Randomized Trial

Effects of Stellate Ganglion Block on Breast Cancer-Related Lymphedema: Comparison of Various Injectates

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Background: Stellate ganglion block (SGB) has been reported to be effective in the treatment of breast cancer-related lymphedema (BCRL).

Objective: To determine the effects of SGB in BCRL patients and the efficacy of corticosteroids in SGB.

Study Design: A double-blinded, randomized, controlled trial.

Setting: A single academic hospital, outpatient setting.

Methods: In total, 32 patients with BCRL were recruited. Patients were divided randomly into 3 groups (Group A: 0.5% bupivacaine 5 mL, n = 12; Group B: 0.5% bupivacaine 4.5 mL + 20 mg of triamcinolone 0.5 mL, n = 10; and Group C: 0.5% bupivacaine 4 mL + 40 mg of triamcinolone 1 mL, n = 10). All patients received 3 consecutive SGBs, every 2 weeks. The primary outcomes were changes in forearm and upper arm circumference. Circumference was measured at baseline, 2 weeks (before the second injection), 4 weeks (before the third injection), and 8 weeks (one month follow-up after 3 consecutive SGBs). Moreover, subjective data were collected using EORTC C-30 at baseline and 8 weeks.

Results: After 3 consecutive SGBs, forearm and upper arm circumferences were decreased significantly from baseline in all groups ($P < 0.05/3$). The upper arm circumference of group C was reduced significantly more than that of group A ($P < 0.05/3$). The subjective data by EORTC-C30 at baseline and one month after 3 consecutive SGBs revealed no statistically significant difference.

Limitations: Relatively few patients were enrolled. We did not compare SGB with any other BCRL treatment, such as complex decongestive therapy.

Conclusions: This study suggests that SGB may be an effective treatment for BCRL. Furthermore, it appears that corticosteroids could have an additive effect in SGB.

Key words: Stellate ganglion block, breast cancer, lymphedema**:**

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Breast cancer-related lymphedema (BCRL) is a frequent problem, characterized by a chronic, swollen arm as a result of a damaged lymphatic drainage system after management of breast cancer (1). The incidence of BCRL is ~20% of the breast cancer survivor population. Furthermore, it is known that the risk of BCRL is higher after an axillary lymph node dissection than a sentinel node biopsy (2). Patients with BCRL may suffer from a sensation of arm fullness, pain, reduced range of motion, skin changes, and lowered quality of life (QoL) (1,3-5).

The treatment of BCRL can include complex decongestive therapy (CDT, also known as combined physical therapy, complete decongestive treatment), manual lymph drainage (MLD), compression bandages or garments, intermittent pneumatic compression, pharmacotherapy, and surgical treatments (6-8). CDT, which consists of MLD, compression bandage, compression garment, therapeutic exercise, and skin care, is currently accepted as the standard treatment for various degrees of BCRL (8,9). CDT has been reported to reduce the volume effectively, improve function, and QoL (9). However, BCRL cannot be cured by any treatment method (6). Furthermore CDT is sometimes criticized as time-consuming and patients may not tolerate it (10). Thus, there is a continuing need for novel, complementary, and alternative treatment modalities to manage BCRL.

Stellate ganglion block (SGB) is a method that involves injecting an anesthetic drug around the cervical sympathetic trunk. SGB is used to treat complex regional pain syndrome (CRPS), postherpetic neuralgia, and hot flashes (11-13). Sweborg et al (14) reported that sympathetic block was effective as a treatment for BCRL. Kim et al (15) also reported that 3 consecutive SGBs, composed of 1% lidocaine 4 mL and 40 mg triamcinolone 1 mL, every 2 weeks, improved BCRL in a pilot study. Furthermore, Woo et al (16) reported that 3 lumbar sympathetic ganglion blocks (LSGBs) using 10 mL of 0.375% ropivacaine at 2-week intervals was effective in treat lymphedema secondary to gynecological cancer.

