RESEARCH ARTICLE

Current Treatments for Breast Cancer-Related Lymphoedema: A Systematic Review

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Abstract

Background and objective: Breast cancer-related lymphoedema (BCRL) is a disabling complication with long term impact on quality on life after breast cancer treatment. Its management remains a major challenge for patients and health care professionals; the goal of this overview was to summarize effects of different treatment strategies for patients with BCRL. Methods: A thorough search was undertaken to allow a systematic review or meta-analysis of treatments for BCRL. Two investigators independently selected studies and abstracted the data. Results: Combined physical therapy (CPT) with different combinations of surgery, oral pharmaceuticals, low-level laser therapy, weight reduction, mesenchymal stem cell therapy, kinesio tex taping, and acupuncture might be effective in reducing lymphoedema, but exercise demonstrated no obvious benefit. The results of direct comparisons showed CPT might be more effective than standard physiotherapy (ST). Manual lymphatic drainage (MLD) may not offer additional benefits to ST for swelling reduction, but could facilitate compression bandaging. MLD seemed to have similar effects with self-administered simple lymphatic drainage (SLD) or using an intermittent pneumatic compression pump (IPC). IPC might also not be associated with additional effectiveness for CPT. Efficacy of stem cell therapy vs. compression sleeve or CPT, as well as the effects of daflon and coumarin could not be established. Conclusion: Although many treatments for BCRL might reduce lymphoedema volume, their effects were not well established. The quality of many of the original studies in the included reviews was not optimal, so that in future randomized control trials are a high priority.

Keywords: Breast cancer- lymphoedema- systematic review- combined physical therapy

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Introduction

Lymphedema is a condition characterized by excess accumulation of protein-rich tissue fluid in extravascular interstitial spaces that causes oedema, chronic inflammation with pain, and tightness and heaviness being felt in the arm (Földi et al., 1989; Chan et al., 2010; Finnane et al., 2015). Impairment of the lymphatic system reduces the capacity to transport macromolecules including protein back into the blood vascular system, resulting in swelling (Földi et al., 1989; Finnane et al., 2015). Breast cancer-related lymphoedema (BCRL) is a disabling complication with long term impact on quality on life after breast cancer treatment (Goker et al., 2013). Risk factors contributing to the development of BCRL include axillary lymph node dissection, postoperative complications, hypertension, high body mass index, chemotherapy and radiotherapy (DiSipio et al., 2013; Goker et al., 2013; Hidding et al., 2014; Zhu et al., 2014). The weighted average of BCRL incidence was 16.6% (95% CI 13.6%–20.2%) and it was about four times higher in women who had an axillary lymph node dissection (19.9%, 13.5%–28.2%) than that in those who had sentinel-node biopsy (5.6%, 6.1%–7.9%) (DiSipio et al., 2013). BCRL is associated with not only feelings of discomfort and heaviness, functional limitation, disfigurement, physio-psychological distress (anxiety or depression), an elevated risk of recurrent infection, but also negative effect on quality of life (Chan et al., 2010; Cheifetz et al., 2010; Fu et al., 2013; Zhu et al., 2014). Its impact on quality of life becomes more substantial as survival after breast cancer diagnosis increases (Goker et al., 2013).

Management of BCRL remains a major challenge for patients and health care professionals (Fu, 2014). There were several treatment strategies that aim to reduce swelling, prevent progression, reduce risk for infection, and alleviate associated symptoms (Fu, 2014; Finnane et al., 2015). These strategies include complete decongestive therapy (Lasinski et al., 2012), low level laser therapy (Bisaia Raposo Mourao e Lima et al., 2014), exercise (Kwan et al., 2011), massage (Pan et al., 2014), surgery (Leung et al., 2015), etc, but there were no overviews

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Material and Methods

A thorough search was undertaken, including both computerized and manual searching, to identify all relevant literatures. We searched the Cochrane Library, PubMed, EmBase, ISI Web of Knowledge using the search term (lymphedema or lymphoedema or elephantiasis or swelling or edema or oedema) AND (“breast cancers” OR “breast cancer” OR “breast neoplasm” OR “breast neoplasms” OR “breast tumor” OR “breast tumors” OR “breast adenocarcinoma”) in title, abstract or keyword. All searches were from the inception of the databases up to date as of 31 December 2015. Searches were limited to human subjects and no language restrictions. We also performed a manual search of references cited by the original published studies and relevant review articles.

