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Prospective Study

The Effect of Lumbar Sympathetic Ganglion Block on Gynecologic Cancer-Related Lymphedema

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Background: Eighteen to 25% of patients after gynecological cancer treatment suffer from lower limb lymphedema (LLL) that decreases the quality of life of gynecological cancer survivors. Lumbar sympathetic ganglion block (LSGB) is widely used in practice for the evaluation and management of sympathetically mediated pain in the lower limbs. Several articles have suggested that sympathetic ganglion block could be an effective treatment for lymphedema.

Objectives: To investigate the effect of LSGB on patients with secondary lymphedema related to the treatment of gynecologic cancer, who do not respond to a conservative treatment.

Study Design: Prospective clinical study.

Setting: A single academic medical center, outpatient setting.

Methods: Eighteen patients with stage II lower limb lymphedema who did not response to the conservative treatment were recruited. The patients underwent fluoroscopy-guided LSGB 3 times at 2-week intervals. The circumference of the thigh and calf was measured in the upright position at the first visit and 2 weeks after each session of LSGB. The pain score of the lower limb was checked at the same time by a numeric rating scale (NRS) from 0 to 10. The patients were asked about their satisfaction with the procedure at the last follow-up visit. The Wilcoxon signed rank test was used for data analysis. Significance was accepted at a P-value less than 0.05/3.

Results: The circumferences of affected thighs and calves decreased from 56.38 ± 4.77 and 35.33 ± 3.51cm to 54.42 ± 5.27 and 34.41 ± 3.35cm, respectively, in a significant manner after 3 consecutive LSGBs ($P < 0.05/3$). The maximal decrease after the third LSGB was 4 cm in the thigh and 2cm in the calf. The pain score also showed a significant decrease after 3 consecutive LSGBs from 2.17 to 1.28. The tightness and heaviness of the affected limb decreased after the first LSGB in 15 patients (83.3%) and after the second LSGB in 2 patients (11.1%). Five of 18 patients (27.8%) answered that the result of the LSGB met their expectations, 10 (55.6%) answered they would undergo the same treatment for the same outcome, 2 (11.1%) answered they did not improve as much as they had hoped, and they would not undergo the same treatment for the same outcome, and only one patient (5.6%) answered the LSGB showed no effect.

Limitations: This study lacks a placebo control group and has only 18 patients. We did not evaluate the quality of life of the patients.

Conclusion: We suggest that LSGB can be one of the treatment options for patients suffering from LLL after gynecologic cancer treatment. Our result could provide a basis for a randomized controlled trial in future investigations. The pain physicians can play an important role as one of the multidisciplinary team for a comprehensive treatment of LLL.

Key words: Lumbar sympathetic ganglion block;gynecologic cancer;lymphedema

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Lymphedema is attributable to the result of protein-rich interstitial volume overload in contrast to edema, which results from an increased interstitial fluid volume that is enough to produce clinical swelling. It occurs from an inherent defect of the lymphatic system and secondary lymphatic damage such as surgery involving lymphatics, radiotherapy, chronic venous insufficiency, and recurrent infection (1). After gynecological cancer treatment, 18-25% of total patients suffer from lower limb lymphedema (LLL) (2,3). Once LLL occurs, it often becomes chronic and then causes a heaviness, tightness, and pain in the legs. This might eventually make it difficult for patients to perform their daily tasks and cause depression (3). The current standard treatment for LLL is a conservative treatment called complex decongestive physiotherapy (CDP) that consists of manual lymphatic drainage, compression therapy, exercise, and skin care. However, there is no definite method for patients who are not responsive to the conservative treatment.

Lumbar sympathetic ganglion block (LSGB) is widely used in practice for the evaluation and management of sympathetically mediated pain in the lower limbs including circulatory insufficiency, causalgia, and a variety of peripheral neuropathy (4,5). In 2001, Asai et al (6) reported that LSGB might be very effective in treating lymphedema following surgery for cervical cancer and radiation therapy via a single case report. In cases of lymphedema of the upper limb, the stellate ganglion block is known to produce a favorable outcome to breast cancer-related lymphedema (7,8). The aim of this study is to investigate the treatment effect of LSGB in patients who developed secondary lymphedema related to the treatment of gynecologic cancer that are not responsive to the conservative treatment.

