Retrospective Study

Sympathetic Block as a New Treatment for Lymphedema

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Background: Breast cancer-related lymphedema (BCRL) not only has physical implications, but also affects the quality of life in breast cancer survivors. Despite numerous studies of various therapies, the optimal treatment for BCRL is unknown.

Objective: In this study, we investigated the efficacy of sympathetic blockade (thoracic sympathetic ganglion block, [TSGB]) in treating BCRL.

Study Design: Retrospective study.

Setting: Tertiary referral center/teaching hospital.

Methods: TSGB was performed in 35 patients under fluoroscopic guidance. First, arm circumference and Lymphedema and Breast Cancer Questionnaire [LBCQ] score were assessed before TSGB and 2 weeks and 2 months after the procedure. Efficacy was defined as a ≥ 50% reduction in the LBCQ score and a ≥ 50% decrease in the circumference difference between the unaffected and affected arms 2 months after TSGB. Second, TSGB efficacy according to the lymphedema stage and the period between BCRL onset and TSGB (< 6 months vs. > 6 months) was evaluated.

Results: The arm circumference and LBCQ score significantly decreased at 2 months ($P < 0.001$), and 65.7% of patients showed good efficacy. Patients with high stage lymphedema showed improved efficacy after TSGB compared to those with low stage disease ($P = 0.045$). The TSGB efficacy did not differ according to the period between BCRL onset and TSGB.

Limitations: This study was not a randomized prospective controlled study and did not compare the therapeutic outcomes to those in a conservative treatment group.

Conclusions: TSGB in BCRL patients appears to be effective in decreasing the affected arm circumference. TSGB may be an alternative option in BCRL patients who do not respond to conservative therapy.

Key words: Breast cancer, lymphedema, thoracic sympathetic ganglion block, quality of life

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Breast cancer is one of the most common neoplasms in women (1). Breast cancer survival has gradually increased due to advances in treatment, and several recent studies have focused on the quality of life in survivors (2,3). Breast cancer-related lymphedema (BCRL) is a form of secondary lymphedema occurring during or after treatment for breast cancer. BCRL is relatively common, affecting 20% of breast cancer survivors, and is more frequent in patients receiving aggressive surgery such as axillary lymph node dissection, numerous lymph node dissections, and total mastectomy (4).

BCRL is caused by damage to the axillary lymphatic system during surgery or radiotherapy (5). When the lymphatic system is disturbed, excess interstitial fluid accumulates, and interstitial proteins increase. This leads to increasing accumulation of excess fluid and chronic tissue changes, including fibrosis, hypertrophy of adipose tissue, and inflammation (6). Shoulder pain and limited joint mobility have been observed in patients with lymphedema (7). BCRL not only causes physical abnormalities and functional impairment (8), but it may also lower self-image and promote depression or social isolation in affected patients (2).

BCRL treatment focuses on reducing the circumference and tissue volume of the affected arm and on enhancing the quality of life (9). Conservative options include complex decongestive physiotherapy (CDP) (10), manual lymphatic drainage (MLD), compression bandaging and garments (11), and benzopyrone administration (12). However, a recent review of these conservative therapies indicated that the therapeutic efficacy was not established despite numerous trials (13). Although each therapy produces some improvement in lymphedema symptoms, large-scale studies are needed to validate the efficacy of these conservative therapies (9). In addition, the response to conservative therapy varies between patients (14) due to differences in compliance and difficulties in maintaining the initial therapeutic response long-term (15,16). BCRL is a chronic and intractable condition, and is not typically cured by conservative modalities.

Sympathetic blockade of the upper extremities, also known as thoracic sympathetic ganglion block (TSGB) or stellate ganglion block (SGB), has been used to treat chronic sympathetic pain in the upper extremities, including complex regional pain syndrome (CRPS), post-therapeutic neuralgia, phantom limb pain, and ischemic vascular disease (17- 19). Sympathetic block also increases skin perfusion and temperature (20,21) through vasodilation at the anesthetized site (22,23).

