

Clinical trials needed to evaluate compression therapy in breast cancer related lymphedema (BCRL). Proposals from an expert group

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Aim. A mainstay of lymphedema management involves the use of compression therapy. Compression therapy application is variable at different levels of disease severity. Evidence is scant to direct clinicians in best practice regarding compression therapy use. Further, compression clinical trials are fragmented and poorly extrapolable to the greater population. An ideal construct for conducting clinical trials in regards to compression therapy will promote parallel global initiatives based on a standard research agenda. The purpose of this article is to review current evidence in practice regarding compression therapy for BCRL management and based on this evidence, offer an expert consensus recommendation for a research agenda and prescriptive trials. Recommendations herein focus solely on compression interventions.

Methods. This document represents the proceedings of a session organized by the International Compression Club (ICC) in June 2009 in Ponzano (Veneto, Italy). The purpose of the meeting was to enable a group of experts to discuss the existing evidence for compression treatment in breast cancer related lymphedema (BCRL) concentrating on areas where randomized controlled trials (RCTs) are lacking.

Results. The current body of research suggests efficacy of compression interventions in the treatment and management of lymphedema. However, studies to date have failed to adequately address various forms of compression therapy and their optimal application in BCRL. We offer recommendations for standardized compression research trials for prophylaxis of arm lymphedema and for the management of

chronic BCRL. Suggestions are also made regarding; inclusion and exclusion criteria, measurement methodology and additional variables of interest for researchers to capture.

Conclusion. This document should inform future research trials in compression therapy and serve as a guide to clinical researchers, industry researchers and lymphologists regarding the strengths, weaknesses and shortcomings of the current literature. By providing this construct for research trials, the authors aim to support evidence-based therapy interventions, promote a cohesive, standardized and informative body of literature to enhance clinical outcomes, improve the quality of future research trials, inform industry innovation and guide policy related to BCRL.

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Incidence and risk factors

Breast cancer related lymphedema (BCRL) is a distressing effect of breast cancer that presents as chronic swelling of the arm and chest wall accompanied by; skin changes, decreased range of motion, pain, limited strength and recurrent infections. These impairments lead to significant functional, psychological and social morbidity and reduced health-related quality of life.¹⁻⁵

Approximately 33% of patients present with lymphedema after breast cancer treatment. Of these, 40% will experience long term chronic swelling and 60% will have transitory symptoms.³ Older age, higher body mass index, more extensive surgery, axillary node dissection, radiation therapy and experiencing one or more postoperative complications are important risk factors.⁶ Sentinel node biopsy may reduce the incidence rates in the short term but longer term studies are needed to assess the degree to which patients remain free from lymphedema.⁶⁻⁸ Recent data demonstrate that the time to onset of lymphedema may only be delayed with sentinel node procedures rather than prevented.⁹

Lymphedema is treatable at any stage of severity. Intervention at the earliest point is optimal as it may prevent the progression to a more severe chronic condition with fibrosis and/or adipose tissue build up, which starts within the first year after lymphedema onset.¹⁰ Early detection requires clinicians to identify patients at high risk, assess subjective and clinical symptoms and intervene based on this presentation. Subjective symptoms can be predictive of the onset of swelling and should be properly assessed.¹¹ Additionally, women with mild lymphedema are three

times more likely to develop advanced forms of the condition, thus warranting treatment.⁸ Even in cases of severe, progressed lymphedema treatment options, although more intense, are effective.

Pathophysiology

BCRL is not simply due to lymphatic obstruction. Prior to edema onset women who later develop BCRL have higher peripheral lymph flows than those not developing BCRL. Peripheral lymph flows may also be elevated in the contralateral arm suggesting that there is a subgroup of women with constitutionally higher lymph flows, and by implication higher capillary filtration rates, who are prone to BCRL after axillary surgery. Therefore, in some cases, following breast cancer treatment, the lymphatic pump fails in the ipsilateral arm because of the chronically elevated lymph load.^{12, 13}

Compression therapy in BCRL

Compression therapy is an integral part of caring for lymphedema at any stage of severity. When lymphedema is detected at its earliest onset conservative compression therapy, and education for protective behaviors may prevent the progression of lymphedema to a more advanced and potentially disabling stage. In manifest stages of lymphedema, compression treatment is an effective component of a multi-modal decongestive therapy intervention. Compression interventions effectively reduce limb volume and maintain volume decongestion.

