ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2022.102.4.177
Annals of Surgical Treatment and Research

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

Eun Ju Ha[1], Jeonghun Lee[2]

[1]Department of Radiology, Ajou University School of Medicine, Suwon, Korea
[2]Department of Surgery, Ajou University School of Medicine, Suwon, Korea

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 ($\alpha = 0.05$, power = 0.8), and the power of this trial was 0.91 with $\mu_1 = 2.7$, $\mu_2 = 1.8$, $\sigma = 0.9$, and $\alpha = 0.05$ (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.
[Ann Surg Treat Res 2022;102(4):177-184]

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

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

Received November 24, 2021, **Revised** February 27, 2022, **Accepted** March 8, 2022

Corresponding Author: Jeonghun Lee
Department of Surgery, Ajou University School of Medicine, 164 World cup-ro, Yeongtong-gu, Suwon 16499, Korea
Tel: +82-31-219-5200, **Fax:** +82-31-219-5755
E-mail: servent-lee@hanmail.net
ORCID: https://orcid.org/0000-0003-4925-9104

prevent hematoma and seroma or to seal the tissue. However, while hemostatic effects are well documented in other fields, its ability to reduce or prevent a seroma formation in the operative field remains controversial in thyroid surgery [5,6]. Regarding this issue, it has been reported that clinicopathologic factors, such as age, sex, body mass index (BMI) or dead space, the amount of fibrin glue used, and surgeon's skill, may affect the outcome; therefore, the data on these factors should be collected to evaluate the actual impact of fibrin glue on the prevention of seroma after thyroidectomy [5,7,8].

In this study, we investigated the effect of the amount of fibrin sealant used on the flow rate of exudate after thyroidectomy performed by a single surgeon based on stratified randomization of clinicopathologic features to prevent a seroma. Additionally, we examined the sample size and the potential harm of future randomized controlled trials (RCTs).

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. KCT0006352).

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/m^2), 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 sternal notch. After dividing the strap muscles in the midline, the thyroid gland was exposed from the strap muscle, and the thyroid was subsequently removed from the thyroid bed after ligating the thyroid vessels with a Harmonic scalpel. 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, and one closed suction drain was placed in all patients. Patients were discharged routinely 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).