Methods

After receiving the Institutional Review Board (IRB) approval and obtaining a written informed consent, we recruited 18 patients with stage II LLL (Table 1), defined by the International Society of Lymphology (9), who did not respond to the CDP and were referred to the pain clinic from the gynecologic oncology center. We excluded the patients with edema and pain from other causes, spine operation history, coagulopathy, hypovolemia, acute infection on the needle entry site, ongoing cellulitis of lower limb, and lymphedema of both limbs.

The patients underwent LSGB 3 times at 2-week intervals, thus receiving it in total for 6 weeks. The circumference of the thigh and calf was measured in the upright position by a single physician at the first visit and 2 weeks after each session of LSGB. The circumference of the thigh was measured at the level of the upper one-third between the anterior superior iliac spine and fibular head. The circumference of the calf was measured at the level of the upper third between the fibular head and lateral malleolus. The pain score of the lower limb was checked at the same time by numeric rating scale (NRS) from 0 to 10. The patients were asked about the degree of satisfaction with the procedure by a 4-point scale at the last follow-up visit: one point (the result met my expectations.); 2 points (I did not improve as much as I had hoped, but I would undergo the same treatment for the same outcome.); 3 points (I did not improve as much as I had hoped, and I would not undergo the same treatment for the same outcome); and 4 points (I am the same or worse than before treatment).

The patients were monitored with noninvasive blood pressure, electrocardiography, and pulse oximetry throughout the procedure. The 500 mL of crystalloid fluid was administered. The patients were placed in the prone position. The skin temperature probes (D-S10, EXACON SCIENTIFIC, Roskilde, Denmark) were attatched to the soles of both feet. The overlying skin was prepared and draped in a sterile fashion. After the needle entry point was identified at the lateral edge of L3 in a 25 to 30-degree oblique projection (10,11), 1% lidocaine was infiltrated at the needle entry site. The 21-gauge, 15-cm curved-tipped Chiba needle (Cook Inc., Bloomington, IN, USA) was introduced at an angle

Table 1. *The stage of the lymphedema by 2009 Consensus Document of the International Societyof Lymphology (9).*

Stage	Description
Stage 0	Swelling is not evident despite impaired lymph transport
Stage I	An early accumulation of fluid relatively high in protein content which subsides with limb elevation
Stage II	Limb elevation alone rarely reduces tissue swelling and pitting is manifest. Late in Stage II, the limb may or may not pit as excess fat and fibrosis supervenes.
Stage III	lymphostatic elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, further deposition of fat and fibrosis, and warty overgrowths have developed.

that allows arrival at the anterolateral aspect of the L3 vertebral body margin via a tunnel vision technique under fluoroscopic guidance. If the needle contacted the side of the L3 vertebral body, the C-arm was rotated to the lateral direction and the needle was advanced along side the vertebral body by the loss of resistence syringe until the retroperitoneal space was reached. The water-soluble contrast medium was injected to check the correct needle position (Fig. 1). Ten mL of 0.375% ropivacaine (Astra Zeneca Pty Ltd., New South Wales, Australia) was injected slowly. The surface temperature was measured for 30 minutes after the procedure and the vital signs and possible complications were monitored for an hour in the recovery room. The LSGB was considered successful when the temperature of the ipsilateral side was increased by more than 2°C (12). If the LSGB was considered to be unsuccessful, the data of the patient was excluded from the statistical analysis.

Statistical Analysis

All the analyses were computed using SPSS 18.0 (Statistical Product and Service Solution) (SPSS Inc., Chicago, IL). The Wilcoxon signed rank test was used for data analysis. The data collected after each session of LSGB were compared with the baseline data. Therefore, statistical significance was accepted as $P < 0.017$. Data was expressed as mean ± SEM.

Results

In the current study, 18 patients were enrolled and their demographic characteristics are listed in Table 2. These patients were composed of 12 cases (66.7%) of cervical cancer, 4 cases (22.2%) of endometrial cancer, and 2 cases (11.1%) of ovarian cancer. In addition, 17 patients underwent surgery with bilateral pelvic lymph node dissection and one did radiotherapy without surgery. Moreover, of the 18 patients in total, 12 (66.7%) underwent radiotherapy. At the first pain clinic visit, the mean age was 57.2 ± 14.25 (range, 32-79) years and the mean duration of LLL was 21.78 ± 22.82 (range, 6-96) months. The mean interval from gynecologic cancer treatment to the onset of LLL was 12.28 ± 18.67 (range, 1-60) months.

