing difficulty and pain due to compression of neck structures. The effective drainage of exudate and decreasing the amount of exudate are methods to reduce the rate of seroma. Both closed suction drain and fine-needle aspiration have been used for effective drainage. According to a meta-analysis, drainage increases nursing time, hospital stay, pain, and infection after surgery [2].

Fibrin glue is a topical biological adhesive, which consists of a solution of human fibrinogen and its other components. Since it promotes wound healing in terms of enhancing hemostasis and angiogenesis while being completely absorbed without foreign body reaction [3,4], many commercialized products are used to

Purpose: A seroma is a collection of exudates after surgical trauma in wound healing. Fibrin glue is used to prevent seroma by reducing the generation of exudate. However, the impact of fibrin glue on the prevention of seroma remains debatable. Therefore, we conducted a randomized controlled pilot trial to investigate the effect of the amount of fibrin glue used on the generation of exudate after thyroidectomy and the sample size of future definitive trials.

Methods: Between February and December 2020, 41 patients were enrolled; 21 patients in the low fibrin group and 20 in the high fibrin group. Stratified randomization was performed based on sex, body mass index, and thyroiditis. All patients underwent total thyroidectomy and bilateral central compartment dissection. In the low and high fibrin groups, 2 mL and 6 mL of fibrin glue were applied to patients, respectively.

Results: Both the total drain volume and flow rate during the first 12 hours were lower in the high fibrin group than in the low fibrin group (65.0 mL vs. 47.6 mL, P = 0.008 and 2.7 mL/hr vs. 1.8 mL/hr, P = 0.002, respectively). The calculated sample size for future randomized controlled trial was 32 patients (α = 0.05, power = 0.8), and the power of this trial was 0.91 with μ₁ = 2.7, μ₂ = 1.8, σ = 0.9, and α = 0.05 (μ = mean, σ = standard deviation).

Conclusion: Six milliliters of fibrin glue could reduce total drain volume and flow rate of exudate after thyroidectomy. Therefore, applying an appropriate amount of fibrin glue after thyroidectomy may reduce postoperative seroma.

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Key Words: Drain volume, Fibrin glue, Randomized controlled trial, Seroma, Thyroidectomy
METHODS

Study design and participants
This pilot study was designed as a prospective, randomized trial. The Institutional Review Board of Ajou University Medical Center approved this study (No. MED-INT-19-306), and informed consent was obtained from all individual participants included in the study. This trial is registered with CRIS (https://cris.nih.go.kr; No. KCT0006552).

The recruitment period was from February to December 2020, followed by the first postoperative outpatient visit from April 2020 to December 2020. The enrolled patients were randomly assigned to 2 groups in a 1:1 ratio in this concurrent parallel study design as follows: (1) 2 mL of fibrin glue application with 1 closed suction drain or (2) 6 mL of fibrin glue application with 1 closed suction drain. A study coordinator (D.K.Y.) performed stratified randomization using a computerized program based on sex, BMI (<25 and ≥25 kg/m²), and thyroiditis (absent/present). Thyroiditis was defined as a parenchymal disease of the thyroid detected on ultrasonography performed by a radiologist (E.J.H). The treatment allocation was performed by the coordinator (D.K.Y.) after preoperative ultrasonography. Participants were allocated to 8 subgroups based on their characteristics, including sex, BMI, and thyroiditis, after combining the factors considered to have a significant impact on the results. Furthermore, stratified randomization was accomplished by performing simple randomization for participants assigned to subgroups. The surgeon was blinded to the allocation of enrolled patients until the time of fibrin glue application on the operative field in the operating room.

The inclusion criteria in this study were as follows: (1) patients who were scheduled to undergo total thyroidectomy with central compartment neck dissection (CCND), (2) patients older than 20 years, (3) malignancy on fine-needle aspiration cytology or core needle biopsies, (4) normal platelet count of 100,000/mL, and (5) availability of informed consent. In contrast, the exclusion criteria were as follows: (1) age of <20 or >65 years, (2) uncontrolled diabetes, (3) on anticoagulation medication, (4) previous thyroid surgery, (5) advanced hepatic or renal disease, (6) cardiovascular disease, (7) on steroid medication, and (8) declination of informed consent.

Intervention
All surgeries were performed by a single surgeon (J.L., who had specialized in endocrine surgery for 10 years). A 5 to 6-cm transverse incision was made 2 finger-breadths above the sternal notch, and the subplatysmal skin flap was created from the thyroid cartilage to the sternothoracic notch. Bilateral central compartments, including fibrofatty tissue within an area limited by the thyroid cartilage cranially, sternal notch caudally, and the carotid artery medially, were removed. Bilateral CCND was performed in all enrolled patients.