We included systematic review or meta-analysis about the treatments for BCRL. Participants were restricted to patients with BCRL. The interventions were not limited, which included all available interventions for BCRL. The outcomes we estimated were lymphedema volume, lymphedema-related symptoms of the affected limb-pain, heaviness, tightness and quality of life. If there were several systematic reviews that reported the same topic, we compared the differences among them and reviewed the most comprehensive one.

Two investigators (Lun Li and Quan Wang) reviewed independently all titles and abstracts for relevant systematic review/meta-analysis, resolved differences by consultation with a third reviewer (Jinhui Tian). Two investigators (Lun Li and Jinhui Tian) independently extracted data and resolved differences by discussion. The data extraction form summarized key characteristics of systematic review, including information on participants, interventions, outcomes and author’s conclusions.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2010), which specifies four levels of quality: high, moderate, low, and very low quality evidence after evaluating five factors (study quality, consistency, directness, precision, and reporting bias) which may lead to its downgrading and three factors (large effects, all plausible residual confounding and dose-response gradient) which can lead to upgrading quality of evidence (Nasser and Fedorowicz, 2011). We produced Summary of Findings (SoF) tables, which would present the main findings of SR and provide key information concerning available data on all outcomes, the effect of the intervention, the quality of evidence.

Results

Search results

We found 1,740 articles by searching (PubMed 704 articles, ISI web of knowledge: 472 articles, Embase: 293 articles, Cochran library: 271 articles) and 15 articles by reference tracking. After screening abstracts and titles, we excluded duplication (541 articles), non-meta analysis (407 articles), non-treatment (378 articles) and RCT (358 articles). We also excluded traditional reviews (37 articles), and others (11 articles) based on screening the full text. Finally, we included 23 articles for this overview of systematic review. Due to several systematic reviews on the same topic, 14 systematic reviews were reviewed in this overview (Table 1).

Complete Decongestive Therapy (Combined Physical Therapy)

Devoogdt et al (Devoogdt et al., 2010) showed that combined physical therapy (CPT) can be considered as an effective treatment modality for lymphoedema, and the oedema volume reduction was from 21% to 56% as compared to standard physiotherapy. No controlled trials investigated the effectiveness of skin care, wearing a compression sleeve and arm elevation. Another review (Moseley et al., 2007) of one single arm study (Swedborg et al., 1993) showed that limb elevation was associated with a significant 3.1% reduction in arm volume.

Manual lymphatic drainage (MLD)