Swedborg et al (24) reported that the sympathetic block was used to successfully treat a BCRL patient. A few studies have used the sympathetic block to alleviate lymphedema on the assumption that the resulting vasodilation would promote edema drainage (24,25). These studies highlight the potential of sympathetic blockade in treating BCRL. However, SGB did not effectively block the dermatomal thoracic sympathetic nerves in several patients in another study (26). This outcome may be caused by the Kuntz's fiber, which is a nerve connecting the second (T2) and third (T3) thoracic sympathetic ganglia to the brachial plexus, bypassing the stellate ganglion; Kuntz's fiber is found in approximately 20% of the population (27). Therefore, TSGB may be a more appropriate method for sympathetic blockade of the upper extremity.

Identification of a clinically significant effect for TSGB may indicate its potential as a treatment option for BCRL, but there have been no known studies examining the effect of TSGB in BCRL patients. The purpose of this study was to investigate the efficacy of TSGB as a potential new treatment for BCRL.

Methods

Retrospective Review

This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB no. B-1308-216-110). After obtaining approval of IRB, the medical records of BCRL patients who underwent TSGB between August 2010 and December 2012 were retrospectively reviewed.

In our pain center, medical charts for BCRL patients were recorded in an itemized pattern. Lymphedema stage, affected arm circumference, unaffected arm circumference, and Lymphedema and Breast Cancer Questionnaire (LBCQ) score were recorded at every visit. Lymphedema was classified into 4 stages (latent to severe) according to the skin condition and severity of swelling (Table 1) (28). The arm circumference was measured at 5 locations: axilla, 15 cm proximal to the lateral epicondyle, elbow, 10 cm distal to the lateral epicondyle, and wrist. The LBCQ is a self-administered survey comprising 19 questions (29). The LBCQ is used to assess limited mobility, swelling, tightness, pain, and numbness of the upper extremity in lymphedema patients and has high reliability and validity (29,30) (Table 2). A higher score indicated more severe edema.

Based on our electronic medical records, we collected 60 patients with BCRL who underwent TSGB. Inclusion criteria were as follows: (1) mastectomy with axillary lymph node or sentinel lymph node dissection; (2) unilateral BCRL; (3) patients who were referred from other departments; conservative treatment of BCRL, including CDP, for at least 3 months; and (4) affected arm circumference was > 2 cm larger than the circumference of the unaffected arm despite conservative treatment. Exclusion criteria were as follows: (1) bilateral BCRL (n = 5); (2) metastatic breast cancer (n = 11); and (3) no follow-up after TSGB (n = 9). Finally, the study group was comprised of 35 patients.

First, 2 weeks and 2 months after undergoing TSGB, arm circumference and LBCQ score in the medical records were reviewed. Next, the patients were divided into 2 groups (effective TSGB group and non-effective

Table 1. *Lymphedema stages*.

Stage	Signs and symptoms
0: Latent (subclinical) lymphedema	• No visible edema • No pitting • Sensations of local heaviness or tightness may be present for months or years before overt swelling occurs
1: Early lymphedema	• Visible edema, with or without pitting
2: Moderate lymphedema	• Visible edema, usually with pitting • Hardened, thickened skin and tissue • Pitting may disappear as fibrosis worsens
3: Severe lymphedema	• Visible edema • No pitting • Enlargement of the affected area • Hardened, thickened skin and tissue • Lymph leaking through damaged skin

TSGB group) according to the observed therapeutic efficacy. Effective TSGB group was defined as a ≥ 50% reduction in the LBCQ score and a ≥ 50% decrease in the circumference difference between the unaffected and affected arms 2 months after the procedure. Second, the TSGB efficacy according to the lymphedema stage and the treatment period (duration between BCRL onset and TSGB) was evaluated. The age, gender, body mass index, surgery type, breast cancer stage, use of radiation therapy and chemotherapy, and symptoms onset were also collected.

