Recent Advances in Medical Treatment for Lymphedema

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As medical treatment for lymphedema, combined physical therapy with guidance regarding daily living is recommended. Recently, training has been conducted on a nationwide scale, and this therapy has gradually and commonly been employed. This therapy consists of daily living guidance to prevent edema deterioration, skin care, manual lymph drainage, compression therapy, and exercise therapy. The number of hospitals in which all procedures can be adequately performed is limited. There is no treatment to completely cure lymphedema. Patients’ self-care based on the contents of treatment is essential for relieving symptoms. (*English Translation of J Jpn Col Angiol 2008; 48: 167-172.)

Keywords: lymphedema, medical treatment, combined physical therapy, intermittent pneumatic compression

INTRODUCTION

It is difficult to completely cure lymphedema. Chronic conditions are more difficult to reduce. As both health care professionals and patients often abandon positive treatment, the absence of care leads to a severer condition in some patients. However, appropriate medical treatment early after the onset of lymphedema and guidance for patients’ self-care may prevent the deterioration of lymphedema, as demonstrated for diet/exercise therapies in patients with lifestyle-related diseases such as diabetes. To instruct patients with lymphedema, health care professionals must acquire knowledge regarding lymphedema treatment. However, currently, few physicians are familiar with the pathogenesis and treatment of lymphedema.

Primary treatment recommended by the International Society of Lymphology1) is presented in Table 1. Concerning surgery, with the recent, widespread application of microscopic lymph vessel-vein anastomosis, its efficacy has been reported. However, there is no recently advanced effective medical treatment technique. For medical treatment, combined physical therapy (CPT) is primarily performed. Internationally, it is employed as standard treatment. However, it has not commonly been selected in Japan; considering this, CPT may be the latest treatment in Japan. At the Lymphedema Training Committee of the “Cancer Rehabilitation Training” program organized by the Ministry of Health, Labour and Welfare in 2009, “complex treatment (conservative treatment involving CPT)” consisting of CPT and guidance regarding daily living was established as standard treatment for lymphedema.

In this article, we introduce the entity of lymphedema treatment, as well as medical treatment with CPT. We also review therapies described in the literature.

ENTITY OF LYMPHEDEMA TREATMENT

Lymphedema is classified into two types: primary lymphedema associated with congenital lymph vessel dysplasia/dysfunction in the absence of etiological factors, and secondary lymphedema resulting from lymph vessel injury related to surgery with lymph node dissection or radiotherapy/chemotherapy for malignant disorders. Regardless of these types, peripheral lymph is not transported from sites with lymph vessel hypo-function, leading to lymphedema through the subcutaneous tissue retention of inter-tissue fluid. Lymphedema is characterized by such edema involving subcutaneous tissue.
Thus, for lymphedema treatment, it is necessary to promote the development of a collateral pathway from the affected toward the normal lymphatic system, decrease leakage from capillaries to inter-tissue spaces, and inhibit the gravity-related transfer of inter-tissue fluid to the periphery of an affected limb. In particular, it is important to control the subcutaneous tissue of an affected limb. Furthermore, prolonged edema may induce subcutaneous-tissue fibrosis or adipose-tissue outgrowth. Therefore, treatment should be started early after onset, when tissue changes are slight.

**CPT**

In the lymphedema-associated literature, CPT is described as complex/complete decongestive therapy (CDT) or complex decongestive physiotherapy (CDP). Many studies have reported its efficacy. Furthermore, the number of reports on its efficacy in Japan has slightly increased. In Europe and the United States, there are several hospitals with beds in which CPT is performed. However, in Japan, CPT is not covered by health insurance. In addition, there are few hospitals to which patients can be admitted.

The purpose of this treatment is to eliminate lymph and inter-tissue fluid retention in an affected limb through skin care, manual lymph drainage (MLD), compression therapy, and exercise therapy under compression, as shown in Table 2. The detailed contents of individual therapies are described in other articles. In this article, we introduce basic constitutive matters and their outlines.