The surface temperature on the ipsilateral side was increased by 2°C after each session of LSGB in all the patients. The initial circumferences on the affected thighs and calves were 56.38 ± 4.77 and 35.33 ± 3.51 cm, respectively, and those on the non-affected side were 52.19 ± 5.55 and 33.28 ± 2.50 cm, respectively. There was no significant difference in the circumference of the 2 points until the second session of LSGB. Following the 3 consecutive LSGBs, the circumference was significantly decreased to 54.42 ± 5.27 and 34.41 ± 3.35 cm in the corresponding order ($P < 0.05/3$) (Fig. 2). The maximal decrease after the third session of

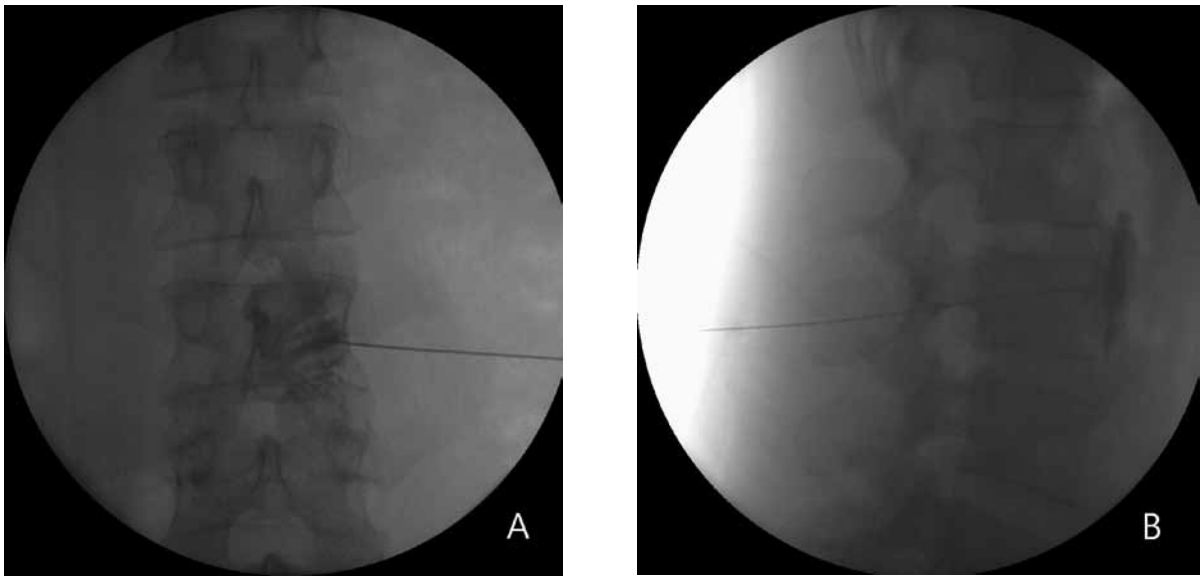

Fig. 1. *Fluoroscopic images during lumbar sympathetic ganglion block. The anteroposterior (A) and lateral (B) images show linear spread of contrast agent in the longitudinal axis without any lateral or posterior extension.*

LSGB was 4 cm in the thigh and 2 cm in the calf. The initial pain score by the NRS ranged from 0/10 to 7/10. Of total patients, 6 had no pain and 12 had pain scored at the level of average 2.17 from 0 to 10 by the NRS at baseline. The pain score also showed a significant decrease from 2.17 to 1.28 after the 3 consecutive LSGBs (Fig. 2). Table 3 shows individual data. The tightness and heaviness of the affected limb was decreased after the first session of LSGB in 15 patients (83.3%) and after the second session of LSGB in 2 patients (11.1%). Five of 18 patients (27.8%) responded that the results of the LSGB met their expectations, 10 (55.6%) said they would undergo the same treatment for the same outcome, 2 (11.1%) said they did not improve as much as they had hoped, and they would not undergo the same treatment for the same outcome, and only one patient (5.6%) said the LSGB showed no effect.