TSGB

TSGB was performed in a surgical suite under fluoroscopic guidance. Each patient was administered Lactated Ringer's Solution intravenously through a peripheral vein before the procedure. The patient was placed in a prone position on a radiological table, and the site was aseptically prepared. Vital signs (blood pressure, SPO2, and electrocardiogram) and skin temperature were monitored using adhesive thermocoupled probes (Solar® 8000M, GE Healthcare, Milwaukee, WI, USA).

The patient was placed in a suitable position for fluoroscopy, and a 22-gauge, 12-cm, Quincke spinal needle (Taechang Industrial Co., Kongju, Korea) was inserted to the lateral margin of the T3 vertebra using the tunnel view technique under fluoroscopic guidance. The needle tip was positioned at one-third along the vertebral body, and the position was confirmed on lateral fluoroscopic images. The site was injected with 1 – 2 mL of contrast agent (Omnipaque; Nycomed Ireland, Ltd., Cork, Ireland) in order to confirm proper positioning of the needle and detect any intravascular, intrathecal, epidural, or intrapleural spread. Once the final tip position was determined, 5 mL of 4% lidocaine was administered. The skin temperature was measured at baseline and monitored at 5-minute intervals for 30 minutes after the lidocaine injection. If the temperature in the affected palm increased ≥ 2°C, then the TSGB was deemed successful (27).

Table 2. *Lymphedema and Breast Cancer Questionnaire (LBCQ) score*[a].

Do you have limited movement of your :	1>Shoulder, 2> Elbow, 3> Wrist, 4> Fingers
Does your arm or hand feel weak? Have you had :	5>Aching, 6> Blistering, 7> Breast swelling, 8> Chest wall swelling, 9> Firmness, 10> Tightness 11> Heaviness, 12> Increased temperature in your arms, 13> Numbness, 14> Rashes, 15> Redness 16> Stiffness, 17> Swelling, 18> Swelling with pitting, 19> Tenderness

a: Patients replied to question, yes/no answers about symptom before and after thoracic sympathetic ganglion block. The number of items answered 'yes' is the score.

Statistical Analysis

The sample size was calculated based on the results of a previous pilot study (17). Assuming a 0.05 type 1 error, 80% power, 30% detection difference, and a repeated-measures analysis of variance, at least 28 patients were required. The statistical analysis was performed using SPSS software (ver. 18.0; SPSS, Chicago, IL, USA). Continuous numerical data (arm circumference and LBCQ) were compared using repeated-measures analysis of variance. Differences in TSGB efficacy ac-

Table 3. *Patient demographics.*

Characteristic	Value
Age (years)	55.88 ± 1.99 (range 38 – 80)
Body mass index (kg/m2)	24.14 ± 2.84
Axillary intervention method; n (%)	
Sentinel lymph node biopsy	4 (11.4%)
Axillary lymph node dissection with SLNB	31 (88.6%)
Lymphedema stage; n (%)	
0	11 (31.4%)
1	11 (31.4%)
2	13 (37.1%)
3	0 (0%)
Chemotherapy; n (%)	35 (100%)
Radiotherapy; n (%)	23 (89.28%)
Duration between surgery and BCRL onset (months)	10.97 ± 2.52
Duration between BCRL onset and TSGB (months)	23.47 ± 4.56

Data are presented as the mean ± standard deviation (range) or the number (percentage) of patients.
BCRL = breast cancer related lymphedema; TSGB = thoracic sympathetic ganglion block; SLNB = sentinel lymph node biopsy.

cording to the lymphedema stage and treatment period were assessed using the χ^2 test and Fisher's exact test. P values < 0.05 were considered statistically significant.

Results

The patient characteristics are summarized in Table 3. The mean patient age was 55.8 ± 1.99 years (range 38 – 80 years), and the mean BMI was 24.14 ± 2.84. All patients underwent mastectomy, and none underwent breast-conserving surgery. A total of 31 (88.6%) patients underwent axillary lymph node dissection (ALND) with sentinel lymph node biopsy, and 4 (11.4%) patients underwent sentinel lymph node biopsy alone. The most frequent diagnosis was stage 2 lymphedema (37.1%). The mean onset of BCRL after surgery was 10.97 ± 2.52 months, and the mean period between lymphedema onset and TSGB was 23.47 ± 4.56 months.