Two systematic reviews (Huang et al., 2013; Ezzo et al., 2015) evaluated the effects of MLD for BCRL. The first one (Ezzo et al., 2015) is a Cochrane reviews which included six RCTs about three categories: MLD + standard physiotherapy versus standard physiotherapy (one trial), MLD + compression bandaging versus compression bandaging (two trials), MLD + compression therapy versus nonMLD treatment + compression therapy. MLD was not associated any more benefits to standard physiotherapy (no significant between-groups differences in percent reduction), but to compression bandaging (no significant between-groups differences in lymphedema volume, volume reduction, but in percent reduction). The third category included three studies and three comparisons: compression sleeve + MLD vs. compression sleeve+ intermittent pneumatic pump, compression sleeve + MLD vs. compression sleeve + self-administered simple lymphatic drainage (SLD), MLD + compression bandaging vs. SLD + compression bandaging. No statistical significances were found in percent reduction. And volume reduction was found in the first comparison, but not in the second comparison. The
| Study | Year | Comparator | Methodology | Evidence level |
|-------|------|------------|-------------|---------------|
| Devoogdt 2010 | CPT | The overall improving in the CPT group was shown to be greater than the SP group but when the evaluation results of both groups were compared before and after treatment, a significant statistical difference in edema according to circumferential and volumetric measurements results was found in favor of CPT. | low |
| Ezzo 2015 | MLD | MLD + standard physiotherapy versus standard physiotherapy: no statistically significant differences. MLD is safe and may offer additional benefit to CB for swelling reduction. | very low |
| Huang 2013 | MLD | The addition of MLD to compression and exercise therapy for BCRL is unlikely to produce a significant reduction in LE volume. | very low |
| Shao 2014 | IPC | The percent of volume reduction: CPT + IPC vs. CPT 4.51 (–7.01, 16.03). Both CDP and IPC could improve symptoms, but no differences existed between CPT + IPC and CPT. Current trials fail to show the superiority of the additional use of IPC. | very low |
| Singh 2015 | Exercise | LE volume: Single bout of exercise -0.1 (-0.3 0.1); Regular exercise -0.1 (-0.3 0.4); Exercise vs. control: -0.1 (-0.3 0.1); Exercise + compression vs. control: 0.2 (0.4). | low |
| Poage 2015 | Botanicals (coumarin, BN165 (gamma benzopyrone)) | The LE volume increased by 21 ml during placebo treatment and 58 ml during coumarin treatment (P=0.80). Evidence supporting the use of botanicals for the treatment of BCRL is insufficient. | low |
| Study | Treatment | Evidence | Level | Conclusions |
|-------|-----------|----------|-------|-------------|
| Moseley 2007 | Daflon | low | 1 | Daflon did not have significant difference in evolution of lymphedema volume in comparison with placebo, despite a tendency in favor of Daflon. 5,6-benzo-[alpha]-pyrone achieved a statistical significance in lymphedema volume reductions and percent reduction as compared with placebo. |
| Leung 2015 | Surgery | very low | 2 | Liposuction reduces the volume and symptoms of LE, but requires continual compressive therapy to avoid recurrence. Lymphatic reconstruction or bypass techniques show promise in reducing LE significantly. The developing modern surgical management of BCRL has a role in the management of these patients. |
| Smoot 2015 | LLLT | low | 9 | LLLT was associated with clinically relevant reductions in lymphedema volume and pain. Greater reductions in volume were found in LLLT than in treatments without it. |
| Ridner 2012 | Weight reduction | low | 1 | The results indicated a significant reduction in swollen arm volume at the end of the 12-week period in the intervention weight-reduction group. Weight loss achieved by dietary advice to reduce energy intake can reduce breast cancer-related LE significantly. |
| Toyserkani 2015 | stem cells | very low | 2 | There was improvement in the volume of LE in autologous stem cells and compression sleeves, with no significant difference. Most studies showed a decrease in LE in an increased physical activities and potential change when treated with stem cells and this reduction may be added to the effect of compression sleeves. BMSC was associated with more decrease than CPT at 3 and 12 months, respectively. |
| Morris 2013 | KTT | low | 1 | No significant differences for limb size, water composition of the upper-limb, LE-related symptoms and health-related quality of life. In the short-term KTT is no more effective than usual care SSB for BCRL outcomes. |
| Dos Santos 2010 | Acupuncture | very low | 1 | Range of shoulder flexion and abduction, degree of LE volume, heaviness or tightness could be improved after traditional acupuncture. There is a paucity of high quality evidence to support the use of acupuncture to decrease range of motion with LE. |
| Garcia 2014 | Acupuncture | very low | 1 | Mean reduction in arm circumference difference was 0.90 cm (0.72-1.07). 33% exhibited a reduction of ≥30% without serious adverse events and infections or severe exacerbations. Acupuncture appears to be safe and may reduce lymphedema. |
Intermittent Pneumatic Compression Pump (IPC)

Shao et al. (Shao et al., 2014) conducted a systematic review and meta analysis and showed no significant differences in the percent of volume reduction and subjective symptoms (heaviness, pain, paresthesia, or tension) between decongestive lymphatic therapy (DLT, also known as CPT)+IPC and DLT groups.

