Randomized Trial

Comparison Between the Effectiveness of Complex Decongestive Therapy and Stellate Ganglion Block in Patients with Breast Cancer-Related Lymphedema: A Randomized Controlled Study

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Background: Breast cancer-related lymphedema (BCRL) of the upper extremities often follows breast cancer treatment. Although complex decongestive therapy (CDT) is currently the standard treatment for BCRL, stellate ganglion block (SGB) has also been reported to be effective.

Objectives: This study aimed to determine the effectiveness of SGB in the treatment of BCRL, and to assess the impact of the treatment on the quality of life (QoL) compared to CDT.

Study Design: A randomized controlled trial.

Setting: A single academic hospital, outpatient setting.

Methods: A total of 38 patients with BCRL were recruited. Patients were randomly divided into 2 groups. Patients enrolled in the CDT group underwent 10 sessions of CDT for 2 weeks, whereas patients in the SGB group received 3 consecutive SGBs every 2 weeks. Changes in circumference, volume, and bioimpedance in the upper extremity were measured at baseline and 2 weeks after treatment and compared between the 2 groups. EuroQol-5 dimensions (EQ-5D) and EuroQol visual analog scale (EQ VAS) for QoL and subjective improvement were monitored.

Results: In both groups, side-to-side difference of circumference after the treatment was decreased significantly from baseline ($P < 0.05$), and side-to-side difference of volume was reduced significantly in the SGB group ($P < 0.05$). No statistically significant difference was noted in the treatment effect between the 2 groups. Results of the EQ-5D, EQ VAS, and questionnaires regarding subjective symptoms administered at baseline and 2 weeks after each intervention revealed no statistically significant difference in the treatment effects between CDT and SGB.

Limitations: Further long-term follow-up studies with a greater number of patients that include analysis according to the severity and duration of symptoms are needed.

Conclusions: The results of this study suggest that SGB is an effective treatment for BCRL and may be considered as an alternative to CDT.

Key words: Stellate ganglion block, complex decongestive therapy, breast cancer, lymphedema, breast cancer-related lymphedema, quality of life, bioimpedance, secondary lymphedema

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Secondary lymphedema results from disruption of the normal lymphatic system caused by disease, such as malignancy, infection, or iatrogenic processes. In the United States, most cases of secondary lymphedema are related to malignancies and their corresponding treatments. Lymphedema of the upper extremity is usually associated with breast cancer (1). The rates of upper extremity lymphedema after total mastectomy were reported between 24% and 49%, and between 4% and 17% after sentinel lymph node biopsy with radiation (2,3). In Korea, in 1992, 22% of breast cancer patients had secondary lymphedema after treatment (4).

The standard treatment for secondary lymphedema is complex decongestive therapy (CDT). CDT typically involves manual lymphatic drainage or massage, compression bandaging, exercise, and skin care (5). Results of randomized controlled studies reported a volume reduction after CDT in as much as 40%-60% of patients with pitting edema (6-8). However, CDT is criticized for being time consuming and can be a burden to the patients and his/her caregivers (1). Also, poor patient compliance can negatively impact long-term outcomes of CDT (9). Therefore, a complementary and alternative treatment to manage breast cancer-related lymphedema (BCRL) is needed.

Cervical stellate ganglion block (SGB) is a treatment method involving injection of a drug mixture around the cervical sympathetic trunk. SGB has been used to treat various medical conditions including hot-flash in breast cancer survivors, postherpetic neuralgia, and complex regional pain syndrome (10-12). In addition, other previous studies used SGB for the improvement of BCRL and reported good results (13-18). Our prior study showed the effectiveness of 3 consecutive SGB for the treatment of patients with BCRL, and corticosteroids can have an additive effect in SGB (16). However, evidence that SGB can be an alternative treatment for lymphedema is lacking. Although many authors advocate SGB for the treatment of BCRL, no randomized prospective study has been performed, and only case series, retrospective studies, or observational studies without control examining the effect of SGB in patients with BCRL have been done. This study aimed to determine the effectiveness of SGB in the treatment of BCRL and to assess the impact of the treatment on the quality of life (QoL) compared to CDT.