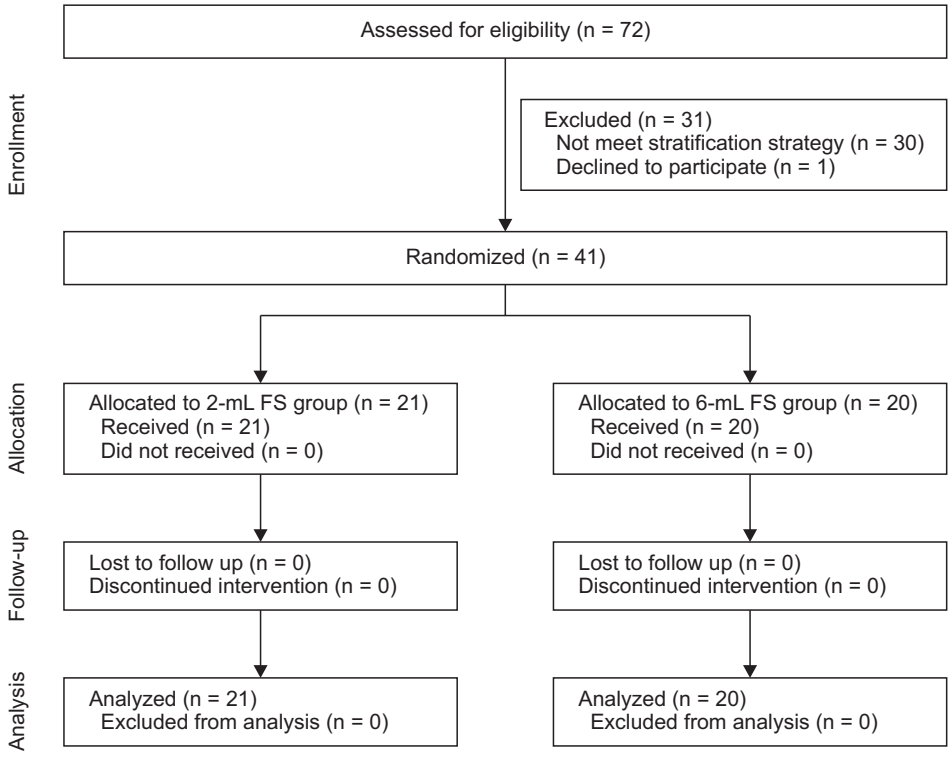

Fig. 1. The diagram of progress through the phases of the trial. FS, fibrin sealant.

Table 1. Clinicopathological features of low fibrin and high fibrin groups

Variable	Data
No. of patients	41
Sex	
Male	11 (26.8)
Female	30 (73.2)
Age (yr)	48.9 ± 10.4
Thyroiditis	
Absent	31 (75.6)
Present	10 (24.4)
Body mass index (kg/m^2)	25.4 ± 3.46
Bilateral CCND	41 (100)
Pathologic type	
PTC	40 (97.6)
MTC	1 (2.4)
T stage	
T1	33 (80.4)
T2	1 (2.4)
T3	6 (14.6)
T4	1 (2.4)
N stage	
N0	20 (48.4)
N1a	21 (51.2)
No. of LNs	
Metastatic LN	1.5 ± 2.25
Retrieved LN	10.4 ± 5.59
Weight of thyroid (g)	25.3 ± 18.84
Seroma	
Absent	38 (92.7)
Present	3 (7.3)
Hypoparathyroidism	
At admission	10 (24.3)
After 1 wk	6 (14.6)
PTH (pg/mL)	
At admission	24.2 ± 12.27
After 1 wk	29.0 ± 17.78
Hospital stay (day)	4.1 ± 0.74
Drain volume (mL)	
Total	56.5 ± 21.49
During 24 hr	41.2 ± 13.95
During 24 hr, <45	27 (65.9)
Flow rate of drain (mL/hr)	
For 12 hr	2.3 ± 0.98
For 24 hr	1.9 ± 0.66

Values are presented as number only, mean ± standard deviation, or number (%).
CCND, central compartment neck dissection; PTC, papillary thyroid carcinoma; MTC, medullary thyroid carcinoma; LN, lymph node; PTH, parathyroid hormone.

Outcomes

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 μ_1 of 2.7, μ_2 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 μ_1 of 2.7, μ_2 of 1.8, σ of 0.9, and $\alpha = 0.05$ 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.

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			0.719
Absent	15 (71.4)	16 (80.0)	
Present	6 (28.6)	4 (20.0)	
Body mass index (kg/m^2)	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.

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 3. Clinicopathological factors related with symptomatic seroma

Variable	No seroma (n = 38)	Seroma (n = 3)	P-value
Sex			>0.999
Male	10 (26.3)	1 (33.3)	
Female	28 (73.7)	2 (66.7)	
Age (yr)	48.5 ± 0.58	54.3 ± 4.63	0.372
Thyroiditis			>0.999
Absent	29 (76.3)	2 (66.7)	
Present	9 (23.7)	1 (33.3)	
Body mass index (kg/m^2)	26.1 ± 3.39	17.0 ± 1.73	0.869
No. of fibrin sealant			0.232
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	P-value	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.

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. 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.

ACKNOWLEDGEMENTS

We would like to thank Mrs Da Kyeong Yea for coordingating this pilot study.

Fund/Grant Support

This study was funded by GC Pharma (grant No: M2020C122800002).