In this study, we hypothesized that SGB could be an alternative method to manage BCRL and corticosteroids would provide an additive positive effect on SGB. However, there has been insufficient clinical trials investigating the effects of SGB for BCRL. Furthermore, to our knowledge, there is no reported study that has examined the efficacy of corticosteroid in SGB for BCRL. Thus, the aim of this study was to determine the effectiveness of SGB in the treatment of BCRL and to compare the efficacy of SGB with and without corticosteroids.

Methods

Study Design and Patients

A single-center, randomized, double-blind, controlled clinical trial was conducted. The study protocol was registered with the Clinical Research Information Service (KCT000300). The study was approved by our hospital Institutional Review Board. Written informed consent was obtained from all patients.

From March 2010 through December 2011, lymphedema patients from our hospital, who were suffering from lymphedema symptoms such as heaviness of the arm, pain, difficulty in use, and reduced function, were recruited if they met the following criteria. Patients aged 20 years or older with BCRL were eligible for the study. The clinical diagnosis of BCRL was established by a circumference difference in the forearm or arm circumference (≥ 2 cm), and lymphatic obstruction, confirmed by lymphoscintigraphy. Exclusion criteria were primary lymphedema and hypersensitivity to local anesthetics.

Treatments

SGB (anterior approach technique). The patient was placed in a supine position with a pillow under the neck. Before injection, the needle path for the SGB was identified using ultrasound to determine hazardous structures, such as the vertebral artery, other arteries, and the esophagus. Antiseptic solution was applied to the lateral side of the cricoid cartilage. After sterilization, aseptic technique was used. At the level of the cricoid cartilage, the sternocleiodmastoid muscle was drawn laterally and the transverse process of the C6 transverse process was palpated between the cricoid cartilage and the carotid artery. A 23-gauge needle was inserted vertically. After bone touch, the needle was withdrawn slightly and aspirated; then, the injection was delivered. Patients were observed for 30 minutes after SGB to monitor early complications.

Each patient was allocated randomly to one of 3 groups using a permuted block method according to injected drug: Group A (0.5% bupivacaine 5 mL), Group B (0.5% bupivacaine 4.5 mL with 20 mg of triamcinolone 0.5 mL), or Group C (0.5% bupivacaine 4 mL with 40 mg of triamcinolone 1 mL). Patients were given 3 consecutive SGBs every 2 weeks. Patients continued any BCRL treatment that had been carried out previously, such as MLD.

Outcome Measures

The primary outcomes were changes in circumferences of the affected forearm and upper arm. The circumferences of the forearm and upper arm were measured at 10 cm below and above the elbow crease. Circumferences were measured at baseline, at 2 weeks (before second SGB), at 4 weeks (before third SGB), and at 8 weeks (one month after the 3 consecutive SGBs).

Secondary outcome measures were global health status and functional scales, including physical, role, emotional, and social functioning, derived from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 (17). Measurements were obtained at baseline and one month after 3 consecutive SGBs.

Statistical Analysis

Patient characteristics were compared between groups using the Kruskal-Wallis test for continuous data and Fisher's exact test for categorical data. A P-value of < 0.05 was considered to indicate statistical significance. The Wilcoxon signed-rank test was performed to compare the circumferences at 2, 4, and 8 weeks from baseline. To compare the 3 groups, changes in forearm and upper arm circumferences between baseline and one month after 3 consecutive SGBs were tested by Kruskal-Wallis test and Mann-Whitney U-test with Bonferroni correction. The Bonferroni correction was used for multiple comparisons, adjusting the P-value ($P < 0.017$ [0.05/3]). The score of EORTC QLQ-C30 was compared using Wilcoxon signed-rank test. Analyses were performed using the SPSS software (ver. 18.0; SPSS Inc., Chicago, IL).

