What's best for our lymphoedema patients? Have we lost the patient as an individual in the quest for good science?

Contributors

NEIL PILLER
Director Lymphoedema Research Unit, Department of Surgery, School of Medicine, Flinders University, Adelaide, South Australia, Australia

ANNA FINNANE (AF)
PHD Student, Queensland University of Technology, Queensland, Australia

HUGO PARTSCH (HP)
Professor of Dermatology, Emeritus, University of Vienna, Austria

BEN SINGH (BS)
Masters Student, Queensland University of Technology, Queensland, Australia

SANDI HAYES
Associate Professor (Supervisor of AF's and BS's contributions), Queensland University of Technology

RICHARD WOODMAN (RW)
Professor of Epidemiology and Biostatistics, Flinders Centre for Epidemiology and Biostatistics, Flinders University, Adelaide, South Australia

In a recent issue of the *Journal of Lymphoedema,* Nickolaidis and Karlsson (2013) indicated that most of the standard treatments for lymphoedema patients were explored and developed early last century, and suggested that holistic assessment of the individual is critical for good outcomes, but that perhaps "less emphasis should be placed on manual lymphatic drainage (MLD) and more on compression, exercise and weight reduction."

In part, this is supported by a systematic review of the literature by Huang et al (2013) who found "the current evidence from randomised controlled trials (RCTs) does not support the use of MLD in preventing or treating lymphoedema." However, they did mention possible issues of "clinical and statistical inconsistencies" confounding the evaluation of the effect of the MLD. Stuiver et al (2013) found that "routine prescription of class II graduated compression stockings after inguinal lymph node dissection should be questioned and alternative prevention strategies should be considered" since there was no statistically significant differences between most of the key parameters of the trial. Yes, this is one study and the other is a systematic review — but how do we know what is best for our patients as a clinician?

If MLD and compression are providing questionable benefits for lymphoedema management, how can clinicians help the patient? What are clinicians left with; exercise? Skin care? Weight management? Have we lost the ability to see the patient in front of us and respond uniquely to that person because of these types of findings? Are clinicians afraid that if the evidence is there against the treatment, one may reasonably think they should not use it? Is the issue that unless the statistics show a treatment is beneficial, it is not likely to be effective or get funded as a treatment option?

So what does a clinician do in light of these findings, whether they are working as a sole practitioner or in a larger public or private hospital? Importantly, what do patients think when they read this on the internet?

Neil Piller

References

Nikolaidis P, Karlsson K (2013) Evidence and tradition in conflict: The Swedish experience of lymphoedema treatment and care. *Journal of Lymphoedema* 8(2): 21–3

Huang TW, Tseng SH, Lin CC et al (2013) Effects of manual lymphatic drainage on breast cancer related lymphoedema: a systematic review and meta analysis of randomised controlled trials. *World J Surg Oncol* 11: 15

Stuiver MM, de Rooij JD, Lucas C et al (2013) No evidence of benefit from class II compression stockings in the prevention of lower limb lymphoedema after inguinal lymph node dissection: results of a randomised controlled trial. *Lymphology* 46(3): 121–31

AF: Theory-based, scientific-based, or anecdotal evidence: what's more important in the treatment of lymphoedema

Despite the large number of intervention studies (n>160), and over 20 reviews of the published literature over the past decade, those with lymphoedema continue to face inconsistent treatment guidelines and conflicting clinical opinions about optimal treatment approaches. Consequently, people with lymphoedema commonly express feelings of frustration and confusion with regard to what constitutes 'optimal' treatment.

There is no doubt that the quality of future research on lymphoedema treatment effect must improve. This will involve the conduct of adequately powered RCTs, clear reporting of methods and results, and a more comprehensive assessment of lymphoedema, as well as other outcomes important to individuals with lymphoedema (e.g. associated symptoms, overall function and quality of life). It will also involve consideration of outcomes that are relevant to decision making at the public health level (e.g. evaluation of cost-effectiveness).

Furthermore, consideration must also be given to the relationship between treatment effect and lymphoedema location, duration and severity. For example, it is plausible that the potential benefit of any given treatment will be dependent on the tissue composition of those with lymphoedema included in the study sample and/or the location of the lymphoedema (e.g. upper *vs* lower-limb lymphoedema).

However, central to the treatment decision-making process is the patient and, as such, future research must acknowledge