Past research endeavours have focused on optimal utilization of standard compression products.^{14, 15} Compression modalities including; garments, compressive short-stretch bandages and intermittent pneumatic compression devices are efficacious in the context of a treatment program.^{16, 18} However, the optimal compression pressure, pressure gradient, type of material and frequency and interval of application as well as combined compression therapy regimens for both prophylaxis and treatment need to be assessed by the principles of evidence based medicine.

Interface pressure measurement is useful to gauge the level of pressure applied to the limb by the compression device, it provides information regarding the gradient of pressure along the limb, consistency of the compression levels along the limb and can assess the compression device pressure changes over time.¹⁹ These measurements can inform investigators and clinicians about compression garment stiffness and pressures being applying against the tissue. Interface pressure measures are also of great interest to industry to assure quality and effectiveness of compression garments.

Aim of the document

The purpose of this document is to provide a review of the current evidence regarding compression use in the treatment of BCRL. Much of the current dogma surrounding compression therapy must be challenged based on new and emerging data about lymphatic system function and associated pathophysiology.¹⁵ We also present recommendations for a research agenda and propose constructs for future BCRL compression therapy trials that may guide and inform researchers, clinicians and industry representatives world-wide in an effort to promote a cohesive, standardized and informative body of literature regarding compression therapy applications and products.

This document is structured to highlight evidence and research recommendations regarding compression modalities into two separate paradigms:

I) Prophylaxis and early intervention during and after primary breast cancer disease treatment

II) Therapy of advanced stage BCRL of the upper extremity (these proposals are specific to extremity lymphedema and do not consider chest-wall or breast lymphedema)

Prophylaxis and early intervention after BC-treatment

CURRENT EVIDENCE

Historical data leads us to believe that only one-third of breast cancer survivors will develop

arm lymphedema after treatment. The onset of lymphedema ranges from 6 months to 20 + years after treatment. This long and erratic latency period is poorly understood, however speaks to the issue that lymphedema is a life-long risk for survivors. Based on this data, however, a large group of survivors will never develop lymphedema, making a true prophylactic compression approach to prevention unrealistic and even unnecessarily constraining for the majority of women.

A more prudent approach focuses on early detection of arm swelling and early intervention. Preliminary research findings suggest that initiating compression therapy at the earliest onset of lymphedema may prevent progression and manifestation of severe lymphedema.²⁰ The concept of early intervention will only be realized if the medical community embraces a prospective surveillance approach to monitoring for and educating patients about lymphedema. In such a model, preoperative assessment of limb volume is essential so that a baseline measure of volume and inter-limb variance can be established. This is followed by a period of interval surveillance where limb volume, along with patient subjective report, is monitored for change. If the limb volume differential exceeds the diagnostic threshold, even in the absence of clinically apparent swelling, a compression intervention is initiated. Early evidence supports this approach, however large scale controlled trials are lacking.

Two prophylactic compression therapy trial constructs should be considered in this prospective surveillance approach (Figure 1):

1) in the context of a prospective surveillance model of care, randomize patients to study (compression) or control (no compression) groups only if they surpass a standardized diagnostic threshold associated with sub-clinical lymphedema at one of their interval follow-up visits;

2) preoperatively randomize all patients to study (compression) or control (no compression) groups regardless of limb volume changes at any point along the study timeline. The study group in this case receives preventive compression garments for wear throughout their post operative period. If patients in the control group develop limb volume changes consistent with the onset of lymphedema they would be further randomized to receive a compression therapy intervention or receive no compression (Figure 1).