Discussion

Our study showed LSGB could be one of the treatment modalities for patients suffering from LLL after gynecologic cancer treatment. The lymph drainage system runs in parallel with the venous one. The lymph vessels drain large proteins, toxins, wastes, bacteria, and cancer cells. In addition, about 10-20% of the fluid circulates throughout the body. The lymphatic fluid moves through the lymphatic capillaries which drain into the larger precollector vessels. The precollectors then drain into the larger collecting lymphatic vessels and the lymph nodes sequentially. Damage to lymphatic vessels by surgical procedure and radiotherapy and/or lymph node dissection interferes with the lymphatic system's ability to remove the fluid from the tissues, resulting in swelling of the soft tissue. Further accumulation of protein-rich fluid results in decreased oxygen tension, inflammation, and fibrosis (13). Therefore, once LLL occurred, prompt treatment should be given. The lymph drainage is subject to the compressive forces along lymphatics, such as movement of the tissues that contain lymphatics, contraction of muscles, and adjacent artery pulsations. The method for increasing the efficacy of this mechanism is complex decongestive physiotherapy (CDP), which is the current standard of care for lymphedema by physiotherapist. In the article about the efficacy of the CDP published by Liao et al (14), the percentage of excess volume was decreased from 32.9 ± 18.4% to 18.8 ± 16.7% after 10-24 sessions of CDP. This indicates that the patients still have an excess volume of 18.8 ± 16.7% on average as compared with the non-affected side after the CDP. Several other treatments such as heat therapy achieved by hot immersion, microwave, eletromagnetic irradiation, and autologous lymphocyte injection have also been reported in the literature, all of which are challenging (15,16). Lymph-venous shunt or debulking surgery can be held for patients who are unresponsive to other treatments. Unfortunately, there are also risks of perioperative morbidity of cancer patients and problems with wound healing (1).

The mechanism of action in LSGB is not fully understood in the current study. We assumed that the effects of LSGB are based on the following 3 factors:

1) A sympathetic ganglion block increases not only the arterial flow but also the venous flow (17). Increased venous flow would reduce the burden on lymphatics to drain the excessive fluid in the tissue.

Table 2. *Demographic characteristics*.

Variable	N (%)	Mean ± S.D. (Range)
Patient	18	
Cervical cancer	12 (66.7%)	
Endometrial cancer	4 (22.2%)	
Ovarian cancer	2 (11.1%)	
Age		57.2 ± 14.25 (32-79)
Height (cm)		156.4 ± 5.3 (140-163)
Weight (kg)		58.5 ± 8.8 (42-70)
Radiotherapy		
Yes	12 (66.7%)	
No	6 (33.3%)	
Postoperative lymphedema onset (months)		12.28 ± 18.67 (1-60)
Lymphedema duration (months)		21.78 ± 22.82 (6-96)