Methods

Study Design and Patients

This study was a single-center, prospective randomized controlled clinical trial, and the protocol was registered with the Clinical Research Information Service. The study was approved by the institutional review board of our institute [1504-082-665]. Written informed consent was obtained from all patients.

From August 2015 through December 2016, patients with BCRL aged 20 years or older admitted to our institute were recruited if they met the following criteria: 1) lymphedema defined as a circumference of the affected arm of 2 cm or more compared to the unaffected arm; and 2) lymphatic obstruction confirmed via lymphoscintigraphy. Patients were excluded from this study according to the following criteria: 1) primary or bilateral lymphedema; 2) contraindication for SGB, such as hypersensitivity to local anesthesia or bleeding tendency; 3) previously treated with CDT or SGB within 4 months; 4) infection or cellulitis; and 5) difficulties in participating in the study. Patients were randomized to one of the 2 intervention groups, that is, CDT and SGB, through a computer-generated code. A total of 38 patients diagnosed with secondary lymphedema after breast cancer treatment were enrolled in the study: 19 in the CDT group and 19 in the SGB group (Fig. 1).

Intervention

SGB

Nineteen patients underwent 3 consecutive SGB (once every 2 weeks) administered by the same physician at the outpatient clinic (14). The procedure was performed while the patients were in supine position with a pillow under the neck. Before injection, the needle path for the SGB was identified using ultrasound to determine delicate anatomic structures. At the level of the cricoid cartilage, the sternocleidomastoid muscles were retracted laterally using the index and middle fingers, and the transverse C6 process was palpated between the cricoid cartilage and the carotid artery. Next, A 23-gauge needle was inserted vertically between the cricoid cartilage and the fingers. After contact with the anterior tubercle of the C6 transverse process, the needle was withdrawn slightly from the periosteum and aspirated. Next, a mixture of 4 mL 0.5% bupivacaine and 1 mL 40 mg triamcinolone was administered. Patients were observed for 30 minutes after SGB to monitor early complications.