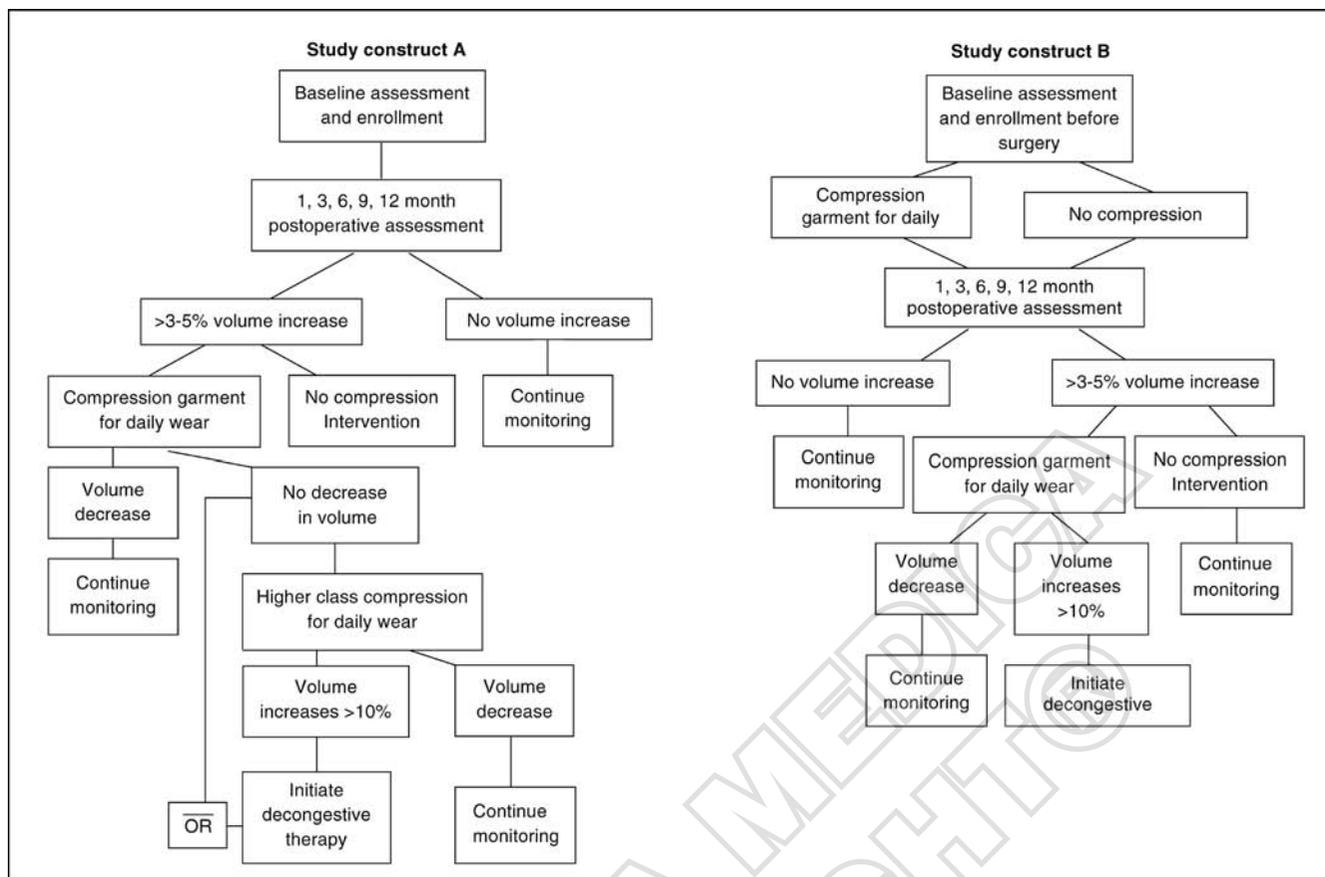


Figure 1.—Prospective prophylaxis and early intervention compression therapy trial recommendations.

WORKING HYPOTHESES

These study constructs explore the hypothesis that compression therapy, applied at the earliest onset of limb volume change, prevents the progression to manifest, chronic lymphedema. However, each construct approaches the preventive model differently. Construct A proposes that in the context of a surveillance model of care, a meaningful limb volume change can be clinically detected and treated. This construct promotes early detection and focuses on treating a measurable impairment; however, it relies on clinical tools and practitioner diagnostic skills that may not be easily extrapolable to the greater population of clinical practitioners.

Construct B proposes that by applying compression to subjects randomized to the study group, there will be a meaningful difference in the onset of lymphedema over time as compared to the control group. This construct simplifies the postoperative surveillance model and definitively

assesses the ability of compression garments to prevent the onset of lymphedema. However, this construct requires that all subjects in the study group receive compression regardless of their known risk factors and potential for developing lymphedema. This may constrain the researcher from identifying confounding variables that may be important in studying the natural history of lymphedema.