Exercise

Four systematic reviews (Kwan et al., 2011; Cheema et al., 2014; Paramanandam and Roberts, 2014; Singh et al., 2016) studied the effects of exercise for BCRL, in which the one by Singh et al (Földi et al., 1989) was the most comprehensive one. This systematic review of 21 studies showed no effect of acute or intervention exercises (aerobic, resistance, mixed, other) with different intervention durations on BCRL or associated symptoms. After excluding these three studies about women at risk of BCRL and with other kinds of cancer, the results did not change.

All interventions were effective for reducing LE volume and the percent reduction ranged from 4% to 66%, which depends on its constituent.

Oral pharmaceuticals

Poage et al (Poage et al., 2015) reviewed the role of botanicals (coumarin, BN165 (gamma benzopyrone)) as an adjunctive treatment for lymphedema, and included only two studies on BCRL. One study showed that the average volume of the affected arm increased by 21 ml during placebo treatment and 58 ml during coumarin treatment (P=0.80) after six months (Loprinzi et al., 1999). Another study noted statistically significant reductions on limb heaviness, tightness, and stiff movement after BN165 (gamma benzopyrone), but placebo might be effective in reducing tightness and stiff movement (Cluzan et al., 2004). But quality of life and volumetry were not different before and after treatment in all groups.

Another systematic review (Moseley et al., 2007) which reviewed Daflon (two tablets/day), Cyclo-fort, and 5–6 Benzo- a-pyrene showed these three oral pharmaceuticals could obtain varying volume reductions and subjective improvements. Daflon (Pecking et al., 1997) did not have a significant difference in evolution of lymphedema volume in comparison with placebo, despite a tendency in favor of Daflon. 5,6-benzo-[alpha]-pyrone achieved a statistical significance in lymphedema volume reductions and percent reduction as compared with placebo (Casley-Smith et al., 1993), and for Cyclo-fort the reduction in volume of arm edema was 12.9% after 3 months of treatment as compared with a placebo (p=0.009) (Cluzan et al., 1996).

Surgery

Two systematic reviews (Penha et al., 2013; Leung et al., 2015) reviewed the surgical techniques used for the treatment of BCRL. The first one (Leung et al., 2015) which included more information showed that liposuction reduced the volume and symptoms of lymphedema, but requires continual compressive therapy to avoid recurrence. Lymphatic reconstruction or bypass techniques including lymph node transfer (inguinal nodes are transferred to the affected limb), lymphatico-lymphatic bypass (lymphatics bypass the axilla using a lymph vessel graft reconstructing lymphatic flow from arm to neck) and lymphaticovenous anastomoses (lymphatics in the arm are joined to the venous system aiding lymph drainage) show promise in reducing lymphedema significantly.

Low-level laser therapy

Four systematic reviews (Omar et al., 2012; Monteiro et al., 2014; MT et al., 2014; Smoot et al., 2015) studied the effects of low-level laser therapy (LLLT) for BCRL, in which the one by Smoot et al (Smoot et al., 2015) was the most comprehensive one. This systematic review of nine studies showed that LLLT reduced 75.7 ml in limb volume and 90.9 ml greater in volume versus not including LLLT. LLLT reduced 13.5 mm (0–100 mm VAS) in pain and did not differ between these two groups.

Others

Weight Reduction

One systematic review (Ridner et al., 2012) reviewed one single RCT of 21 breast cancer survivors with lymphedema, and showed that weight loss was related significantly to reduction in swollen arm volume (Shaw et al., 2007).