(1) **Skin care**

For lymphedema treatment, it is most important to avoid the onset/deterioration of edema in patients’ daily lives. Excessive exercise and travelling may cause edema. However, lymphedema rapidly deteriorates after inflammation such as cellulitis. In affected limbs, the lymph vessel function is damaged, and bacterial infection may become severer. Inflammation enhances capillary permeability, leading to the deterioration of edema.

To prevent affected-limb infection, it is important to avoid skin injury and clean the skin. When edema of the fingers or toes is present, inter-finger/toe wetness may induce trichophytia. Caution is needed.

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### Table 1 Treatment of lymphedema

<table>
<thead>
<tr>
<th>Non-operative Treatment</th>
<th>Operative Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Physical therapy</td>
<td>1. Microsurgical procedures</td>
</tr>
<tr>
<td>a. Combined physical therapy (CPT)</td>
<td>a. Reconstructive methods</td>
</tr>
<tr>
<td>b. Intermittent pneumatic compression</td>
<td>b. Derivative methods</td>
</tr>
<tr>
<td>c. Massage alone</td>
<td>2. Liposuction</td>
</tr>
<tr>
<td>d. Wringing out</td>
<td>3. Surgical resection</td>
</tr>
<tr>
<td>e. Thermal therapy</td>
<td></td>
</tr>
<tr>
<td>f. Elevation</td>
<td></td>
</tr>
</tbody>
</table>

2. Drug therapy
   a. Diuretics
   b. Benzopyrones
   c. Antimicrobials
   d. Filariasis
   e. Mesotherapy
   f. Immunological therapy
   g. Diet

3. Psychosocial rehabilitation

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### Table 2 CPT

1. Skin care
2. Manual lymph drainage (MLD)
3. Compression by multi-layered bandage-wrapping or compression garments
4. Exercise

CPT: combined physical therapy
(2) MLD

In this procedure, inter-tissue fluid and lymph retaining in the subcutaneous tissue of an affected limb are slowly induced to the normally functioning lymphatic system with soft stimuli. Treatment is focused on the subcutaneous tissue of an affected limb. “Soft compression” transmitting from the skin surface to the entire subcutaneous tissue is appropriate. Strong forces such as digital compression and massage are not necessary.

Lymph should always be induced from the affected limb toward normal lymph nodes. The detailed procedures are described in another article. However, it is important to treat affected limbs involving the trunk. Before affected-limb treatment, deep lymphatic flow should be promoted, and the trunk involving the central end of the affected limb must be massaged. Sites of marked fibrosis or sclerosis are sometimes more strongly massaged compared to other areas.

A study indicated the efficacy of simple lymphatic drainage, which refers to guidance-based self-MLD. In our hospital, patients are also instructed to perform CPT as self-care. However, its effects are insufficient in some patients due to their ages and natures.

(3) Compression therapy

For CPT, compression therapy is the most important. Even when MLD is thoroughly performed, edema does not reduce in the absence of compression. In contrast, when compression is adequately carried out despite insufficient MLD, edema reduces. Inadequate compression in the topical area of the affected limb may deteriorate edema, although compression therapy is important. Caution is needed.

The reasons for affected-limb compression include the inhibition of leakage from capillaries through an increase in the subcutaneous tissue pressure, prevention of lymph regurgitation from an injured lymph vessel to subcutaneous tissue, prevention of gravity-related tissue fluid transfer, and improvement of venous return.

For compression therapy, elastic garments (elastic stockings/sleeves/gloves) and bandages are employed. Individual tools are selected in accordance with the condition. In patients with dermal sclerosis in the chronic phase and those with marked articular ring constrictions related to a severe status, adequate elastic garments must be introduced after treatment with elastic bandages. When only elastic garments are employed, excessive compression in the articular region may promote dermal sclerosis in some cases; improvement in edema may not be achieved.

Compression with elastic bandages should be performed at an appropriate pressure so that daily activities are not restricted. In addition, the periphery of the affected limb should be rolled with a bandage at a maximum pressure so that the bandage gradually loosens toward the central side.