After total thyroidectomy and CCND, the operative bed was irrigated with 100 mL of normal saline after hemostasis. Subsequently, a coordinator was asked to reveal the allocation concealment, and fibrin glue specially prepared for the clinical trial by an annotated pharmacist was applied to the thyroid bed and the inner side of the sternothyroid muscle, including the thyroid cartilage, trachea, esophagus, carotid artery, and jugular vein, by a surgeon (J.L.). As per the protocol, 2 mL and 6 mL of fibrin glue (Greenplast Q PFS kit, GC Pharma, Yongin, Korea) were applied to patients in the low and high fibrin groups, respectively. Fibrin glue is a liquid form of a mixture of fibrin and thrombin, which is dispensed via a dual syringe set with 2 chambers, a Y-tube, and an application needle. Anti-adhesive agent (Regencol 1 g, Dongsung, Seongnam, Korea) was applied to both the thyroid bed and the subplatysmal space after the application of fibrin glue. A closed suction drain was placed in all patients. Patients were discharged on postoperative day 4 ± 1 and were routinely followed up between postoperative days 10 and 14 at an outpatient clinic based on the routinely implemented clinical practice guidelines.

Outcome measurements
The primary outcomes of this study were the drain volume observed during the hospital stay and rate of flow of drain fluid for the first 12 and 24 hours postoperatively, the sample size, and potential harm of future definitive RCTs. The drain volume and check times were assessed by nursing staff who were blinded to the treatment allocation and study design. The drain volumes were measured every 8 hours until discharge. When
the amount of drain reduced to <45 mL over a 24-hour period, the drains were removed. In contrast, secondary outcomes were symptomatic seroma formation and the duration of hospital stay. Although patients were routinely discharged within 4 days based on the clinical practice pathway, early or delayed discharge was done according to the clinical features, including drain volumes and postoperative complications such as hypoparathyroidism, pain, hematoma, and infection.

Wound infections were determined to include erythema and/or purulent discharge or aspirate from the incision site and were treated with an oral antibiotic. Symptomatic seromas were assessed on follow-up visits at an outpatient clinic based on the physical examination, patients’ symptoms, and aspiration if needed.

**Statistical analysis**

This pilot study initially planned to enroll 40 patients, with a sample size of 20 patients in each group. However, during stratified randomization, 41 patients were included; 21 in the low fibrin group and 20 in the high fibrin group.

Stratified randomization was performed using Microsoft Excel 2016 (Microsoft, Redmond, WA, USA). Continuous and categorical variables were reported as mean ± standard deviation (SD) and proportion, respectively. Two-tailed Student t-test, Mann-Whitney U-test, or chi-square test were used to evaluate the difference in measures between the 2 study groups. Correlation analysis with Pearson correlation and 2-way analysis of variance was used to evaluate the independent factors related to total drain volume of seroma. The analyses were performed using IBM SPSS Statistics ver. 23 (IBM Corp., Armonk, NY, USA). Statistical significance was set at P-value of <0.05, and sample size and power were calculated using PASS 2011 (NCSS, LLC., Kaysville, UT, USA).

**RESULTS**

**Patients**

Fig. 1 is a flowchart delineating the processes involved in enrollment, randomization, and follow-up in this study. Between February and December 2020, 72 patients were eligible for inclusion. Of these 72 patients, 31 declined to participate or were excluded during stratified randomization. The remaining 41 patients were randomly allocated to each group. No patients were excluded during follow-up and data analyses, and the postoperative follow-up period was from April 2020 to December 2020.

Table 1 summarizes the demographic characteristics of the included patients. The mean age was 48.9 years, and the ratio of males to females was 1:3. The random variables (sex, thyroiditis, and BMI) were not statistically different between the 2 groups. Similarly, there were no significant differences between the 2 groups in terms of tumor/lymph node (LN) stage, numbers of metastatic LNs, number of retrieved LNs, and weight of thyroid (all P > 0.05, respectively).