Mesenchymal stem cells therapy

Toyserkani et al (Toyserkani et al., 2015) reviewed the evidence of mesenchymal stem cells for BCRL and included two studies before July 2014. The first RCT by Maldonado et al (Maldonado et al., 2011) showed stem cell therapy was as effective as compression sleeve therapy, but only stem cell therapy has an irreversible effect. Meanwhile, stem cell treated group was associated with reduced BRCL associated co-morbidities of pain and sensitivity. The second RCT by Hou et al (Hou et al., 2008) showed significant differences in the reduction of arm volume and pain between bone marrow stromal cells therapy and complex decongestive physiotherapy (CDT, also known as CPT) at 3 and 12 months.

Kinesio Tex taping (KTT)

Morris et al (Morris et al., 2013) included one high-quality RCT that compared KTT and usual care to the standard short-stretch-bandage (SSB) and usual care. And this study showed no significant differences in limb size, water composition of the upper-limb, lymphedema-related symptoms and health-related quality of life.

Acupuncture

One systematic review (Dos Santos et al., 2010) reviewed the effects of acupuncture on BRCL based on one single-arm pilot study (Aleem and Gurgel, 2008), and this study showed significant improvements in range of movement of shoulder flexion and abduction, degree of
Lymphoedema is a debilitating condition, manifesting in excess lymphatic fluid and swelling of subcutaneous tissues due to obstruction, destruction, or hypoplasia of lymphatic vessels, and one of the great challenges in plastic surgery, where a satisfactory solution has not yet been found (Toyserkani et al., 2015). Management of established lymphedema has been addressed by clinical practice guidelines, and a whole set of modalities have been presented. Based on this review, CPT, MLD + standard physiotherapy, MLD + CB, MLD + CS, SLD + CS, SLD + CB, CPT + IPT, CS+ IPT, IPT, standard physiotherapy, CB, liposuction, lymphatic reconstruction or bypass techniques including lymph node transfer, lymphatico-lymphatic bypass and lymphaticovenous anastomoses, weight Reduction, acupuncture, Daflon, Cyclo-fort, 5–6 Benzo- a-pyrone, stem cell therapy, KTT, standard short-stretch-bandage (SSB), and low-level laser therapy might be effective in reducing the lymphedema volume, but only low-level laser therapy, MLD, 5,6-benzo-[alpha]-pyrone, Cyclo-fort and coumarin were tested in placebo or sham treatment controlled studies. Based on the results of controlled studies, low-level laser therapy, 5,6-benzo-[alpha]-pyrone and Cyclo-fort might be effective in treating lymphedema, but the results for coumarin varied.

The results of direct comparisons showed CPT might be more effective than standard physiotherapy, but MLD may not offer additional benefit to standard physiotherapy in swelling reduction, but to compression bandaging. MLD seemed to have similar effects on SLD or IPC. IPC might also not be associated with addition effectiveness to CPT. For exercise, it is safe for patients with BCRL to participate in progressive, regular exercise without experiencing a worsening of lymphedema or related symptoms. KTT is as effective and safe as SSB, but the effects of stem cell therapy vs. compression sleeve or CPT were not established.

The evidence levels evaluated by GRADE for all different interventions varied from very low to low. We did not find high level evidence, which might be because of small sample size, high risk of bias, and/or inconsistency across studies.

Discussion

Lymphoedema is a debilitating condition, manifesting in excess lymphatic fluid and swelling of subcutaneous tissues due to obstruction, destruction, or hypoplasia of lymphatic vessels, and one of the great challenges in plastic surgery, where a satisfactory solution has not yet been found (Toyserkani et al., 2015). Management of established lymphedema has been addressed by clinical practice guidelines, and a whole set of modalities have been presented. Based on this review, CPT, MLD + standard physiotherapy, MLD + CB, MLD + CS, SLD + CS, SLD + CB, CPT + IPT, CS+ IPT, IPT, standard physiotherapy, CB, liposuction, lymphatic reconstruction or bypass techniques including lymph node transfer, lymphatico-lymphatic bypass and lymphaticovenous anastomoses, weight Reduction, acupuncture, Daflon, Cyclo-fort, 5–6 Benzo- a-pyrone, stem cell therapy, KTT, standard short-stretch-bandage (SSB), and low-level laser therapy might be effective in reducing the lymphedema volume, but only low-level laser therapy, MLD, 5,6-benzo-[alpha]-pyrone, Cyclo-fort and coumarin were tested in placebo or sham treatment controlled studies. Based on the results of controlled studies, low-level laser therapy, 5,6-benzo-[alpha]-pyrone and Cyclo-fort might be effective in treating lymphedema, but the results for coumarin varied.