The arm circumference was significantly decreased at all locations 2 weeks after TSGB (P < 0.05). At 2 months after TSGB, the arm circumference remained significantly decreased at all locations (P < 0.05), except the wrist (P = 0.198). The arm circumference did not decrease significantly between 2 weeks and 2 months (Fig. 1). The LBCQ score was significantly decreased 2

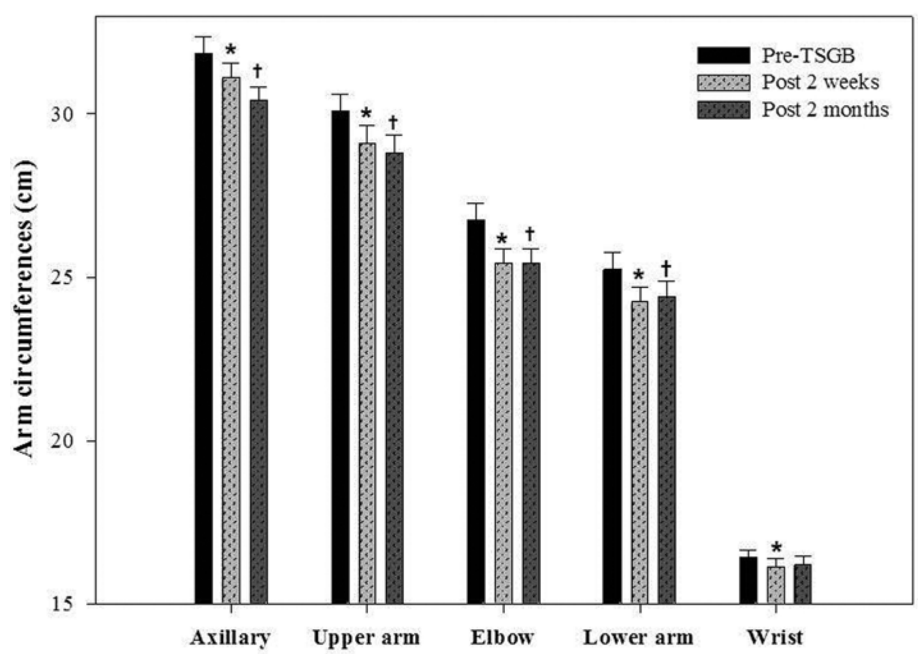

Fig. 1. *Arm circumference after TSGB. The arm circumference was significantly decreased at all locations, except the wrist, at 2 weeks and 2 months after TSGB. *P < 0.05, between pre-TSGB and 2 weeks post-TSGB: axilla, P = 0.016; upper arm, P = 0.020; elbow, P = 0.001; lower arm, P = 0.003; and wrist, P = 0.042. †P < 0.05, between pre-TSGB and 2 months post-TSGB: axillary, P = 0.004; upper arm, P = 0.024; elbow, P = 0.001; lower arm, P = 0.028; and wrist, P = 0.198.*

weeks after TSGB compared with pre-TSGB measurements ($P < 0.001$). There was no significant difference in the LBCQ score between 2 weeks and 2 months after TSGB (Fig. 2). The most improved item on the LBCQ was stiffness (83.33%), followed by heaviness (71.42%), which are indicators of skin resistance.

The TSGB showed good efficacy at 2 months in 23 (65.7%, effective TSGB group) of 35 patients. Patients with higher stages of lymphedema were associated more frequently with the effective TSGB group when compared to the non-effective group ($P = 0.045$; Table 4). At 2 months after TSGB, the arm circumference and LBCQ score were ≥ 50% improved in 9/11 (81.81%) stage 1, 10/13 (76.92%) stage 2, and 4/11 (36.36%) stage 0 lymphedema patients. The efficacy of TSGB did not differ significantly between patients who received early TSGB (≤ 6 month period between BCRL to TSGB) and those who received late TSGB (> 6 month period). Late TSGB showed good efficacy in 60.86% of patients ($P = 0.03$; Table 5).

