

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

Asian Pac J Cancer Prev, 17 (11), 4875-4883

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 (Biscaia 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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that comprehensively reviewed the effective treatments for BCRL. A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question (Higgins JPT and S.). Well conducted systematic reviews which involve scientific strategies, objective searches of the literature, predetermined inclusion and exclusion criteria, and critical appraisal and synthesis of all relevant studies (Li et al., 2012), are the cornerstone of evidence based health care as they can provide the highest level of evidence (Pieper et al., 2015), as they use explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made (Higgins JPT and S.). So the goal of this overview is to review the effects of different treatment strategies for patients with BCRL.

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 lymphodema 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 reduction, percent reduction, 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)

Combined Physical Therapy (CPT)

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

Table 1. Summary of Included Reviews

Study	Treatment	Search time	Included study No.	Results	Conclusions	Evidence level
Devoogdt 2010	CPT	-	2	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.	In the patients with upper extremity LE, the shoulder mobility can be increased and edema can be decreased by the use of CPT.	low
Ezzo 2015	MLD	2013.5.24	6	MLD + standard physiotherapy versus standard physiotherapy: no statistically significant between-groups difference in per cent reduction MLD+CB vs. CB: LE volume: -60.73 (-194.43 72.96); volume reduction: 26.21 (-1.04 53.45); per cent reduction: 7.11% (1.75% 12.47%)	MLD is safe and may offer additional benefit to CB for swelling reduction. In trials where MLD and sleeve were compared with a nonMLD treatment and sleeve, volumetric outcomes were inconsistent within the same trial. For symptoms such as pain and heaviness, 60% to 80% of participants reported feeling better regardless of which treatment they received.	very low
Huang 2013	MLD	2012.12	10	CS + MLD vs. CS+ IPD: LE volume: 122 (-57.59 301.59); volume reduction: 47 (15.25 78.75); per cent reduction: 8 (-0.75 16.75) CS + MLD vs. CS + SLD: LE volume: -230 (-450.84 -9.16); volume reduction: 10 (-90.54 110.54); per cent reduction: -2.40 (-14.11 9.31) MLD + CB vs. SLD + CB: per cent reduction: 11.80 (-2.47 26.07)	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	2013.12.20	7	reduction in arm volume: 75.12 (-9.34 159.58) 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 effectiveness of the addition of IPC to the routine management of BCRL.	very low
Singh 2015	Exercise	2015.1.1	25	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. exercise : -0.2 (-0.5 0.1) Heaviness: Single bout of exercise 0.0 (-0.3 0.3)	Exercise, irrespective of mode, appeared to have no effect on LE and related symptoms. There were no benefit of wearing compression for LE and associated symptoms, and exercise without compression does not exacerbate LE.	low
Poage 2015	botanicals (coumarin, BNI165 (gamma benzopyrone))	2011	2	Tightness: Single bout of exercise 0.1 (-0.3 0.4) pain: Regular exercise vs. control: -0.1 (-0.6 0.1) 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

Table 1. Continued

Study	Treatment	Search time	Included study No	Results	Conclusions	Evidence level
Moseley 2007	Daflon /Cyclo-fort/	2004	01/01/2001	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. 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).	Varying volume reductions and subjective improvements could be obtained from oral pharmaceuticals such as Daflon (1000 mg) and Cyclo-fort, with the greatest limb reduction (840 ml, 35.6%) being obtained from the 5-6 Benzo-a-pyrone (200 mg).	
Leung 2015	5-6 Benzo-a-pyrone Surgery	2014.2	03/02/2006	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.	very low
Smoot 2015	LLLT	2014.10.16	9	LE volume: within-group: -0.52 (-0.78 -0.25); between-groups: -0.62 (-0.97 -0.28) pain: within-group: -0.62 (-1.06 -0.19); between-groups: -1.21 (-4.51, 2.10)	LLLT was associated with clinically relevant within-group reductions in volume and pain. Greater reductions in volume were found in LLLT than that in treatments without it.	low
Ridner 2012	Weight reduction	2011	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.	low
Toyserkani 2015	stem cells	2014.7.31	2	There was improvement in the volume of LE in autologous stem cells and compression sleeves, with no significant difference. There were decreases in LE volume and pain in BMSC transplantation and CPT. BMSC was associated with more decrease than CPT at 3 and 12 months, respectively.	Most studies showed a decrease in LE and an increased lymphangiogenesis when treated with stem cells and this treatment modality has so far shown great potential.	very low
Morris 2013	KTT	2012.4	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.	low
Dos Santos 2010	acupuncture	2009.4	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.	very low
Garcia 2014	acupuncture	2011.12	1	Mean reduction in arm circumference difference was 0.90 cm (0.72-1.07). 33% exhibited a reduction of $\geq 30\%$ without serious adverse events and infections or severe exacerbations.	Acupuncture appears to be safe and may reduce arm circumference.	very low