Results

In total, 32 patients were assessed and enrolled in the study: 12 in Group A, 10 in Group B, and 10 in Group C (Fig. 1). At baseline, age, weight, height, laterality, onset of lymphedema, history of breast cancer treatment, and history of lymphedema treatment were self-reported. The demographic characteristics of the 3 groups did not differ significantly (Table 1). All

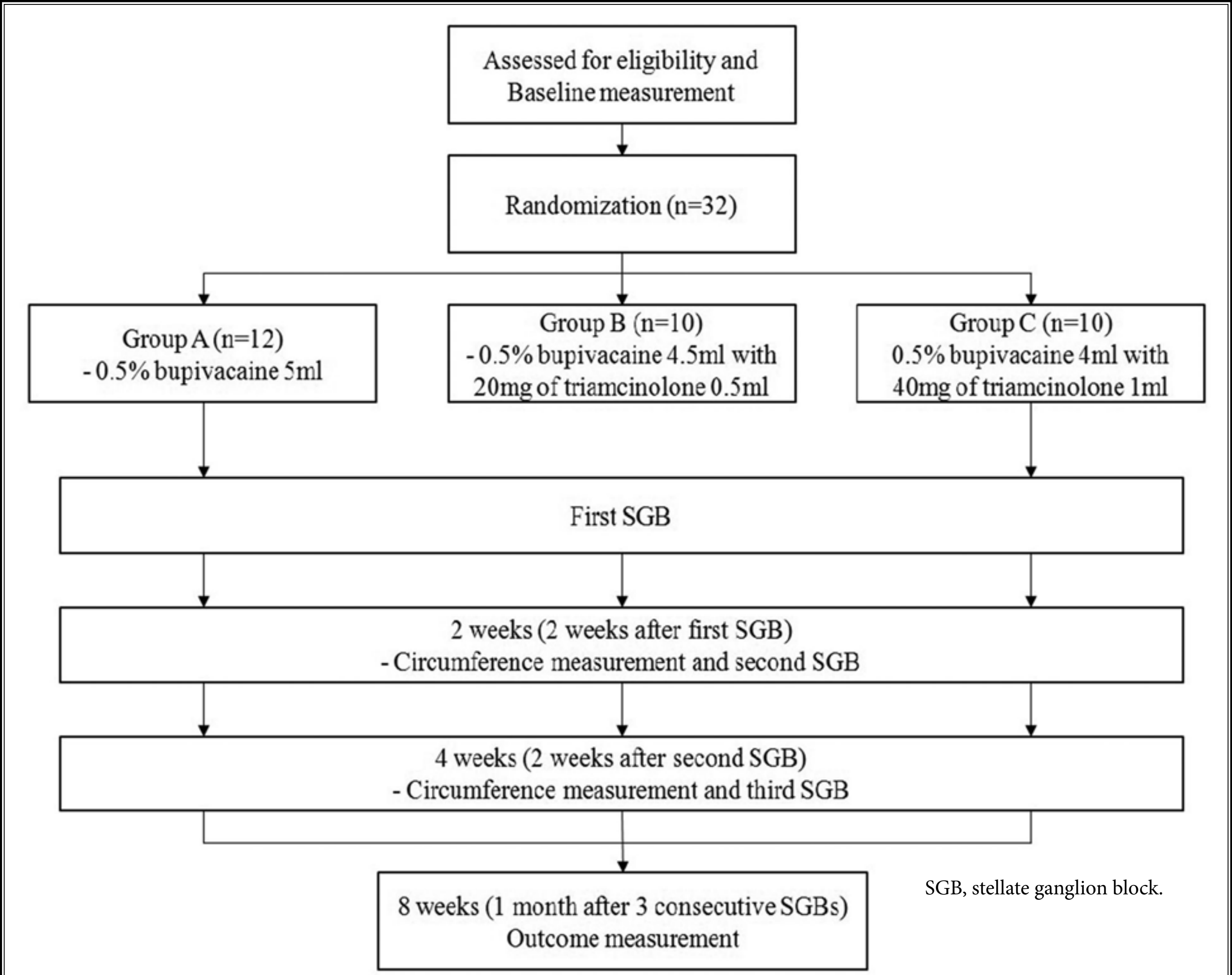


Fig. 1. *Flow chart of patients through the study.*

Table 1. *Baseline characteristics of patients (mean [±SD] or n [%]).*

	Group A (n = 12)	Group B (n = 10)	Group C (n = 10)	*P*-value
Age, years	55.5 (±12.3)	50.5 (±7.3)	55.6 (±7.8)	0.42
Height, cm	154.1 (±5.3)	156.9 (±5.2)	156.1 (±5.0)	0.39
Weight, kg	58.8 (±5.6)	61.2 (±8.4)	60.1 (±6.5)	0.82
BMI, kg/m2	24.8 (±2.9)	24.8 (±2.3)	24.7 (±2.9)	0.80
Onset of lymphedema, month	22.3 (±14.6)	30.2 (±21.3)	30.3 (±18.0)	0.58
Location of breast cancer				0.67
Right	6 (50)	5 (50)	3 (30)	
Left	6 (50)	5 (50)	7 (70)	
Lymph node dissection				0.63
Yes	12 (100)	10 (100)	9 (90)	
Lymph node metastasis				0.18
Yes	12 (100)	10 (100)	8 (80)	
Chemotherapy				1.00
Yes	11 (91.2)	10 (100)	9 (90)	
Radiation therapy				0.26
Yes	9 (75)	10 (100)	7 (70)	
History of CDT				0.53
Yes	9 (75)	7 (70)	5 (50)	
Circumference of affected forearm, cm	25.1 (±2.7)	26.8 (±2.9)	24.6 (±1.6)	0.17
Circumference of affected upper arm, cm	30.7 (±3.9)	32.8 (±3.5)	30.7 (±2.3)	0.32
Δ in circumference				
Forearm, cm	3.4 (±1.7)	4.0 (±1.6)	2.6 (±1.1)	0.15
Upper arm, cm	3.2 (±1.5)	4.3 (±3.0)	3.7 (±1.8)	0.51