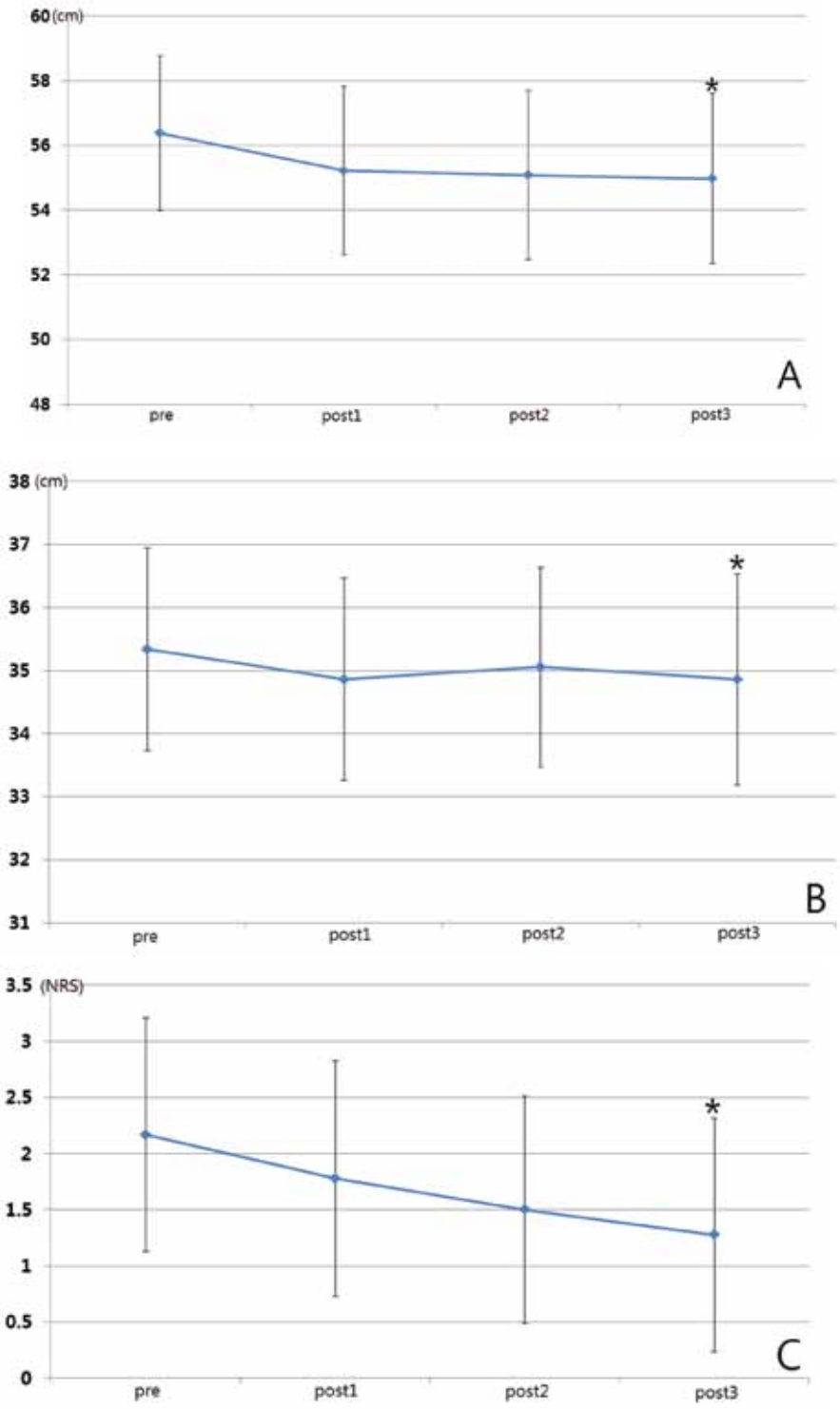

Fig. 2. *Circumferences of thighs and calves and NRS of pain. Circumferences of the thighs (A) and calves (B) decreased after 3 consecutive LSGBs in the significant manner. Pain score by NRS (C) also decreased significantly after 3 consecutive LSGBs. pre: baseline, post1: 2 weeks after the first session of LSGB, post2: 2 weeks after the second session of LSGB, post3: 2 weeks after the third session of LSGB, NRS: numeric rating score. *: P < 0.05/3 versus pre-LSGB.*

Table 3. *The patient data showing circumferences of thighs and calves, and pain score. T: circumference of thigh, C: circumference of calf, NRS: numeric rating score, pre: baseline, post1: 2 weeks after the first session of LSGB, post2: 2 weeks after the second session of LSGB, post3: 2 weeks after the third session of LSGB. * : P < 0.05/3 versus pre-LSGB.*

Patient No.	T-pre	T-post1	T-post2	T-post3* (cm)	C-pre	C-post1	C-post2	C-post3* (cm)	NRS-pre	NRS-post1	NRS-post2	NRS-post3*
1	55.5	52	53.5	54	33	33	33	33	5	4	3	2
2	46	43	44	43	31	29	30.5	29	2	1	1	0
3	62	61	62	61	43	42	42	42	3	3	1	1
4	57	57	54	55	38	37.5	37	36.5	1	0	0	0
5	54	53	52	52	34	33	33	33	3	2	1	1
6	54	53.5	54	54	38	37	38	38	7	8	8	8
7	60	59	60	60	41	41	41	41	3	2	2	2
8	66	65	64	64	33	33	32.5	33	4	4	4	4
9	59	59	58	58	38	38	37.5	37.5	0	0	0	0
10	53	52	51	51.5	34	33	33	32.5	0	0	0	0
11	63	62.5	62.5	62	38	38	39	39	0	0	0	0
12	58	57	56	56	35	34	35	35	4	2	1	0
13	53.3	52	53	53	30.5	31	31	31	2	2	2	2
14	55	53	54	54	34.5	34	34.5	34	4	3	3	3
15	50	49	47.5	46	31	31	31	30	0	0	0	0
16	59	58	59	59	37	37	37	37	0	0	0	0
17	54	53	52	52	35	34	34	34	0	0	0	0
18	56	55	55	55	32	32	32	32	1	1	1	0