STUDY CONSTRUCTS

Both study constructs rely on prospective multicenter randomized controlled trials. All patients are seen preoperatively for baseline measurements of arm volumes and all are followed in the post-operative period at three month intervals to one year.²⁰⁻²² Recommendations for measurable outcome variables are included in Table I.²³⁻⁵³

The inclusion criteria should enable the broadest representation of women having breast can-

TABLE I.—Recommended Study Outcome

Variables.
Primary outcomes
– Arm volume change overtime
– Edema volume of affected limb (affected - unaffected arm volume at each time point)
– Pitting test
– Moisture measuring systems
– Range of motion (ROM) – upper quadrant
– Subjective symptoms ⁴¹
– General and Disease specific quality of life (QOL) measures: ⁴²⁻⁴⁷
– Psychology General Well-Being scale (PGWB)
– Nottingham Health Profile (NHP)
– European Organisation for Research and Treatment of Cancer (EORTC)
– Disability of Arm, Shoulder and Hand (DASH)
– Shoulder Pain and Disability Index (SPADI)
– Functional Assessment of Cancer Therapies – Fatigue (FACT- F)
– Health related quality of life changes: Short Form -36 (SF-36) (disease specific and generalist tools)
– Interface pressure of compression device
– Compliance with compression devices ⁵³
– Good ≥90% compliant with recommendations
– Fair = 60-89% compliant with recommendations
– Poor ≤60 % compliant with recommendations
Secondary outcomes
– Durometer
– Tonometry
– Muscle strength (dynamometry)
– Bio-impedance – anthropometric measures
– Skin assessment – skin folds, skin change
– Cost-benefit
– Weight changes
– Comfort of the garment

TABLE II.—PATIENT CHARACTERISTICS*

Age
Medical comorbidities (hypertension, diabetes, etc.)
Lab values (blood counts)
Body Mass Index
Affected arm (Right/Left)
Dominant arm (Right/Left)
Sensory integrity
Presence of venous disease
Degrees of range of motion (shoulder, elbow)
Time course of symptoms/condition
Lymphedema ISL-stage: 0-III
Segmental deformities and edema distribution
Baseline absolute volume (mL) for each limb
Baseline volume differential (mL) (Volume of affected limb [pending surgical intervention] vs. contralateral limb)
Baseline pain in affected limb – Visual Analog Scale (VAS)
Baseline heaviness - VAS
Baseline numbness - VAS
Pitting test
Presence of fibrosis
History of infections
Number of previous infection episodes
Type of surgery
Type of axillary procedure and number of nodes removed
Post-operative complications (seroma, axillary web syndrome, infection etc.)
Tumor characteristics (TNM classification)
Lymph node characteristics (positive vs. negative)
Adjuvant chemotherapy and drugs delivered
Radiotherapy and location of field
Hormonal therapy and drugs delivered

*Adopted from Vignes et al.62

TABLE III.—Exclusion criteria.

– Bilateral lymph node dissection*
– Prior history of lymph node dissection*
– Prior history of radiation therapy to the adjacent chest wall*
– Metastatic disease*
– History of severe shoulder / arm trauma or surgery*
– Bilateral arm swelling
– Clinical manifestation of infection at enrollment (cellulitis, erysipelas)
– Acute venous thrombosis or phlebitis
– Flaccid paralysis of the limb
– Decompensated heart failure
– Severe pulmonary insufficiency
– Active and clinically significant liver or renal disease
– Contact allergies relevant to compression materials (latex)
– Serious psychiatric disorders (severe depression, schizophrenia)
– Significant mental delay that prevents comprehension and/or learningi

* Primarily concerning in prophylactic intervention trials.

cer treatment. Therefore, outside of those who have evidence of metastatic processes, all stages of disease should be included. Additional variables regarding treatment interventions, patient characteristics, demographic information and co-morbidities as well as additional objective and self-reported outcomes can be captured in both of the study models. These variables contribute richly to the profile of the patient who develops lymphedema and may aid in enhancing risk stratification. Further they enable researchers to draw conclusions about the patients' functional, social and psychological domains as they relate to lymphedema.²³ Table II presents recommendations for patient characteristic data to be captured.

Exclusion from study participation is recommended for conditions that may skew results (Table III). Every effort should be made to include subjects of various racial and ethnic backgrounds. Language barriers must be overcome to enable broad capture of the patient population.