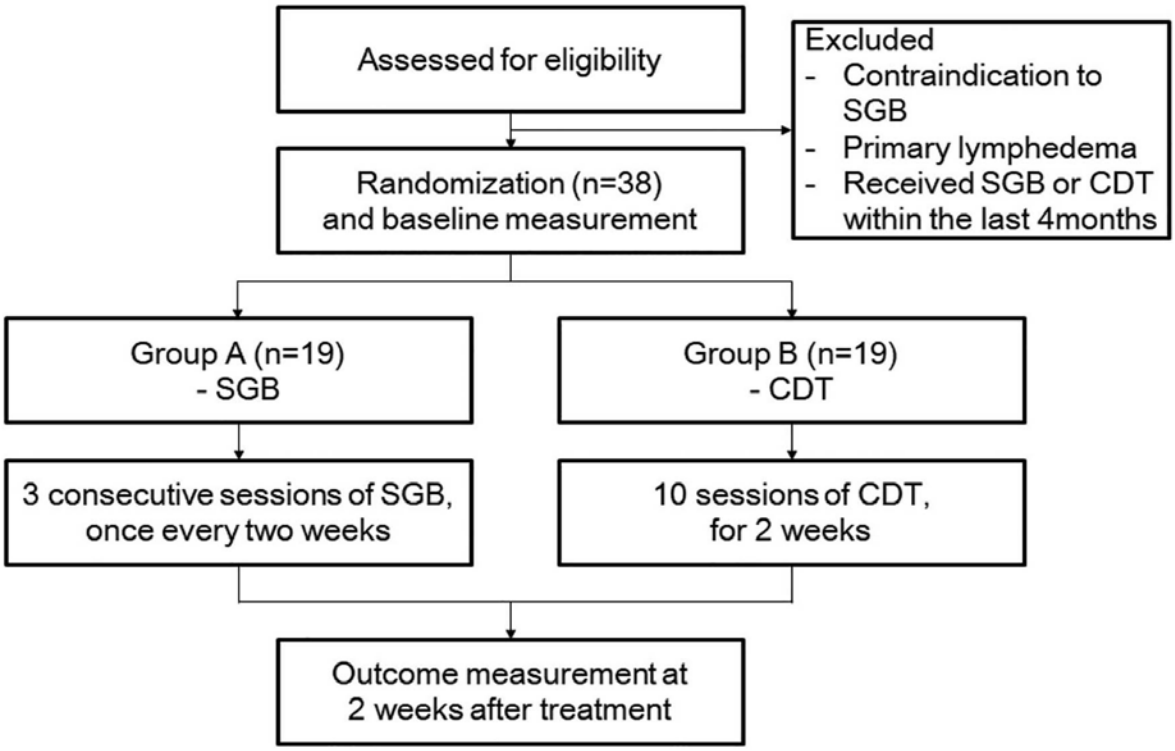

Fig. 1. *Flow chart of patients through the study.*

CDT

Patients enrolled in the CDT group had 10 sessions of CDT administered in 2 weeks, from Monday to Friday of the following week, by the same physical therapist in an outpatient clinic. Each session lasted for 40 minutes and consisted of manual lymphatic drainage (15 minutes) entailing stimulation of the movement of fluid in the tissue, bandaging (15 minutes) in compression garments, and exercise (10 minutes).

Outcome Variables

The primary outcomes were changes of side-to-side difference in 1) circumferences of the forearm and upper arm; 2) volume of the forearm, upper arm, and whole arm; and 3) bioimpedance. The circumferences of the forearm and upper arm were measured at 10 cm below and above the cubital crease between the medial and lateral epicondyle. The volume of the forearm, upper arm, and whole arm was assessed using a perometer (Perometer 350S; Nam Buk Surgical, Seoul). A perometer is an optoelectric measurement device used to calculate the volume using data gathered electronically from the limb and inserted into a vertically or horizontally oriented frame that emits infrared light beams at right angles to each other. Bioimpedance measurements were recorded using a swept frequency bioimpedance meter (InBody S10; InBody, Seoul). The impedance at the characteristic frequency (1 kHz) and calculated extracellular water (ECW) was determined. Secondary outcome measures were items of the EuroQol-5 dimensions (EQ-5D) questionnaire and EuroQol visual analog scale (EQ VAS). The measurements were obtained at baseline before treatment and 2 weeks after the treatment. Moreover, the degree of symptom improvement was evaluated using a questionnaire that contained items for assessing the degree of subjective symptom improvement, whether lymphedema had softened after treatment, willingness to be treated again, and recommendation of the treatment to others.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences Version 19.0 (IBM Corporation, Armonk, NY). The sample size was determined assuming that the expected mean change of upper limb circumference after CDT was 0.66 cm, and the standard deviation was 1.04, according to the clinical data of our institute. A calculated sample size of 19 patients in each group was needed, and analysis was based on an alpha of 0.05 and a power of 80%. Demographic data were analyzed using an independent t test and the Chi-square test according to the number of possible responses for each item. Moreover, a paired t test was performed to investigate the side-to-side difference of circumference, volume, and bioimpedance within each treatment group. Additionally, an independent t test was used for comparing the side-to-side difference of each parameter between the 2 groups. Also, results of the EQ-5D and EQ VAS used for evaluating QoL were assessed using an independent t test. Kolmogorov-Smirnov test was used as the normality test, which confirmed that the data follow the normal distribution.

All analyses were performed using 2-tailed testing, and differences were considered significant at $P < 0.05$.