Discussion

Of the 35 patients, 65.7 % patients showed good efficacy at 2 months after TSGB. Additionally, the TSGB efficacy was greater in patients with higher lymphedema stages. Also, late TSGB showed good efficacy.

Despite these findings, the hemodynamic mechanisms underlying the clinical effects of sympathetic blockade in BCRL patients remain in question. The relationship between the lymphatic and vascular system and the sympathetic nervous system is the likely source. The lymphatic system comprises deep and superficial lymphatic channels (31). The superficial lymphatic system within the skin includes the small lymphatic capillaries and serves as the primary drainage route. The deep lymphatic system, with its larger precollector vessels, collects and discharges waste debris and fluid from the superficial lymphatic system into the systemic circulation.

TSGB is thought to promote dilation of precollector vessels, which increases the drainage of excess fluids into the systemic circulation. Svensson et al (32) reported that mean axillosubclavian perfusion, measured by Doppler ultrasound, increased substantially in the swollen arm of a BCRL patient compared to that in the contralateral normal arm. They surmised that dilation of precollector vessels facilitated entry of excess interstitial fluid into the systemic circulation. Sympathetic control of the precollector vessels in BCRL patients is thought

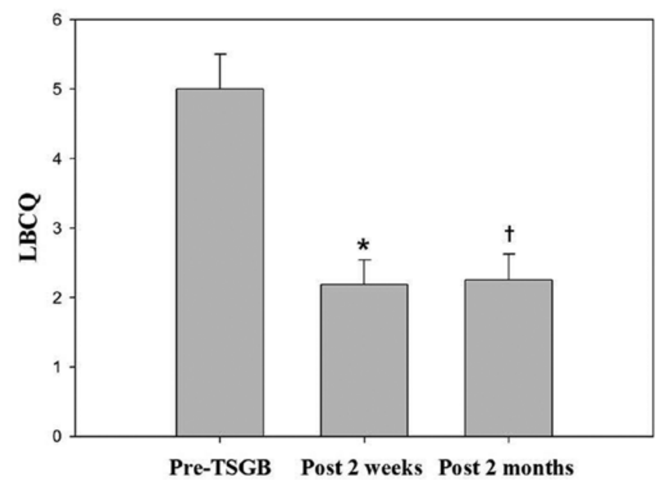

Fig. 2. *LBCQ scores after TSGB. The mean LBCQ score was decreased at 2 weeks and 2 months after TSGB. *P < 0.001, between pre-TSGB and 2 weeks post-TSGB; † P < 0.001, between pre-TSGB and 2 months post-TSNB.*

Table 4. *Efficacy of thoracic sympathetic ganglion block according to the lymphedema stage.*

Lymphedema stage	Non-effective TSGB group (n = 12)	Effective TSGB group* (n = 23)
0	7	4
1	2	9
2	3	10

*Significantly more high-stage patients formed the effective TSGB group than the non-effective TSGB group (P = 0.045). TSGB = thoracic sympathetic ganglion block.

Table 5. *Efficacy of thoracic sympathetic ganglion block according to time of procedure.*

Time of TSGB	Non-effective TSGB group (n = 12)	Effective TSGB group (n = 23)
≤ 6 months	10	9
> 6 months*	2	14

*TSGB performed > 6 months after BCRL onset showed good efficacy (P = 0.03). Patients were classified according the duration between BCRL onset and the TSGB procedure (≤ 6 month vs. > 6 month period). TSGB = thoracic sympathetic ganglion block; BCRL = breast cancer-related lymphedema.

to be normal as well (5). Another study examined the effect of TSGB on the superficial lymphatic system, which has received particular attention as a cause of BCRL (33). When interstitial fluid in BCRL patients is excessive, the small lymphatic capillaries enlarge to increase drainage, with the sympathetic response maintained throughout (34). Over time, the resistance of the lymphatic capillaries gradually decreases, which decreases skin elasticity and worsens lymphedema. Stanton et al (35) also reported that the mean perfusion measured per 100 mL of tissue (skin to subcutaneous) was decreased in the affected arm of BCRL patients. Thus, TSGB may also improve local vasodilation and relieve the fluid load on lymphatic capillaries.