Standardization of the protocol, regardless of the chosen study construct, is paramount to assuring valid outcomes. The inclusion criteria should be standardized based on the limb volume at initial evaluation. We suggest that a subclinical lymphedema is defined as an excess volume of 3-5% with consideration for the contralateral limb.²⁰ Excess volume can be described either as (1) an absolute volume in ml (excess volume (absolute) = affected arm-non-affected arm) or expressed as (2) percent (excess volume [%] =

[affected arm-non-affected arm]/non-affected arm] x 100) with % volume change expressed as: excess volume change = (excess volume_{time 0} - excess volume_{time 1})/excess volume_{time 0} x 100.

Arm volumetry of both arms will be tracked at each visit along with patient compliance with compression therapy and subjective symptom assessment. Interface pressure measurements will be assessed at ongoing intervals. Compression garments should be of a standardized compression level and ideally from the same manufacturer. The same garments should be given to all patients with a standard educational handout addressing; wear time, washing intervals and interval of garment replacement.

Cost considerations are of growing concern due to finite health care resources. Efforts should be made to capture cost data specific to the intervention and compression device(s) used. Cost data is usefully translated to enable; cost utility analyses, the benefit gained per cost of intervention, cost effectiveness analyses, comparing two or more interventions for optimal cost benefit. Cost analyses and the implications of such analyses will vary among nations depending on the societal perspective, availability of resources and current reimbursement structures. These important data can be extrapolated globally to support national payment and reimbursement structures.

METHODOLOGY

Arm volumetry will be the primary outcome to assess effectiveness of the compression intervention. Many different techniques are reliable for measuring and quantifying limb volume, these include; circumferential measurements at predefined increments along the limb to enable calculation of volume using standardized geometrical formulas,²⁴ water displacement, optoelectronic Perometer® and bioelectrical spectroscopy devices.²⁵⁻²⁹ Standardized positioning of the patient and technique for measurement should be assured.

Interface pressure should be measured at the dorsal (lateral) aspect of the arm, after application and before removing the compression device.^{30, 31} The exact position of the measuring probe will be standardized at three points along the limb; distal lower arm, largest part of lower arm and mid upper arm, as suggested by the Ger-

man institute for quality control of compression garments.³² Change in interface pressure during exercise (e.g., fist closures) assesses the stiffness of the compression product.³³ Standardization must be assured and it is advisable to use the same pressure measuring device for all patients in the trial.

Additional tests and measures include; tests of pitting edema,³⁴ water content in the tissue that may be measured by bioimpedance,³⁵⁻³⁸ high frequency ultrasound³⁶ or moisture meters,^{39, 40} durometry (tonometry) can be performed⁴¹ and muscle strength may be another parameter of interest.⁴²

Subjective sensory changes should be monitored at each follow-up visit using a standardized measurement tool such as that described by Armer *et al.*⁴³ Quality of life assessment instruments can be integrated as well.⁴⁴⁻⁵¹ Additional subjective assessment may include; the number of infections (“dermato-lymphangio-adenitis DLA⁵²”), the comfort of the compression garment and the subjects compliance with compression wear.

Other variables of interest including; joint mobility, pain, activity participation, and fatigue are informative to compression therapy trials.⁵³⁻⁵⁶ Optimally a trial will consider incorporating several measures to further demonstrate and compare sensitivity and specificity of the various techniques for detecting early limb volume changes.

Of profound importance is the follow up protocol for ongoing assessment. Preoperative assessment and enrollment will be followed by postoperative follow-up at one month and then at three month intervals there after for at least the first year.^{57, 58} Sample size should be estimated based on follow up data after surgical therapy and shall be calculated depending on the predefined outcome parameters. Risk reduction by compression therapy and number needed to treat (NNT) are additional outcomes of importance.

Therapy of advanced stage BCRL

CURRENT EVIDENCE

Chronic lymphedema is optimally treated with Decongestive Lymphatic Therapy (DLT); a multimodal intervention that includes; manual lym-

phatic drainage, compression bandaging, exercise, skin care instruction, compression garments and may also include intermittent pneumatic compression therapy. Compression therapy is a mainstay in the treatment and ongoing care of a lymphedematous limb. Initial decongestion of the limb requires astute compression application of short stretch bandages.^{17, 59} Upon limb volume reduction with DLT, compression garments will maintain limb volume provided that they are appropriately measured for and prescribed.^{16, 59} Compression bandaging is utilized to manage the limb if the swelling exacerbates, assuring optimal limb volume for compression garment fit and effectiveness.¹⁷ Additionally, pneumatic compression devices play a role in the comprehensive approach to lymphedema management to aid in decongestion and limb volume maintenance.⁶⁰ Non-compliance concerning the use of compression is the most important risk factor for reappearance of arm swelling.^{61, 62}

Optimal parameters for the use of compression devices at all phases of treatment and management are unclear. Many purport compression therapy to be a successful adjunct to other therapeutic modalities, however in the absence of other modalities, we do not know which compression mode is optimal and under what clinical circumstances it will promote the best outcomes.