AVAILABLE ON DRUG TARIFF

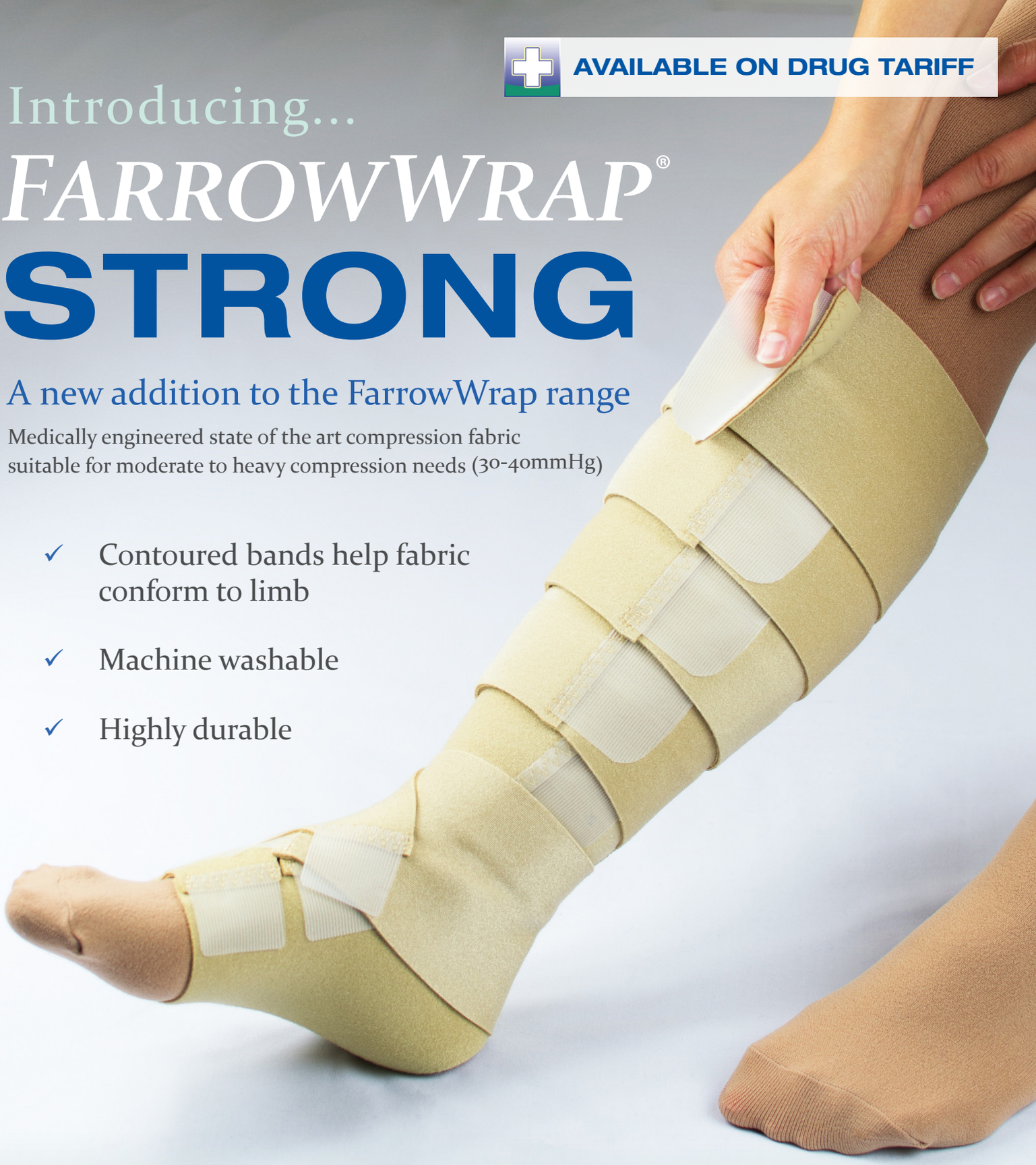
Introducing...

FARROWWRAP® STRONG

A new addition to the FarrowWrap range

Medically engineered state of the art compression fabric suitable for moderate to heavy compression needs (30-40mmHg)

- ✓ Contoured bands help fabric conform to limb
- ✓ Machine washable
- ✓ Highly durable



HADDENHAM®

Haddenham Healthcare

Problem Solving Compression Therapy

HADDENHAM CODE FINDER

"The easy way to find our Pip-Codes"

GET IT ON Google play

Available on the App Store

Also available on our website

Email: fp10@hadhealth.com Tel: 01844 208842 Web: www.hadhealth.com

and address the adherence barriers to prescribed lymphoedema treatment. For example, while current scientific evidence supports the use of compression garments for reducing limb volume, if an individual cannot, or chooses not to use a compression garment, perhaps due to cost barriers, discomfort, skin irritation or visual appearance, alternatives need to be identified and implemented (e.g. finding a garment of lower cost, but with minimal change in treatment effect).

Also, patient perspectives regarding what is deemed a clinically relevant improvement must also be taken into consideration. While the extent of swelling reflects the primary outcome for the majority of lymphoedema treatment studies, associated symptoms experienced and reported by those with lymphoedema include heaviness, tightness, numbness, pain, reduced fitness and function, and impairments in quality of life.

For some, changes in these 'associated' outcomes may be more important than a change in swelling. Therefore, if the aim of treatment is to improve the quality of life of people with lymphoedema, clinicians must consider the condition from the patient's perspective, beyond measurable swelling, as well as the long-term burden of treatment.

HP Confusing trials in lymphoedema therapy, uncertain benefits and knowing what is best for the patient

Decongestive lymphatic therapy (DLT) or complete decongestive therapy (CDT) is the basis of conservative management of lymphoedema. This treatment modality, which is entirely based on experience, was recommended long before the principles of evidence-based medicine were instituted. This still causes considerable problems with occasionally confusing study results found.