The third role of TSGB may be in the direct interaction between the sympathetic and lymphatic systems. TSGB is used to treat nerve conditions including complex regional pain syndrome (CRPS), which also shows peripheral edema similar to BCRL. Sympatho-afferent coupling is a known contributor in the pathologic mechanism of CRPS (36). It involves activation of the sympathetic nervous system, which causes injury to the nociceptive nerve system. Several studies have reported remarkable efficacy of sympathetic nerve block or neurolysis in reducing edema caused by CRPS (21,37,38). The sympathetic nervous system is also thought to directly regulate lymphatic flow. After a chemical lumbar sympathectomy was performed in patients with CRPS affecting the lower extremities, the peripheral edema improved, and lymphatic flow increased on lymphoscintigraphy (39).

We observed that the efficacy of TSGB in patients with higher lymphedema stages was improved compared to the efficacy in patients with lower stage lymphedema. The patients with high stage disease showed visible edema, hardened and thickened skin, and decreased skin elasticity due to the accumulated interstitial debris and fluid. Sympathetic block reportedly decreases the skin resistance in patients with lymphedema (40), which may be involved in the improvement we observed in patients with severe lymphedema. We suspect that TSGB prevents aggravation of lymphedema symptoms such as fibrosis and cellulitis, and decreases skin resistance, which helps remove accumulated debris and fluid in the subcutaneous tissue and skin. The clinical effect of TSGB on decreasing the skin resistance was also evident in the stiffness and heaviness items of the LBCQ, which were markedly improved in our results.

Of the 35 patients, TSGB showed good efficacy for up to 2 months in 23 (65.7%) patients. However, the arm circumference and LBCQ score did not change significantly between 2 weeks and 2 months after the procedure. Thus, the persistence of the clinical effects of TSGB remains questionable. A recent report by de Godoy (41) showed that intense physical therapy 3 to 4 hours weekly decreased edema by an average 70% in BCRL patients over a one year period. These results appear to be consistent with our present findings. However, 3 – 4 hours per week of aggressive physical therapy requires far greater interaction between the medical team and patient than a single TSGB procedure. In addition, aggressive physical therapy still shows difficulties in maintaining the therapeutic effect after the initial improvement, similar to other conservative therapies. The advantage of the more invasive TSGB over conservative therapies is that it appears to be effective in high stage BCRL regardless of when the procedure is performed. Another advantage of TSGB is that clinical improvement is evident quickly, and it does not rely on patient compliance. Based on our findings, TSGB may be recommended in patients with high stage lymphedema and in patients who have not responded to conservative therapy. To maintain the clinical effects of TSGB long-term, a repeat nerve block, thermocoagulation, or neurolysis should be considered (18).

This study has some limitations. First, this study was not a randomized prospective controlled study and did not compare the therapeutic outcomes to those in a conservative treatment group. Regardless, TSGB shows promise for treating BCRL in this trial, and additional study is needed directly comparing TSGB with conservative treatment. Second, the period between BCRL onset and TSGB was long (23.47 ± 4.56 months, Table 3). As a result, we did not detect any significant impact of TSGB on BCRL, and the therapeutic efficacy of late TSGB was equal to that of early TSGB.

Conclusion

In conclusion, TSGB may decrease the arm circumference of BCRL patients by reducing lymphedema. TSGB can be considered as an alternative option in patients who do not respond to conservative treatments. However, additional clinical studies are needed to establish the efficacy of sympathetic blockade in treating patients with lymphedema.

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