STUDY CONSTRUCTS

Study constructs aimed at exploring the effectiveness of compression interventions during and after intensive therapy are necessary. Duration of compression application as well as optimal pressures and mode of compression should be explored through well designed and controlled trials. Additional studies should be conducted investigating a comparison of the effectiveness of different compression modalities.

Two primary study constructs are highlighted in Figure 2:

1) comparison of two different modes of compression intervention during the intensive therapy phase to determine if one is superior to the other;

2) comparison of various compression devices during the maintenance phase of treatment.

Both study constructs rely on prospective multicenter randomized controlled trials. All patients are enrolled at the inception of their intensive therapy regimen (Construct A) or as they are entering the maintenance phase of therapy (Construct B) illustrated in Figure 2. Each of the studies will randomize patients to a compression group using one of the selected devices and will appropriately standardize frequency and duration of compression wear. Recommendations for

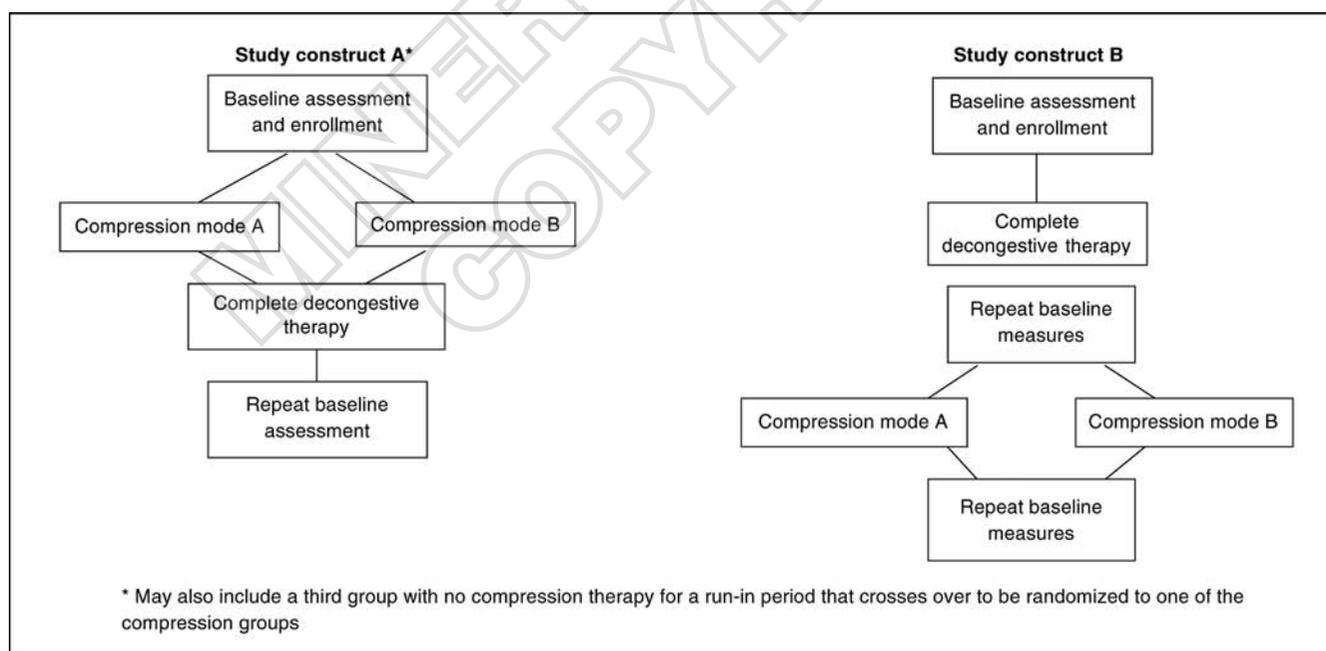


Figure 2.—Decongestive compression therapy trial recommendations for chronic lymphedema.

specific comparative studies are summarized in the Appendix 1 to this article.