SD, standard deviation. Group A, 0.5% bupivacaine 5 mL, Group B, 0.5% bupivacaine 4.5 mL with 20 mg of triamcinolone 0.5 mL, Group C, 0.5% bupivacaine 4 mL with 40 mg of triamcinolone 1 mL. BMI, body mass index. CDT, complex decongestive therapy. Δ in circumference, circumference of the affected side – circumference of the unaffected side.

patients reported one of following symptoms within a few minutes after SGB: ipsilateral ptosis, ipsilateral miosis, flushing, lacrimation, or nasal congestion. No serious complication was reported.

Changes in the circumferences of the forearm and upper arm are summarized in Table 2 (mean ± standard error of the mean). Forearm circumferences were decreased significantly at one month after the 3 consecutive SGBs in all groups. Although statistically insignificant, there was a trend towards a decrease in forearm circumference at 2 and 4 weeks in Groups B and C. The circumferences of the upper arm were reduced significantly at 8 weeks in Group A, at 4 weeks in Group B, and at 2 weeks in Group C. Global health status and functional scales obtained with EORTC QLQ-C30 did not change significantly after 3 consecutive SGBs in any group.

Fig. 2 shows a box plot representing changes in circumference from baseline to one month after 3 consecutive SGBs. There was no significant difference in the changes in forearm circumference between the 3 groups ($P = 0.426$). A significant difference was found in the upper arm between Groups A and C ($P = 0.007$). No significant difference was found in the upper arm change between Groups A and B ($P = 0.059$) or Groups B and C ($P = 0.436$). There was no significant difference between the 3 groups in global health status or functional scales obtained from EORTC QLQ-C30.