LE, lymphedema; CPT, complete decongestive therapy (combined Physical Therapy, complex decongestive physiotherapy, decongestive lymphatic therapy); BMSC, bone marrow stromal cells; IPC, Intermittent Pneumatic Compression Pump; LLLT, low-level laser therapy; MLD, Manual lymphatic drainage; CB, compression bandaging; CS, compression sleeve; SLD, simplified/self-MLD; KTT, Kinesio Tex taping

second systematic review (Huang et al., 2013) combined the results of all these included studies and showed no significant difference between the MLD and standard treatment groups in arm volume reduction.

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-pyrone 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 (Alem and Gurgel, 2008), and this study showed significant improvements in range of movement of shoulder flexion and abduction, degree of

lymphoedema, and sense of heaviness and tightening in the affected limb after six months of therapy.

We also identified another single-arm pilot study (Cassileth et al., 2011) from another review (Garcia et al., 2014), which showed that mean reduction in arm circumference difference was 0.90 cm (95% CI, 0.72-1.07). Among all patients, 33% exhibited a reduction of $\geq 30\%$ after acupuncture treatment without serious adverse events and infections or severe exacerbations.

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.

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.

The issues in studies about interventions on BRCL

The first issue is lack of proper study design. Too many studies were observational studies, which only focused on the lymphedema volume reduction after treatments. In these studies, even significant reductions could be found, can the effectiveness of the treatment be

shown? The best study design for establishing a causal relationship between an intervention and outcome is the well designed and conducted RCT (Smoot et al., 2015). In the study that focused on the effects of Daflon on BCRL, although patients treated with Daflon experienced a 7% volume reduction, no significant difference in evolution of lymphedema volume in comparison with placebo was found (Pecking et al., 1997). This suggested that there might be placebo effect in RCTs, and was confirmed by Cluzan et al (Cluzan et al., 2004). This 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). This kind of placebo effect was common. A recent meta analysis of five clinical trials in locally advanced or metastatic differentiated (DTC) and medullary thyroid cancer (MTC) showed placebo could achieve 1.6% (0.6-3) and 6.4% (3.4-10.3) partial response rates in DTC and MTC respectively, and 40.5% (34.6-46.9) and 53.9% (44.3-64.4) stable disease rates in DTC and MTC respectively (Llavero-Valero et al., 2016). So for those treatments, such as acupuncture and surgery, which were only studied in observational studies, their effectiveness should be restudied in RCTs and adjusted by placebo or sham treatments. For those diseases which have the standard treatments, the novel treatments should be compared with the standard treatments in RCTs. The current standard care for BCRL is CPT, which has been shown to be effective in volume reduction as a multimodal treatment. CPT is currently recognized as the standard of care in lymphedema treatment and consists of manual lymph drainage (MLD), compression bandaging, exercises, skin care, and compression garments (Lasinski et al., 2012). Even for CPT, its effectiveness was not well established and the levels of evidence rating by Stakeholders were different, but nearly same: likely to be effective or effectiveness not established. From our review, we did not identify one RCT which compared CPT with placebo or sham treatments, but identified one RCT which compared CPT with standard physiotherapy (Didem et al., 2005). This means even if some treatments were superior as compared to CPT, their treatments should be well reconsidered. For future design of RCTs on BCRL, the effectiveness of CPT should be well studied, and then CPT could be a comparator, or placebo-controlled studies should be conducted.

Another issue is that the sample sizes of the original studies varied and were small. For studies that evaluated the effects of LLLT, the sample size ranged from 8 to 64 and the total sample size across all studies was 289 (Smoot et al., 2015). Studies of small sample size always have bigger estimates, which might lead to overestimation of the study results. Meta-epidemiological studies showed that small trials are more likely to report larger beneficial effects than large trials in critical care medicine, which could be partly explained by the lower methodological quality in small trials (Nuesch et al., 2010; Zhang et al., 2013). So for future RCTs, the sample size calculation should be done at the beginning of study design in order to get enough statistical power.

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 BRCL 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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