The inclusion criteria should be standardized based on the limb volume at initial evaluation along with consideration for the patient's physical status and comorbid conditions. Patients showing greater than 5-10% interlimb discrepancy in excess volume provide a sound cohort for which meaningful change can be documented over time. In larger cohort studies stratification based on severity can be considered in examining volume outcomes.

Table II contains a list of recommended patient characteristics. Exclusion should be considered for co-morbid conditions that may skew outcomes (Table III). Also, patients who have experienced intensive decongestive therapy within the last six months may not be optimal subjects for inclusion into interventional protocols under Construct A, as their greatest volume decrement may have already been achieved. Optimally, patients included in Construct B studies should have very recently completed decongestive therapy and transitioned to a maintenance self care phase of treatment.

Limb volume change over time is the primary outcome variable. Subjective symptoms and quality of life assessment tools should be incorporated⁴³⁻⁵¹ along with measures of joint mobility, frequency of recurrent infections and tolerability of and compliance to compression therapy.⁵³⁻⁵⁹ Joint range of motion (ROM) is an important variable interrelated both with edema formation but also with some limitations that may be temporarily caused by compression bandaging.⁵³⁻⁵⁶ ROM should be documented for the elbow and shoulder joints to characterize the initial status and to assess changes during the trajectory of treatment. Shoulder strength and stabilization correlate to overall functional status after breast cancer and impairments in the shoulder should be captured.⁵⁵ Risk factors closely associated with breast cancer related lymphedema and outcome variables of interest are numerous⁶³⁻⁶⁵ and listed in Table I. All measures will follow standard protocol for pre- and post-treatment.

METHODOLOGY

Arm-volumetry measured with a reliable tool is a prerequisite for including a patient into a

TABLE IV.—CHARACTERISTICS OF COMPRESSION DEVICES AND MATERIALS .

- Sleeves
- Differentiation between custom made or ready-made
- Compression Class (German RAL regulations) ³²
- I: 15-21 mmHg (Low)
- II: 23-32 mmHg (Medium)
- III: 34-46 mmHg (High)
- Sleeve style
- Method of application
- Bandages
- Materials applied (foam padding, short-stretch)
- Number of layers
- Application method ⁷⁹
- Intermittent pneumatic compression: ^{80, 81}
- Single chamber sleeve pumps
- Multichamber sleeve non-gradient pumps
- 4-or less chambers
- 5 and more chambers
- multichamber gradient pressure pumps with pressure regulation
- 4 or less chambers
- 5-9 chambers
- 10 or more chambers
- multichamber extremity sleeve and trunk garment

compression trial. Previously discussed methods for volumetric assessment can be applied to this patient cohort as well. These interventional studies employ a pre- and postintervention measurement strategy. Controls must be rigorous to assure consistency of DLT treatment modalities, patient education and compression application. Ideally measurements are taken at repeated intervals by the same rater and treatment interventions are completed by a separate rater to blind the results.

Severity assessment may be utilized based on simple inter-limb volume differences assessed as minimal (<20% increase), moderate (20-40% increase), or severe (>40% increase).⁶⁶ This stratification enables a standardized measure of incremental change over time as well as categorization of treatment response based on severity. This also enables the researcher to draw conclusions about the intensity, duration and frequency of treatment for subjects with various levels of disease severity.

Measurement of interface pressure, as discussed in part I, should be part of any trial dealing with compression therapy regardless of the mode of compression. Interface pressure measures should be standardized along the limb to provide comparable data within each cohort. Inter and intra rater reliability with use of the pres-

sure monitor should be assessed before the trial begins to assure standardization.

Documentation of compression materials, bandaging technique, intervals of application, initial interface pressure, level of intervention, compliance, follow-up intervals, and prescription of new sleeves or bandages shall be noted. The compression class of garments for the upper extremity should be specified as should some practical specifications of the characteristics of the compression modality and materials (Table IV).⁶⁶⁻⁸¹

Additional methods may be used to assess lymph drainage capacity including; lymphoscintigraphy, fluorescence-microlymphangiography, indirect lymphography, MRI-lymphography, and Indocyanine-green test.⁶⁷⁻⁷² These tests provide an additional objective measure to further substantiate the impact of compression therapy on the lymphatic system.