![Fig. 1. The diagram of progress through the phases of the trial. FS, fibrin sealant.](image-url)
Table 2 presents the outcomes of the low and high fibrin groups according to intention-to-treat analysis. The primary outcomes, including total drain volumes and flow rate of drain fluid in the first 12 hours after surgery, were significantly different between the 2 groups. Additionally, both the total drain volume and flow rate, during the first 12 hours postoperatively, were significantly lower in the high fibrin group than in the low fibrin group (65.0 mL vs. 47.6 mL, P = 0.008 and 2.7 mL/hr vs. 1.8 mL/hr, P = 0.002, respectively). Although the flow rate of drain fluid during the first 24 hours after surgery was lower in the high fibrin group, no statistical significance was observed (1.6 mL/hr vs. 2.1 mL/hr, P = 0.060).

The calculated sample size of future RCT was 32 patients (16 in the low and high fibrin groups, respectively) with μ₁ of 2.7, μ₂ of 1.8, α of 0.05, and power of 0.8, as revealed by PASS statistics. Additionally, the power for a sample size of 41 patients was 0.91 with μ₁ of 2.7, μ₂ of 1.8, σ of 0.9, and α = 0.05 according to PASS 2011 (μ = mean and σ = SD for both groups).

As for the secondary outcomes, there were only 3 patients (7.3%) in the low fibrin group (Table 3); however, the difference was not statistically significant (P = 0.232). Symptomatic seroma at the outpatient clinic was related to the amount of drain during the first postoperative 12 hours (P = 0.004). In 3 patients, the drainage volume was 11 mL more than those who did not develop seroma (29.5 mL vs. 40.6 mL). Among 3 patients, 1 patient was discharged on postoperative day 1 and the others on postoperative day 2. The volume of aspirate was <5 mL in all 3 patients. There was no patient with hematoma formation or wound infection during hospitalization or follow-up visits. The duration of hospital stay was not statistically different between the 2 groups (P = 0.414).

Table 4 presents the correlation analysis between the total drain volumes and clinicopathological features. Both the duration of hospital stay and the amount of fibrin glue used were statistically correlated factors in the estimation of total drain volume after thyroidectomy (P < 0.05). An interaction between the amount of fibrin glue and the hospital stay could not be demonstrated in this study (F = 0.94, P = 0.4). There was no patient with hematoma, reoperation, or wound infection in this study.

DISCUSSION

In this prospective RCT, we aimed to evaluate the actual impact of the amount of fibrin glue used on the prevention of seroma formation after thyroidectomy as well as the sample size and harm of future definitive RCTs. In this study, the application of 6-mL fibrin glue helped to obtain better clinical outcomes by decreasing the total drain volume and flow rate of exudate during the first 12 hours after surgery compared to the 2-mL fibrin glue application. The amount of fibrin glue used was the only statistically significant factor in estimating the total drain volume after thyroidectomy on multivariable analysis. Additionally, the fact that this trial’s power was sufficient (power = 0.91) further supports the results.
The incidence of seroma after thyroidectomy ranged from 1.3% to 14% [9-11]. Although not life-threatening, seromas are implicated in the patients' discomfort and morbidity, including pain, regional swelling, surgical site infection, prolonged hospitalization, and higher admission costs. Although the overall etiology and pathophysiology of the seromas are not completely understood, several factors reportedly influence the seroma formation, such as the oozing of small vessels, creation of a cavity caused by the removal of tissue, lesion of the lymphatic vessels, and inflammatory reaction [12]. However, the mechanism of prevention of seroma formation after thyroidectomy remains unclear [13]. Although insertion of a closed suction catheter is a conservative option in other operative fields, the routine usage of drain has been controversial after thyroid surgery because it can cause inflammatory reaction, infection, and discomfort [2]. As symptomatic seroma occurred at the first outpatient visit in 14% of those in the low fibrin group in our study, an alternative