Table 1. *Patient characteristics*.

	CDT	SGB	*P* value
Patients (n)	19	19	
Age (yr)	53.63 ± 8.55	57.26 ± 11.03	0.264
Time since surgery (mo)	52.21 ± 36.95	52.84 ± 68.79	0.972
Baseline circumference (cm)			
Upper arm	30.00 ± 2.80	30.72 ± 5.92	0.636
Forearm	26.11 ± 2.86	24.92 ± 2.74	0.199
Baseline impedance			
1 kHz (Ω)	304.76 ± 61.45	304.82 ± 63.24	0.998
ECW (mL)	0.76 ± 0.20	0.68 ± 0.20	0.274
Baseline volume (mL)			
Upper arm	671.16 ± 127.14	697.84 ± 171.66	0.589
Forearm	1111.89 ± 237.82	1070.79 ± 200.24	0.568
Total	1795.53 ± 359.55	1768.63 ± 362.02	0.820
Laterality			
Right/left	12/7	10/9	0.743
Type of surgery			0.191
Modified radical mastectomy	8	13	
Lumpectomy	11	6	
Lymph node dissection			0.187
Axillary/sentinel/no	13/1/1	19/0/0	
Chemotherapy			1.000
Yes/no	19/0	19/0	
Radiotherapy			1.000
Yes/no	18/1	19/0	
Cancer stage			0.708
I/II/III/IV	1/5/8/0	0/8/10/0	

Abbreviations: CDT, complex decongestive therapy; SGB, stellate ganglion block.

Results

Demographics

Table 1 shows the demographic information of the 38 patients (CDT: n = 19 patients; mean age, 53.63 ± 8.55) (SGB: n = 19 patients; mean age, 57.26 ± 11.03). All patients received chemotherapy, and 18 patients (95%) in the CDT group and 19 patients (100%) in the SGB group received radiotherapy. The demographic data were evenly distributed between the CDT and SGB groups, including baseline circumference of the forearm and upper arm, baseline impedance, baseline volume, type of surgery, and cancer stage.

Effect of CDT

The baseline side-to-side differences of circumference were 3.09 ± 1.97 cm at the upper arm and 3.88 ± 2.40 cm at the forearm. After treatment, the side-to-side differences of circumference were 2.57 ± 1.82 cm at the upper arm and 2.94 ± 2.15 cm at the forearm, showing a significant reduction in each ($P < 0.05$) (Table 2). The side-to-side differences of bioimpedance (i.e., ECW) was 0.204 ± 0.163 mL at baseline and 0.163 ± 0.129 mL at 2 weeks after treatment, showing a significant reduction ($P < 0.05$).

Effect of SGB

The side-to-side differences of circumference of the upper arm and forearm were 3.45 ± 5.13 cm and 3.20 ± 2.01 cm, respectively, at baseline and were 2.27 ± 1.94 cm and 2.16 ± 2.10 cm, respectively, at 2 weeks after treatment, which showed a significant reduction at the forearm ($P < 0.05$). The side-to-side differences of bioimped-

Table 2. *Side-to-side difference of each parameter.*

	Baseline	After Treatment	*P* value
CDT			
Circumference (cm)			
Upper arm	3.09 ± 1.97	2.57 ± 1.82	*0.017
Forearm	3.88 ± 2.40	2.94 ± 2.15	*0.002
Bioimpedance			
1 kHz (Ω)	92.35 ± 48.70	78.32 ± 54.91	0.079
ECW (mL)	0.204 ± 0.163	0.163 ± 0.129	*0.028
Volume (mL)			
Upper arm	146.11 ± 102.24	134.05 ± 86.49	0.362
Forearm	271.05 ± 192.46	233.32 ± 159.43	0.162
Total	417.16 ± 285.52	364.63 ± 239.10	0.139
SGB			
Circumference (cm)			
Upper arm	3.45 ± 5.13	2.27 ± 1.94	0.329
Forearm	3.20 ± 20.1	2.16 ± 2.10	*0.001
Bioimpedance			
1 kHz (Ω)	87.17 ± 44.89	54.15 ± 47.85	*0.001
ECW (mL)	0.163 ± 0.155	0.104 ± 0.133	*0.001
Volume (mL)			
Upper arm	131.95 ± 90.24	104.47 ± 74.31	*0.008
Forearm	222.79 ± 155.17	164.21 ± 162.61	*0.001
Total	353.05 ± 226.03	258.05 ± 231.21	*< 0.001