Endpoints for each of these constructs are different (Figure 2). In Construct A, favorable outcomes will be evidenced by limb volume decongestion and improvements in the physical and functional domains. In Construct B, favorable outcomes will be evidenced by how the compression modality supports the limb and prevents reaccumulation of fluid in the limb. Recognizing that subjects in Construct B will be in a self-care phase of treatment, much education must be done regarding study protocols to control for variables that may confound. Standardized monitoring through a journal or log will assist in assessing compliance, compression wear time and activity levels.

General study recommendations

Good clinical practice

The formal requirements from Good Clinical Practice recommendations, based on the Helsinki declaration, must be fulfilled. This also includes the agreement of a local Ethics Committee.^{73, 74} Patients have to be included within the intention to treat analysis and the status of the patient needs to be defined at the point of leaving the trial. Trial registration in the International Standard Randomised Controlled Trial (ISRCTN) register⁷⁵ or with the United States

National Institutes of Health Clinical Trial registry⁷⁶ is recommended.

Drop-out and adverse events

A report of informed consent is necessary and all trials are voluntary for patients. The reason for a discontinuation of the study shall be specified. Adverse events of particular interest to patients with lymphedema include; acute inflammatory episodes, erysipelas, rapid volume increase, skin breakdown (rashes), blood clots and recurrent cancer.^{77, 78} Events need to be documented and each investigator will make individual decisions about whether the subject continues in the trial

Interventions/examples and proposals

As a primary outcome of this article, the authors offer specific recommendations for future studies involving compression therapy trials. These recommendations are outlined as "PROPOSALS 1-16" in the Appendix. This is intended to guide researchers towards cohesive efforts to remedy current deficits in the literature. Collaborative global efforts should be made in undertaking these trials to enable results that transcend national borders. Study results should aim to inform clinical best practice, but will also be useful in contributing to policy and payment structures. Large studies demonstrating not only efficacy and effectiveness of compression interventions, but also cost-effectiveness can directly improve delivery of services, access to materials and interventions and promote best practice.

Conclusions

This document represents the culmination of an expert panel discussion regarding the current state of the science of compression use in breast cancer related lymphedema treatment. We identify gaps in the current evidence as for early stage and manifest lymphedema and provide recommendations to drive future research trials. We recommend that this document be taken into advisement by researchers undertaking future compression therapy trials and encourage international collaboration in undertaking large-scale trials to support compression interventions.

Appendix 1

Proposed compression trials

I) Prophylaxis of arm lymphedema

PROPOSAL

1. Prospective multicenter RCT measuring arm volume before and monitoring after surgery*

- Group A: compression sleeves, *e.g.*, Class I (15-21 mmHg)
- Group B: no compression, no other specific treatment

*Such a study can follow constructs in Figure 1 either a) Patients presenting postsurgical arm-swelling between 3 – 5 % compared to the contralateral side or model b) all patients after breast cancer surgery.

II a) Initial treatment phase

PROPOSAL

2. Sleeves higher pressure (Class II or III) *vs.* low pressure (Class I)
3. Sleeves higher stiffness *vs.* lower stiffness exerting the same pressure
4. Sleeves *vs.* bandages
5. Sleeves *vs.* velcro device
6. Bandages *vs.* velcro device
7. Bandages *vs.* bandages (different types and pressures)
8. IPC and sleeves (or bandages) *vs.* same sleeves (or bandages) alone
9. IPC and basic compression *vs.* IPC and same basic compression (different types and pressures of IPC, *e.g.*, 30-50 mmHg *vs.* 120-150 mmHg)

Proposal concerning sleeves for the initial treatment phase:

Due to the volume reduction of the limb to be expected especially in the first days of treatment a sortiment of ready made stockings with different sizes should be available (staying in the property of the investigating institution).

II b) Maintenance phase

PROPOSAL

10. Sleeves custom-made (flat knitted) *vs.* ready made (round knitted), same pressure
11. Sleeves ready-made (flat knitted) *vs.* ready made (round knitted), same pressure
12. Sleeves high pressure (*e.g.*, Class II) *vs.* low pressure (Class I)
13. Sleeves *vs.* velcro device
14. IPC and sleeves *vs.* same sleeves alone
15. IPC and sleeves *vs.* IPC and same sleeves (different types and pressures of IPC)
16. IPC 3-4 chamber non-gradient pump *vs.* 10 and multi-chamber pump with possibility to add a trunk garment in case of trunk edema

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