Table 2. Comparison between of control and experimental groups

| Variable                  | Control (n = 21) | Experimental (n = 20) | P-value |
|---------------------------|-----------------|-----------------------|---------|
| Sex                       |                 |                       | 0.734   |
| Male                      | 5 (23.8)        | 6 (30.0)              |         |
| Female                    | 16 (76.2)       | 14 (70.0)             |         |
| Age (yr)                  | 49.2 ± 1.73     | 48.6 ± 2.86           | 0.848   |
| Thyroiditis Absent        | 15 (71.4)       | 16 (80.0)             | 0.719   |
| Thyroiditis Present       | 6 (28.6)        | 4 (20.0)              |         |
| Body mass index (kg/m²)   | 25.6 ± 0.85     | 25.1 ± 0.67           | 0.682   |
| Pathologic type           |                 |                       | 0.488   |
| PTC                       | 21 (100)        | 19 (95.0)             |         |
| MTC                       | 0 (0)           | 1 (5.0)               |         |
| T stage                   |                 |                       | 0.305   |
| T1                        | 16 (76.2)       | 17 (85.0)             |         |
| T2                        | 1 (4.8)         | 0 (0)                 |         |
| T3                        | 3 (14.3)        | 3 (15.0)              |         |
| T4                        | 1 (4.8)         | 0 (0)                 |         |
| N stage                   |                 |                       | >0.999  |
| N0                        | 10 (47.6)       | 10 (50.0)             |         |
| N1a                       | 11 (52.4)       | 10 (50.0)             |         |
| No. of LNs                |                 |                       |         |
| Metastatic LN             | 1.8 ± 0.58      | 1.2 ± 0.39            | 0.390   |
| Retrieved LN              | 12.1 ± 1.27     | 8.7 ± 1.10            | 0.580   |
| Weight of thyroid (g)     | 21.9 ± 1.76 (n = 20) | 29.6 ± 6.67 (n = 16) | 0.228   |
| Seroma                    |                 |                       | 0.232   |
| Absent                    | 18 (85.7)       | 20 (100)              |         |
| Present                   | 3 (14.3)        | 0 (0)                 |         |
| Hypoparathyroidism        |                 |                       |         |
| At admission              | 4 (19.0)        | 6 (30.0)              | 0.484   |
| After 1 wk                | 2 (9.5)         | 4 (20.0)              | 0.393   |
| PTH (pg/mL)               |                 |                       |         |
| At admission              | 26.9 ± 2.58     | 21.3 ± 2.75           | 0.143   |
| After 1 wk                | 33.3 ± 4.08     | 24.4 ± 3.55           | 0.109   |
| Hospital stay (day)       | 4.1 ± 0.14      | 4.0 ± 0.17            | 0.414   |
| Drain volume (mL)         |                 |                       |         |
| Total drain volume        | 65.0 ± 5.04     | 47.6 ± 3.51           | 0.008   |
| During 24 hr              | 47.0 ± 3.10     | 35.2 ± 2.47           | 0.006   |
| Drain volume during 24 hr, <45 | 11 (52.4)   | 16 (80.0)             | 0.079   |
| Flow rate of drain (mL/hr) |               |                       |         |
| For 12 hr                 | 2.7 ± 0.21      | 1.8 ± 0.17            | 0.002   |
| For 24 hr                 | 2.1 ± 0.15      | 1.6 ± 0.11            | 0.060   |

Values are presented as number (%) or mean ± standard error.
PTC, papillary thyroid carcinoma; MTC, medullary thyroid carcinoma; LN, lymph node; PTH, parathyroid hormone.
method to the use of drain is required.

Therefore, fibrin glue can be used as an alternative to reduce seroma. However, the actual impact of fibrin glue on the prevention of seroma formation remains debatable. Although several studies have reported the positive effect of fibrin glue, its utility was not demonstrated in a meta-analysis by Edwards et al. [14], where it failed to cause a statistically significant reduction in seroma formation. In addition, 2 RCTs on thyroid surgery reported contrasting results [5,6]. In a study by Kim et al. [6], there was no reduction in the drain volume in the fibrin glue (+) group, wherein 1 set (1 mL) of fibrin glue was applied, compared with those in the fibrin glue (−) group, in whom no fibrin glue was applied. However, in another study by Sözen et al. [5], the amount of drain was not investigated, the application of 6-mL fibrin glue significantly reduced the seroma formation. Several clinical factors are likely to contribute to this discrepancy, with sex, BMI, thyroiditis, amount of fibrin glue used, and surgeon’s skill possibly affecting study outcomes. Previous studies reported that the drain volume after thyroidectomy might be significantly increased in male patients (P = 0.001) and those with a higher BMI (P = 0.019) [8,15]. In addition, we included chronic thyroiditis as a confounding factor in our study.