Abbreviations: CDT, complex decongestive therapy; ECW, extracellular water; SGB, stellate ganglion block. *: $P < 0.05$

ance and volume were also significantly reduced ($P < 0.05$) (Table 2).

Comparison of the Effect between CDT and SGB

The changes in side-to-side differences of the circumference, bioimpedance, and volume after treatment were evaluated (Fig. 2). The side-to-side difference in the upper arm circumference was reduced by 0.52 cm in the CDT group and by 1.18 cm in the SGB group, which was not significantly different. Also, the side-to-side differences in the forearm circumference were reduced by 0.94 cm in the CDT group and 1.04 cm in the SGB group, but the difference was also not significant. Similarly, the changes in the side-to-side difference in bioimpedance and volume were not significantly different between the CDT and SGB groups.

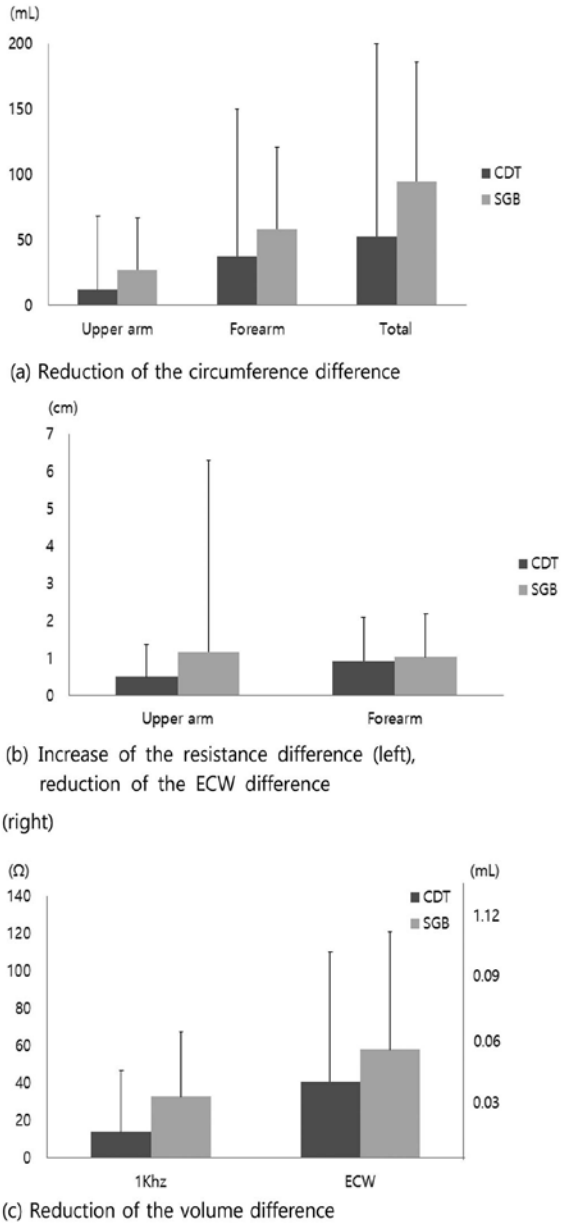

Fig. 2. *Changes of side-to-side differences of the circumference, bioimpedance, and volume were not significantly different between the CDT and SGB groups. (A) The reduction of the circumference difference in the upper arm (P = 0.581) and forearm (P = 0.802) was not significantly different. (B) The change of the bioimpedance difference did not show significant differences in resistance (P = 0.090) and ECW volume (P = 0.470). (C) The reduction of the side-to-side difference of volume were not significantly different at the upper arm (P = 0.335), forearm (P = 0.485), and total arm (P = 0.292).*