Compression with elastic garments is essential for maintaining lymphedema-reducing effects. The size of elastic garments should be determined in accordance with the affected limb’s circumference. The pressure must also be established (standards: ankle, 30 mmHg; and wrist, 20 mmHg; an optimal pressure should be reviewed based on the affected limb’s condition). As excessive elastic garment-related compression of the affected limb leads to the deterioration of edema, stocking-type garments are employed in many patients with edema of the lower limbs, including unilateral-limb edema. In those with upper-limb edema, sleeves with gloves are also used. The characteristics of elastic garments vary; edema improvement depends on the type of garment. Therefore, health care professionals must select elastic garments appropriate for affected limbs based on their experience.

Compression therapy is contraindicated for conditions with acute inflammation such as cellulitis, congestive heart failure, and acute-phase venous thrombosis. This therapy must also be carefully selected in patients with sensory paralysis, neuroparalysis, or occlusive peripheral artery disease (contraindicated for limbs with severe ischemia).

Concerning compression therapy with elastic bandages, it is also possible to instruct patients to perform self-care. However, this is difficult in some patients, as described for MLD.

(4) Exercise therapy under compression

Exercise under adequate compression of the affected limb is effective for lymphedema. When the affected limb is compressed on the skin surface, muscular movement-related pumping actions are added to the subcutaneous tissue, showing massage effects through intermittent increases in the tissue pressure. Leakage from capillaries is inhibited, leading to edema improvement. Furthermore, the lymph vessel pressure improves the valve function, promoting lymph induction. However, excessive exercise may cause inflammation. It should be avoided.
Patients with edema of the lower limbs should do exercise to move each joint, such as walking. Even when walking is difficult, the ankles and knees should be flexed/extended while on a bed. In those with upper-limb edema, repeated gripping movement and flexion/extension/pronation/supination of each joint are effective.

(5) CPT as palliative care

The progression of malignant disorders also induces edema. In some cases, CPT is also performed to relieve symptoms. In such cases, edema improvement is not achieved. However, when patients wish to reduce edema due to the edema-related reduction of activities of daily living (ADL), treatment is performed to relieve symptoms.

For CPT as a part of palliative care, affected limbs are compressed with elastic bandages more loosely in comparison with general lymphedema treatment in many patients after evaluating the general condition, such as the progression of cancer and presence or absence of pleural effusion/ascites. For MLD, low-level stimuli should be given under a weak pressure in a short duration. This must be conducted in accordance with patients’ conditions. In particular, skin contact on MLD exhibits supportive effects including mental actions; this procedure is useful for palliative care. It must be considered that excessive elastic garment-related compression deteriorates cancerous pain.

Other Medical Treatments

We introduce other treatments presented in Table 1. However, there are only a few high-evidence-level reports.

(1) Elevation

Simple elevation of the affected limb reduces swelling in some patients with initial-phase lymphedema. However, edema deteriorates during the daytime, when the affected limb is suspended. Therefore, elastic garment-reduced conditions should be maintained.

(2) Intermittent pneumatic compression

In this procedure, a cuff is worn on the affected limb, and air is intermittently infused from the periphery of the affected limb toward the center for compression. Its therapeutic effects remain controversial. However, treatment with this system is performed in most hospitals in which CPT has not been introduced to treat lymphedema. The limitation of this system is the order of compression. Edematous fluid at the periphery is transported to the central region of the affected limb, which may deteriorate edema in the central region. Therefore, MLD must be additionally conducted in the central region of the affected limb and trunk before and after this procedure. Furthermore, strong compression for a long duration should be avoided, considering the risk of lymph vessel injury.

This procedure does not replace MLD, and should be recognized as an MLD-assisting method. Health care professionals must understand this. Furthermore, compression with elastic garments/bandages after the use of this system is essential.

(3) Massage therapy

This therapy refers to massage as single therapy. Few studies have examined the effects of classical massage or rubbing. Their effects may be limited because the affected limb is not compressed, differing from CPT. Excessive partial compression may damage lymph vessels. This is contraindicated.