2) LSGB may affect the immune system of the lymphedematous limbs. In support of this, Yokoyama et al (18) reported that the sympathetic nerve block modulated the immune response. LSGB also raises the skin temperature. Frank et al (19) reported the temperature of the great toe, calf, and thigh was increased from 23.6 ± 0.6, 30.3 ± 0.4, and 31.8 ± 0.3 to 33.8 ± 0.9, 32.6 ± 0.5, and 33.6 ± 0.5, respectively. Meanwhile, heat therapy is one of the treatments for LLL and Liu et al (16) showed a regression of the inflammatory changes in lymphedematous skin following regional heat therapy. It caused a near resolution of perivascular cellular infiltration, disappearance of the lymph lakes, and the dilatation of capillaries. In our study, the histological change after LSGB was not evaluated.
3) The peripheral lymphatics are under autonomic control. Howarth et al (20) described that peripheral lymphoscintigraphy in CRPS type 1 patients with lower limb swelling revealed a delay in the lymphatic flow in the affected limb, which turned to rapid and symmetrical lymphatic flow in the lower limbs after LSGB. This suggests that peripheral lymphatic function is controlled by the autonomic nervous system, which can be modulated by LSGB.

In our study, 6 (33.3%) of 18 patients had no pain and the others (66.7%) had pain at the level of average 2.17 from 0 to 10 by the NRS before initiation of LSGB. A chief complaint of patients with LLL is discomfort such as legs feeling heavy and/or tight resulting from swelling rather than pain itself. It has been reported that 20-41% of patients with LLL experienced pain in their legs (3). Because pain is usually mild and secondary to swelling itself, we assume that physicians should concentrate on the management of swelling and then the pain would be relieved as swelling is controlled.

There were no complications related with LSGB

in this study. The most common complication is the genitofemoral neuralgia with an incidence of 4% after a single needle technique. Other complications include necrosis of the psoas muscle, injury of kidney and ureter, bleeding, hypotension, and impotence (4). Serious complications with LSGB are rare and the procedure can be usually performed at the outpatient unit.

We performed LSGB every 2 weeks, thus doing it 3 times in total for 6 weeks, and then evaluated the outcomes 2 weeks after each session of LSGB. However, the onset and peak effect of LSGB and the duration of the effect for LLL have not been established. We first reported the effect of LSGB for LLL. There is no consensus about the interval between the procedures for chronic pain management in the literature. In our institution, we perform LSGB from twice a week to once a week or every 2 weeks depending on the degree of pain improvement in chronic pain patients. Our study showed a significant improvement in swelling after the third session of LSGB, while 15 of 18 patients presented with a decreased heaviness and tightness after the first session of LSGB. The duration of the peak effect for LLL may be shorter than 2 weeks and the cumulative effect on consecutive procedures is also possible. If LSGB is effective but the duration of the effect is not satisfactory, radiofrequency lesioning and/or chemical neurolysis of the sympathetic ganglion can be considered.

There are several limitations in this study as shown below:

1) Our study enrolled a small number of patients and it is not a placebo-controlled trial. We did not have a placebo-controlled group because we considered it unethical to give a placebo-injection to cancer survivors. Despite the significant results of the current study, we could not recommend LSGB with strong evidence. Further randomized, controlled studies are therefore warranted to establish LSGB as an effective modality for LLL.
2) We focused only on circumferences of the thigh and calf to evaluate the efficacy of LSGB. Despite problems of reliability, the measurement of the circumference has been the method that is used the most frequently to evaluate the efficacy of the treatment, which is based on the convenience of the method, the low cost, and an ability to generate quantitative data (21). The volumetric measurement, lymphangiography of the limbs, and assessment of quality of life and psychological aspect may be useful for comprehensive evaluation. Further large-scale, long-term, placebo-controlled, follow-up studies are warranted to investigate the optimal interval and duration of treatments.

Conclusion

We suggest that LSGB can be one of the treatment options for patients suffering from LLL after gynecologic cancer treatment. Our result could provide a basis for a randomized controlled trial in future investigations. Pain physicians can play an important role as one of a multidisciplinary team for the comprehensive treatment of LLL.

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