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The evidence levels evaluated by GRADE for all different interventions varied from very low to low. We did not find high level evidence, which might be because of small sample size, high risk of bias, and/or inconsistency across studies.
A third issue is lack of high quality of RCTs. This means that the methodological qualities of original studies are low. For systematic review of LLLT, none of the eight studies included in the review addressed the all criteria for scientific rigor (Smoot et al., 2015). In the review conducted by Shao et al. (Shao et al., 2014) and Huang et al. (Huang et al., 2013), the included studies varied in the study quality and most studies were of high risk of bias. A meta analysis of high-quality RCTs provides the highest level of evidence, but unfortunately, there are limited numbers of methodologically rigorous studies on the treatment of lymphedema.

Besides these issues, there were several flaws in the design of the original studies, such as differences of the severity and duration in the subjects/group at baseline, length of follow-up, treatment protocols, co-interventions, comparators, and outcome measures (Oremus et al., 2012). All prevented us from assessing whether any one treatment was superior, although many studies showed that most active treatments reduced the size of lymphatic limbs. Due to a lack of high-quality studies it is difficult to make conclusions and offer recommendations about the interventions.

**Strengths and limitations**

This overview was the first one which systematically reviewed the current treatments on breast cancer-related lymphoedema. However, this overview still has several limitations: first: From a patient’s functional perspective, the aim of lymph therapy is to reduce lymphoedema and maintain or increase the patient’s activity and participation (Karki et al., 2009). In this review, a great deal of research into the treatment of BCRL was conducted, but the most effective treatment was still not found. Now lymphoedema treatment, however, still lacks much of evidence-base and yet it is associated with significant investments of time and financial resources, and the field of research into treating lymphoedema is open to advancement (Oremus et al., 2012). Second: The original studies were of high risk of bias and small sample size, low methodological quality. For lymphoedema volume reduction, only calculation of the reduction before and after the treatment is not enough to judge whether the treatments were effective or not.

**Implications to clinical practices and research**

The first implication is that: what should be prescribed to patients with BCRL? We found that all available treatments except exercise might be effective in reducing lymphoedema volume. And different combinations of CPT constituent may show different effects. In our opinion, CPT could be basic and standard treatment for BCRL, although the efficacy of CPT and different combinations of its constituent were not well established. Others including low-level laser therapy, acupuncture, Daflon, Cyclo-fort, 5–6 Benzo-a-pyrone, and KTT could be complementary treatments. The surgery and mesenchymal stem cells therapy could also be effective, but they could be prescribed to patients if all treatments failed.

The knowledge of the methodological flaws in the current trials can be utilized in designing future studies in this field. The future studies should be of low risk of bias and big sample size, and well reported. The best study design for assessing the effectiveness of a specific treatment is placebo or CPT controlled RCTs for BCRL. In the future, RCTs should consist of a comprehensive plan to reduce the bias, including the details of randomization, conceal allocations, blinding, intend-to-tend analysis, baseline comparability and sample size calculation. The lymphoedema volume reduction effects should be controlled by placebo or CPT, and between group differences should be calculated and reported in order to guide the clinical practice.

Although lots of treatments on BCRL might reduce lymphoedema volume, their effects were not well established, and in the future well designed, conducted and reported placebo or CPT controlled trials are needed to test their effects and safety.

**Conflict of interest:** none

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