(4) Diet therapy

Factors deteriorating lymphedema include obesity. It is important to maintain an “optimal body weight.” In our hospital, body weight control reduced lymphedema in some obese patients, whereas marked obesity deteriorated lymphedema in others. Although there is no specific diet therapy, the combination of “caloric restriction” and a “guidance-based exercise program” for obese patients in combination with CPT is more useful for reducing swelling of the affected limb. Furthermore, excessive salt/water ingestion should be avoided, as indicated for other types of edema.

(5) Drug therapy

① Diuretics: Diuretics promote the excretion of whole-body water as urine. Therefore, in the initial phase, these agents are effective in some patients. However, lymphedema treatment is limited, and these agents may induce body-fluid/electrolyte imbalance. Long-term administration should be avoided.

② Benzopyrones: Oral benzopyrones may hydrolyze tissue protein while activating the lymph transport route,
promoting its absorption. In Japan, a melilous extract (Esberiven) has been employed, but is not commercially available. However, this agent does not replace CPT. A long interval is required until the appearance of its effects. Long-term or massive therapy may cause hepatopathy.

③ Antimicrobial agents: Antibiotics are employed to treat acute infectious inflammation of affected limbs. Inflammation is characterized by flare, swelling, pain, fever, and septic shock, which is rare. After confirming hematological findings of inflammation, such as leucocytosis and positive reactions to C-reactive protein (CRP), broad-spectrum antibiotics, including penicillins and cephems, should be administered, and CPT must be discontinued for resting. Antibiotic therapy should be discontinued based on hematological data to avoid incomplete treatment or excessive administration.

④ Traditional Chinese herbal medicines: Various traditional Chinese herbal medicines are employed. However, these agents may not exhibit any marked effects.

(6) Immunotherapy

For auto-lymphocyte arterial injection therapy, autologous lymph activated and infused into arteries may activate macrophages in the affected-limb interstitial tissue, decomposing an excess level of protein. However, its persistent effects remain to be clarified.

(7) Gene therapy

In patients with primary lymphedema, gene abnormalities were reported. Gene therapy has also been examined. Recent studies reported hepatocyte growth factor (HGF)-related neovascularization. Currently, a basic study regarding lymph vessel neogenesis therapy with HGF is being conducted. Clinical studies of HGF were carried out to investigate peripheral vascular growth in limbs with severe ischemia. HGF-related lymph vessel neogenesis in a rat breast cancer model was reported. Furthermore, the motor ability of lymph vessels was maintained. In the future, a clinical study will be conducted.

Strategies for the Widespread Application of Lymphedema Treatment

As marked changes in medical environments regarding lymphedema treatment in Japan, the “lymphedema guidance/management fee” and “medical benefit for elastic garments” became covered by health insurance when medical fees were revised in 2008. Since 2008, a clinical path to lymphedema treatment and leaflets for guidance have been prepared by the Anti-Cancer Global Strategy Research Business Team, Ministry of Health, Labour and Welfare, and published on the “Cancer Information Service” homepage. Since 2009, training for “lymphedema guidance” with cancer rehabilitation, as described above, has been performed so that the instructors’ level meets the widespread application of CPT for lymphedema. In the future, an authorization/qualification system for health care professionals engaged in lymphedema treatment will be established.

Conclusion

As lymphedema is associated with irreversible changes in the lymphatic system, it is difficult to develop radical treatment. In particular, it is more difficult in chronic-phase patients with dermal sclerosis and an increase in the volume of fibrous and adipose tissues. Recent advances in medical treatment are not marked. Conventional CPT is still primarily selected. However, recently, education of health care professionals responsible for treatment early after onset and self-care guidance for patients have been emphasized. In Japan, CPT has not yet been applied on a nationwide scale. There is no system for all lymphedema patients to undergo sufficient treatment. However, in the future, a system for lymphedema patients to similarly receive guidance/treatment throughout Japan should be established, as introduced for guidance regarding diet/exercise therapies for lifestyle-related diseases.

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