Conflicts of Interest

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

ORCID iD

Eun Ju Ha: https://orcid.org/0000-0002-1234-2919
Jeonghun Lee: https://orcid.org/0000-0003-4925-9104

Author Contribution

Conceptualization, Formal Analysis, Project Administration: JL
Investigation: EJH
Methodology: All authors
Writing – Original Draft: JL
Writing – Review & Editing: All authors

REFERENCES

1. Pogson CJ, Adwani A, Ebbs SR. Seroma following breast cancer surgery. Eur J Surg Oncol 2003;29:711-7.
2. Portinari M, Carcoforo P. The application of drains in thyroid surgery. Gland Surg 2017;6:563-73.
3. Budd DC, Cochran RC, Sturtz DL, Fouty WJ Jr. Surgical morbidity after mastectomy operations. Am J Surg 1978;135:218-20.
4. Carless PA, Henry DA. Systematic review and meta-analysis of the use of fibrin sealant to prevent seroma formation after breast cancer surgery. Br J Surg 2006;93:810-9.
5. Sözen S, Topuz O, Tükenmez M, Keçeli M. The use of fibrin sealant after total thyroidectomy for benign disease obviates the need for routine drainage. Results of a randomized controlled trial. Hippokratia 2011;15:247-51.
6. Kim TW, Choi SY, Jang MS, Lee GG, Nam ME, Son YI, et al. Efficacy of fibrin sealant for drainage reduction in total thyroidectomy with bilateral central neck dissection. Otolaryngol Head Neck Surg 2012;147:654-60.
7. Eweida AM, Ebeed HM, Sakr MF, Hamza Y, Gabr E, Koraitim T, et al. Independent predisposing factors for subcutaneous and deep wound collection after total

thyroidectomy, a prospective cohort study. Ann Med Surg (Lond) 2018;36:10-6.
8. Kim HK, Kim SM, Chang H, Chun KW, Kim BW, Lee YS, et al. Anti-adhesive agent (Guardix-SG®) does not influence the drainage volume after thyroid cancer surgery. Korean J Endocr Surg 2013;13:251-6.
9. Barbaros U, Erbil Y, Aksakal N, Citlak G, Işsever H, Bozbora A, et al. Electrocautery for cutaneous flap creation during thyroidectomy: a randomised, controlled study. J Laryngol Otol 2008;122:1343-8.
10. Thomusch O, Machens A, Sekulla C, Ukkat J, Lippert H, Gastinger I, et al. Multivariate analysis of risk factors for postoperative complications in benign goiter surgery: prospective multicenter study in Germany. World J Surg 2000;24:1335-41.
11. Ayyash K, Khammash M, Tibblin S. Drain vs. no drain in primary thyroid and parathyroid surgery. Eur J Surg 1991;157:113-4.
12. Miri Bonjar MR, Maghsoudi H, Samnia R, Saleh P, Parsafar F. Efficacy of fibrin glue on seroma formation after breast surgery. Int J Breast Cancer 2012;2012:643132.
13. McCaul JA, Aslaam A, Spooner RJ, Louden I, Cavanagh T, Purushotham AD. Aetiology of seroma formation in patients undergoing surgery for breast cancer. Breast 2000;9:144-8.
14. Edwards SJ, Crawford F, van Velthoven MH, Berardi A, Osei-Assibey G, Bacelar M, et al. The use of fibrin sealant during non-emergency surgery: a systematic review of evidence of benefits and harms. Health Technol Assess 2016;20:1-224.
15. Ramouz A, Rasihashemi SZ, Daghigh F, Faraji E, Rouhani S. Predisposing factors for seroma formation in patients undergoing thyroidectomy: cross-sectional study. Ann Med Surg (Lond) 2017;23:8-12.
16. Lee I, Kim HK, Soh EY, Lee J. The association between chronic lymphocyticthyroiditis and the progress of papillary thyroid cancer. World J Surg 2020;44:1506-13.
17. Farwell AP, Braverman LE. Thyroiditis. In: Randolph GW, editor. Surgery of the thyroid and parathyroid glands. 2nd ed. Philadelphia: Saunders/Elsevier; 2013. p. 42.