QoL and Degree of Subjective Improvement

The EQ-5D score showed no significant improvement in QoL after CDT and SGB treatment. Moreover, the EQ VAS score also showed no significant difference in QoL between the CDT and SGB groups. No significant difference was noted in the degree of subjective symptom improvement and whether lymphedema had softened after treatment between the 2 groups. The results of the questions regarding willingness to be treated again or recommendation of the treatment to other patients are shown in Fig. 3.

Discussion

Lymphedema is a progressive pathologic condition of subcutaneous tissue swelling that results from the interstitial accumulation of protein-rich fluid, owing to a lymphatic obstruction or compromised lymphatic system (1). If the lymphatic system is compromised, then transportation of the interstitial fluid to the blood is reduced, resulting in lymphatic stasis that in turn leads to protein accumulation within the interstitium. This increased protein concentration increases the tissue colloid osmotic pressure, drives fluid into the interstitium, and causes the clinical symptoms of lymphedema (1,19). Most secondary lymphedema develops after treatment of malignant tumor, particularly breast cancer (1).

Our study demonstrated that CDT was effective for reducing the side-to-side difference of the forearm and upper arm circumference. The results were in accordance with those of several previous studies. Andersen et al (7) reported that CDT was effective in treating BCRL, and the mean reduction in lymphedema was 43% after one month. Boris et al (20) reported an enduring lymphedema reduction in breast cancer patients treated with CDT. They reported that lymphedema was reduced by an average of 62.6% after CDT in the 56 patients, and this improvement was maintained after 36 months. Similarly, the result of our trial showed enough decrement of forearm and upper arm circumference after CDT, indicating that CDT is a clinically valuable treatment modality for secondary lymphedema.

In the present study, SGB resulted in a marked reduction of side-to-side difference of volume in the forearm, upper arm, and whole arm. The side-to-side difference of circumference in the forearm and bioimpedance was also significantly reduced. The effect of sympathetic ganglion block in lymphedema has already been shown in several studies. Swedborg et al (13) reported that thoracic sympathetic ganglion block was effective in treating BCRL. Kim et al (14) also found that the volume of the affected arm reduced after 3 consecutive SGBs comprising 4 mL 1% lidocaine and 1 mL 40 mg triamcinolone. Furthermore, Woo et al (15) reported that 3 consecutive lumbar sympathetic ganglion blocks using 10 mL 0.375% ropivacaine at a 2-week interval were effective as a treatment for lymphedema secondary to gynecologic cancer. Recently, Choi et al (17) found that thoracic sympathetic block in patients with BCRL appeared to be effective in decreasing the arm circumference. Kim et al (18) reported a decrease of circumference in 2 patients treated with cervical SGBs after developing intractable lymphedema post-breast cancer surgery. Moreover, our previous study noted the effectiveness of 3 consecutive SGBs for patients with BCRL, and the additive effect of corticosteroid in SGB (16). However, Hardy and Wells (21) reported that SGB did not effectively block the dermatomal thoracic sympathetic nerves. This outcome may be caused by the Kuntz's fiber, which is found in approximately 20% of the population. Kuntz's fiber is a nerve connecting the T2 and T3 sympathetic ganglia to the brachial plexus, and it bypasses the stellate ganglion (22,23). Also, it could be owing to the insufficient concentration of local anesthetic solution to block sympathetic fibers to the upper extremities. There have been many attempts to define the minimal volume of local anesthetic that is need for successful SGB. Hardy and Wells (21) conducted a study of the extent of sympathetic blockade after SGB using 2 volumes (10 mL and 20 mL) of 0.5% bupivacaine. Although upper cervical block was present in all patients, there was a significant difference in distribution of lower cervical sympathetic blockade between 2 groups. The larger volume was associated with a significant incidence of lower cervical sympathetic blockade and side effects. And if the needle is placed properly, 5 mL of local anesthetic is required for general SGB, and 10 mL of local anesthetic is needed to block the sympathetic fibers to the upper extremities (24). Also, Lee et al (25) reported a minimum of 4 mL of local anesthetic required for SGB, Katz (26) reported a minimum of 8-10 mL, and Brevik et al (27) reported a minimum of 15-20 mL. Our previous research using a mixture of 0.5% bupivacaine 4 mL and 40 mg of triamcinolone 1 mL suggested that 3 consecutive SGBs at a 2-week interval were effective for improving both upper arm and forearm BCRL (16). Further studies are necessary to define the most suitable local anesthetic and the most effective volume.