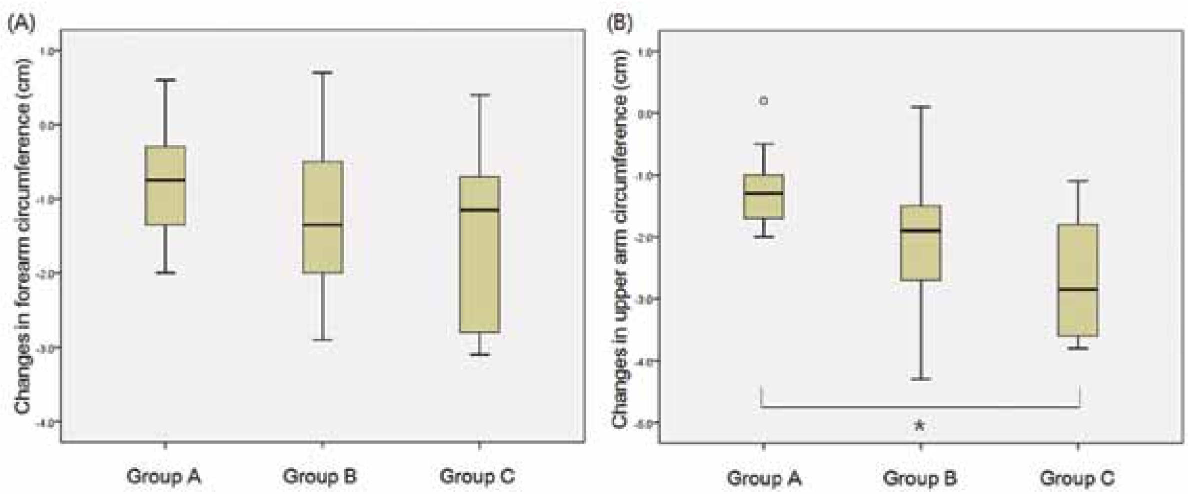
Discussion

The findings of this double-blind, randomized, controlled trial suggest that 3 consecutive SGBs at 2-week interval were effective for improving both upper arm and forearm BCRL and the use of corti-

Table 2. ***Summary of forearm and upper arm circumferences (mean ± SEM [P-value]).***

		Baseline	2 weeks (2 weeks after first SGB)	4 weeks (2 weeks after second SGB)	8 weeks (one month after third SGB)
Forearm	Group A	25.1 ± 0.79	25.0 ± 0.75 (0.582)	24.9 ± 0.75 (0.288)	24.3 ± 0.87 (0.010)*
	Group B	26.8 ± 0.93	26.1 ± 0.74 (0.036)	25.5 ± 0.74 (0.028)	25.5 ± 0.72 (0.016)*
	Group C	24.6 ± 0.52	23.7 ± 0.59 (0.021)	24.0 ± 0.43 (0.050)	23.2 ± 0.61 (0.011)*
Upper arm	Group A	30.7 ± 1.14	30.8 ± 1.13 (0.814)	30.4 ± 1.11 (0.126)	29.5 ± 1.26 (0.003)*
	Group B	32.8 ± 1.10	32.0 ± 1.02 (0.047)	31.4 ± 0.97 (0.005)*	30.7 ± 0.97 (0.007)*
	Group C	30.7 ± 0.73	29.8 ± 0.78 (0.009)*	29.7 ± 0.63 (0.012)*	28.2 ± 0.63 (0.005)*

SEM, standard error of the mean. SGB, stellate ganglion block. Group A, 0.5% bupivacaine 5 mL, Group B, 0.5% bupivacaine 4.5 mL with 20 mg of triamcinolone 0.5 mL, Group C, 0.5% bupivacaine 4 mL with 40 mg of triamcinolone 1 mL. *$P < 0.017$ compared with baseline (Wilcoxon signed-rank test).



SGB, stellate ganglion block. Group A, 0.5% bupivacaine 5 mL, Group B, 0.5% bupivacaine 4.5 mL with 20 mg of triamcinolone 0.5 mL, Group C, 0.5% bupivacaine 4 mL with 40 mg of triamcinolone 1 mL. Circle indicates possible outlier. Negative values mean a reduction in circumference. *$P < 0.017$ (Mann-Whitney U-test).