### Table 3. Clinicopathological factors related with symptomatic seroma

| Variable                        | No seroma (n = 38) | Seroma (n = 3) | P-value |
|---------------------------------|-------------------|---------------|---------|
| Sex                             |                   |               |         |
| Male                            | 10 (26.3)         | 1 (33.3)      | >0.999  |
| Female                          | 28 (73.7)         | 2 (66.7)      |         |
| Age (yr)                        | 48.5 ± 0.58       | 54.3 ± 4.63   | 0.372   |
| Thyroiditis                     |                   |               |         |
| Absent                          | 29 (76.3)         | 2 (66.7)      | >0.999  |
| Present                         | 9 (23.7)          | 1 (33.3)      |         |
| Body mass index (kg/m²)         | 26.1 ± 3.39       | 17.0 ± 1.73   | 0.869   |
| No. of fibrin sealant           |                   |               |         |
| 1                               | 18 (47.4)         | 3 (100)       |         |
| 3                               | 20 (52.6)         | 0 (0)         |         |
| No. of LNs                      |                   |               |         |
| Metastatic LN                   | 1.5 ± 0.37        | 1.3 ± 0.88    | 0.832   |
| Retrieved LN                    | 10.1 ± 0.82       | 14.3 ± 6.38   | 0.618   |
| Weight of thyroid (g)           | 26.1 ± 3.39 (n = 33) | 17.0 ± 1.73 | 0.430   |
| Hospital stay (day)             | 4.1 ± 0.14        | 4.0 ± 0.17    | 0.414   |
| Drain volume during 12 hr (mL)  | 29.5 ± 2.07       | 40.6 ± 3.17   | 0.044*  |
| Flow rate of drain for 12 hr (mL/hr) | 2.2 ± 0.14 | 3.6 ± 0.76    | 0.051   |

Values are presented as number (%) or mean ± standard error.

LN, lymph node.

Fisher exact test for categorical variables or Mann-Whitney U-test for continuous variables; *P < 0.05.

### Table 4. Correlation analysis between total drain volume and clinicopathological features

| Variable                      | Total drain volume | Bivariate analysis | Two-way ANOVA |
|-------------------------------|--------------------|--------------------|---------------|
|                               |                    | Pearson            | F-value       | P-value |
| Sex                           | −0.035             | 0.828              | -             | -       |
| Thyroiditis                   | 0.087              | 0.590              | -             | -       |
| Body mass index               | −0.007             | 0.963              | -             | -       |
| Weight of thyroid             | −0.059             | 0.735              | -             | -       |
| No. of retrieved lymph nodes  | 0.058              | 0.718              | -             | -       |
| Hospital stay                 | 0.331              | 0.034*             | 3.73          | 0.020*  |
| Amount of fibrin glue         | −0.410             | 0.008*             | 6.76          | 0.014*  |
| Hospital stay × amount of fibrin glue | 0.90 | 0.400 |

ANOVA, analysis of variance.

*P < 0.05.
factor. Since the presence of chronic thyroiditis affects the size of the thyroid gland and the number of retrieved central LNs, it may increase the amount of drainage due to the increased size of a dead space [16,17]. In this study, the effects of these confounding factors were minimalized through stratified randomization and a surgeon’s performance of all surgical procedures, which kept both groups homogeneous with the same surgical scope and identical surgical instrument. Therefore, we observed that 3 sets of fibrin glue (6 mL) could reduce the total drain volume and flow rate better than 1 set of fibrin glue (2 mL) when the effects of other factors were excluded through stratified randomization with high power (power = 0.91).

Symptomatic seroma developed only in the low fibrin group using 2 mL of fibrin sealant, but there was no statistically significant difference between the 2 groups. However, we observed that drain volume during the first postoperative 12 hours was related to symptomatic seroma. In 3 patients with seroma, the drain volume was 40 mL during the first postoperative 12 hours, which was 11 mL higher than those in patients without seroma. Therefore, drainage may be used as an indicator for symptomatic seroma in patients who undergo total thyroidectomy and bilateral CCND if early removal is performed.

Regarding hospital stay, the proportion of patients whose amount of drain during the first 24 hours postoperatively was <45 mL in the high fibrin group was higher (80.0%) than that (52.4%) in the low fibrin group; however, there was no statistically significant difference between the 2 groups (P = 0.079). It may be attributed to the clinical practice pathway over the 4-day course because no difference was observed among postoperative complications, such as hematoma, reoperation, or hypoparathyroidism.

This study has some limitations. While the influence of fibrin dose on drain volume was clarified, it was uncertain whether a specific fibrin dose was necessary to decrease drain volume in an individual. Hence, in the future, large-scale studies individualizing the dose of fibrin in patients should be performed.

In conclusion, 6 mL of fibrin glue could reduce exudate generation by decreasing the volume of drainage and flow rate of exudate after thyroidectomy, compared with 2 mL of fibrin glue application, in a prospective randomized trial with sufficient power. Except for symptomatic seroma in 3 patients in the low fibrin group, there were no adverse effects of fibrin or postoperative complications.

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Conflicts of Interest
No potential conflict of interest relevant to this article was reported.

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