Because several previous studies already reported that sympathetic ganglion block reduced swelling in

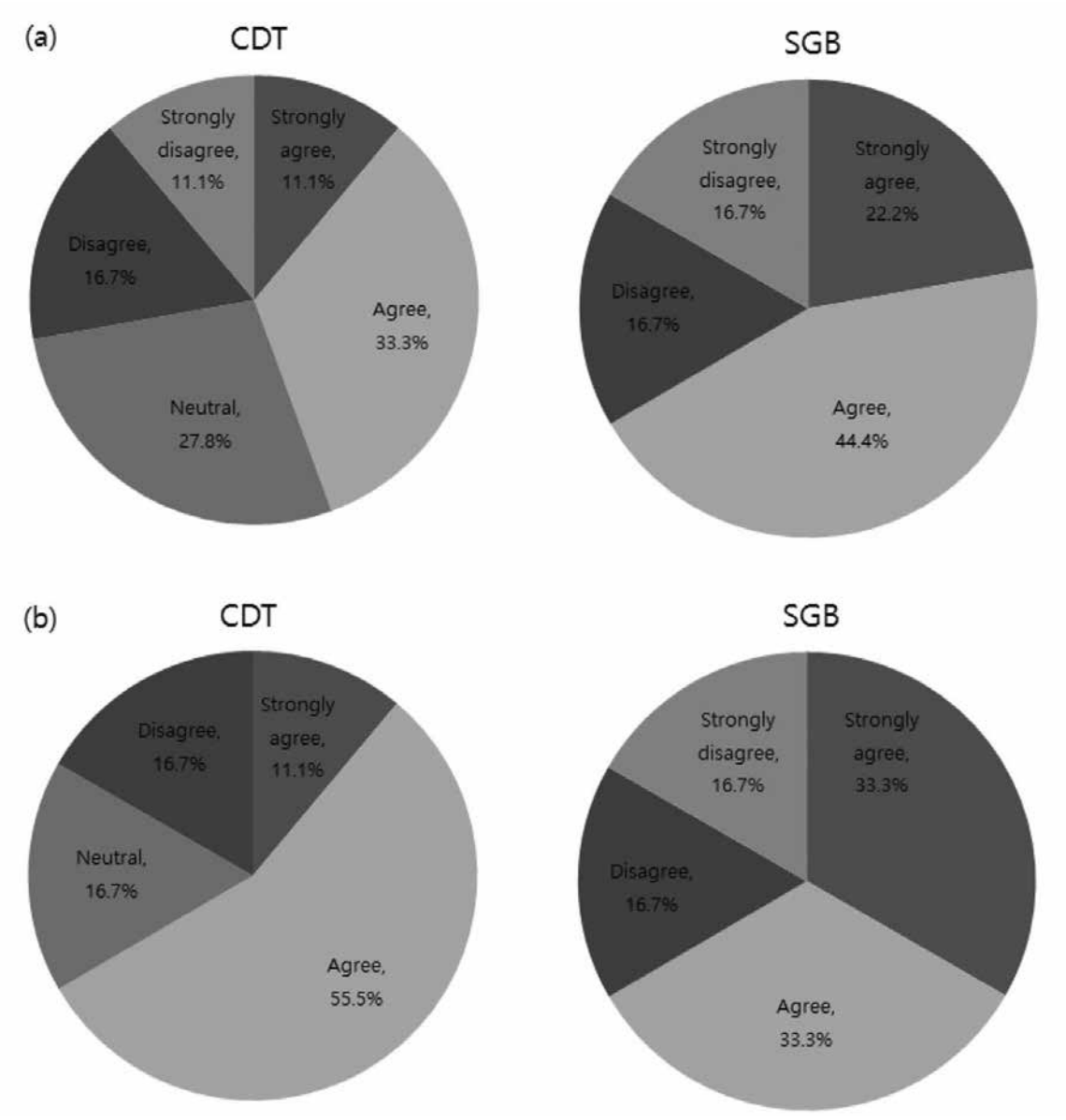

Fig. 3. *Results of questions regarding (A) willingness to be treated again or (B) recommendation of the treatment to other patients.*

BCRL (13-18), we expected that the effect of SGB might be similar to CDT. Indeed, our results showed no significant difference in treatment effect between the 2 groups. The treatment mechanism of CDT and SGB are different. CDT typically involves skin care, manual drainage massage, bandage therapy, and exercise (5). In 1965, Vodder (28) suggested that these methods constituting CDT increase lymphatic contractility and cutaneous lymphatic flow, leading to reduced lymphatic fluid. Meanwhile, the mechanism of SGB in patients with BCRL is yet to be clearly defined. SGB is thought to regulate the relationship between the autonomic nervous system and lymphatic system, which is composed of superficial and deep lymphatic channels (29). These

collecting lymphatic vessels are innervated by autonomic nerve fibers (30), and SGB promotes dilatation of these vessels, which releases the accumulated interstitial fluid into the venous system (13). The second role of SGB may be the effect on venous flow. An animal study showed evidence of increased blood flow of brachial vessels after SGB (31). The movement of the venous wall was also found to be significantly reduced after surgery in patients with BCRL, which could increase the risk of BCRL (32). The other possible mechanism is immune modulation effect of SGB. Studies have revealed the roles of macrophages in the regulation of lymphangiogenesis (33-35). Furthermore, Yokoyama et al (36) found that SGB altered lymphocyte subsets and NK cell activity. Also, our previous study demonstrated that corticosteroid addition in SGB can promote a therapeutic effect (16). These findings support that SGB influences the immune system. Because SGB and CDT act via different mechanisms, their combination may further enhance treatment outcomes.

The results of our study showed no statistically significant difference in QoL before and after treatment regardless of treatment methods. However, 44.4% of patients in the CDT group and 66.6% of those in the SGB group reported that they were willing to receive treatment again. Furthermore, 66.6% of patients in both the CDT and SGB groups said that they would like to recommend the treatment to others. These results indicate that, although not statistically significant, patients were satisfied with both treatments.

Although, to the best of our knowledge, this study is the first prospective randomized controlled clinical trial to compare the effectiveness of CDT and SGB, there are several limitations of the present study that need to be acknowledged. First, the long-term follow-up were not stated in this study. The research was designed to evaluate the short-term effect of SGB in patients with BCRL, but these patients are still following. We are planning a further study to report the long-term follow-up results. Second, this study could not examine the data by the severity of the lymphedema and by the duration of the lymphedema. Further long-term follow-up studies with a greater number of patients that include analysis according to the severity and duration of symptoms are needed.

Conclusions

The results of this study show that SGB is an effective intervention for arm lymphedema secondary to breast cancer. Therefore, SGB may be considered as an alternative treatment option in managing BCRL.

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