Fig. 2. ***Change in circumference from baseline to 3 consecutive SGBs (box plot). (a) forearm and (b) upper arm.***

costeroids in SGB might have beneficial effects in reducing upper arm circumference more rapidly and significantly.

The lymphatic vasculature of the upper extremity consists of superficial and deep lymphatic vessels. BCRL more severely affects the subcutis and skin that drains the lymph via the superficial lymphatics (1,18). Lymph moves through lymphatic capillaries, precollector vessels, collecting lymphatic vessels, and lymph nodes. The transport of lymph is induced not only by an extrinsic lymphatic pump, but also intrinsic lymphatic pumps (19,20). The extrinsic lymphatic pumps consist of the pulsating heart and arteries, skeletal muscle contraction, peristaltic movements, movements due to respiration, and skin compression. The intrinsic contractility is induced by smooth muscle cells that are present in collecting lymphatic vessels (20). The collecting lymphatic vessels are innervated by sympathetic and parasympathetic nerve fibers (21). Dysfunction in the lymphatic system due to removal of lymph nodes or radiotherapy can lead to the accumulation of plasma protein-rich fluid, which results in BCRL.

The effects of SGB in lymphedema in this study are similar to those reported previously (15,16). Kim et al (15) reported that the circumferences of the upper arm and forearm in BCRL patients decreased significantly after 3 consecutive SGBs using 1% lidocaine 4 mL and 40 mg triamcinolone 1 mL. Furthermore, a significant decrease in upper arm and forearm circumference appeared after the first SGB. Woo et al (16) described that the circumferences of thighs and calves decreased significantly after 3 consecutive LSGB using 10 mL 0.375% ropivacaine. There was no significant decrease until the second LSGB. In the previous studies (15,16), 3 consecutive injections were performed every 2 weeks and the circumference was measured 2 weeks after SGB or LSGB. Circumferences were decreased at one month after 3 consecutive SGBs in this study. However, it is still unknown whether the effects of SGB persist beyond one month.

The mechanism of SGB in BCRL is not well known. One possible mechanism is autonomic regulation of lymphatic vessels due to SGB. As mentioned previously, collecting lymphatic vessels are innervated by sympathetic and parasympathetic nerve fibers (21). The contractility of collecting lymphatic vessels is impaired in BCRL patients (1). The sympathetic nerve fibers in lymphatic vessels contain neurotransmitters, inducing vessel contraction (21). Furthermore, Howarth et al (22) reported that lymphatic flow in edematous lower extremities in CRPS type-1 patients improved after LSGB. These findings suggest that SGB may modulate the lymphatic system.

A second possible mechanism is that SGB may enhance venous flow. Movement of axillary vein walls is reduced in BCRL patients (23). It was also found that brachial artery and brachial venous flow were increased after SGB in an animal study (24). Thus, SGB could improve BCRL by enhancing venous flow.

Another plausible hypothesis is immune modulation due to SGB. A chronic inflammatory response has been found in lymphedema (25). In an animal model of lymphedema, intense inflammatory changes were observed (26). Furthermore, Yokoyama et al (27) described modulation of the immune response by SGB. In this study, upper arm circumference decreased more and faster in Group C than Group A. This suggests that the corticosteroid addition could enhance immune modulation by SGB.

This study has some limitations. First, the number of participants was small. Second, we did not compare SGB with any other treatment for BCRL. Third, there are few studies that have investigated the effects of SGB in BCRL, such as animal studies. Fourth, the long-term effects of SGB on BCRL have not been evaluated. Thus, there is a need for further studies, including larger numbers of participants, comparisons with other BCRL treatments, animal models of SGB, and longer duration of follow-up.

Conclusions

In conclusion, the results of this study demonstrate that SGB could be an alternative treatment for BCRL patients. Furthermore, the corticosteroid addition in SGB may induce more and faster improvements.

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