Actually, DLT does not correspond to a clearly defined therapy, but is a combination of different, vaguely defined treatment modalities — compression, exercises, skin care and MLD are the main constituents. In most of the RCTs performed during recent years, comparisons have been made between DLT as the standard and some form of modified DLT — where one component is changed or omitted.

The scientific evidence of such trials concerning the assessment of one component is mostly poor. This is especially true when effective compression is maintained in both arms and when, for instance, MLD is withheld in one arm. When examining volumetric outcomes, little difference may be expected because the same type of efficient compression therapy in both arms will overcome a potential benefit from MLD. However, when quality-of-life parameters are also taken into consideration, there might be a difference.

Future studies should, therefore, concentrate on comparisons between single components of DLT (e.g. compression modality *vs* compression modality without additional therapeutic measures. The impact of confounding variables and also ethical problems could be minimised by choosing shorter study periods.

Before a clinical study is planned, acute experiments may reveal valuable information concerning a 'dose-response relationship' by comparing the exerted pressure or the frequency and different sequence of physical interventions for specific predefined outcome parameters. The volume reduction of a lymphoedematous limb by compression device A *vs* device B or by pump A *vs* pump B would reveal important results after an application time of just one or two hours. It is difficult to understand why such basic trials, promising clear-cut results are still missing from the literature.

References

Partsch H, Damstra RJ, Mosti G (2011) Dose finding for an optimal compression pressure to reduce chronic edema of the extremities. *Int Angiol* 30(6): 527–33

BS Preventing and treating lymphoedema with exercise

It is true that evidence supporting the effect of a range of conservative treatment options is varied, with inconsistent findings for a number of lymphoedema treatment options or insufficient evidence from studies of high-quality design to consider other treatments as 'evidence-based'. That is, with the exception of exercise.

The effect of exercise on the musculoskeletal and cardiovascular systems are well-documented; exercise improves the function of these physiological systems at the cellular through to the systems level, with these benefits, in turn, aiding the efficiency of the lymphatic system (Schmitz, 2009). Therefore, in theory at least, exercise has the potential to be a prevention and treatment strategy for lymphoedema, with this relationship becoming a topic of scientific evaluation over the past decade.

Today, there is evidence from cross-sectional, as well as prospective, cohort studies demonstrating that those who are regularly active have significantly lower odds of developing lymphoedema compared with those sedentary or insufficiently active (that is, participating in <150 minutes of weekly physical activity) (Hayes et al, 2008; Gho et al, 2013). Furthermore, a large RCT has demonstrated that participating in a 12-month resistance exercise intervention reduced incidence of lymphoedema following treatment for breast cancer, in particular for those women who received more extensive surgery (≥ 5 lymph nodes dissected) (Schmitz et al, 2010). There is also evidence supporting exercise as an effective treatment strategy (Schmitz, 2009).

Over 10 studies, including case-control studies, pre-post intervention studies and RCTs have demonstrated that, at worst, participating in exercise neither initiates new cases nor exacerbates existing cases of lymphoedema (Schmitz, 2009; Kwan et al, 2011). In addition, the largest RCT showed that twice-weekly resistance exercise over 1 year reduced the amount and severity of lymphoedema-associated symptoms and reduced by half the incidence of lymphoedema exacerbations requiring specialist treatment (Schmitz et al, 2009).

Overall, there is compelling and growing evidence that supports exercise of various modalities (aerobic- and resistance-based exercise) as a safe and effective form of therapy for lymphoedema. However, this evidence needs to be applied with caution, acknowledging that the exercise evaluated in the above-mentioned studies was mostly supervised by qualified allied health professionals and individually progressed, with consideration of lymphoedema severity, patient preferences and comorbidities. Also, lymphoedema was clinically assessed regularly, taking into account changes in patient-reported symptoms, to

ensure appropriate exercise prescription and safety.

At a minimum, exercise may provide lymphoedema patients with widespread benefits such as reducing the risk of subsequent chronic disease (e.g. diabetes, osteoporosis or cancer recurrence), improved strength and mobility of the affected limb and improvements in overall fitness, function and quality of life. Therefore, exercise is considered a form of evidence-based medicine that should be undertaken by those with lymphoedema, irrespective of participation in other forms of lymphoedema treatment.

References

Gho SA, Steele JR, Jones SC, Munro BJ (2013) Self-reported side effects of breast cancer treatment: a cross-sectional study of incidence, associations, and the influence of exercise. *Cancer Causes Control* 24(3): 517–28

Hayes SC, Janda M, Cornish B et al (2008) Lymphedema after breast cancer: incidence, risk factors, and effect on upper body function. *J Clin Oncol* 26(21): 3536–42

Kwan ML, Cohn JC, Armer JM et al (2011) Exercise in patients with lymphedema: a systematic review of the contemporary literature. *J Cancer Surviv* 5(4): 320–36

Schmitz KH (2009) Balancing lymphedema risk: exercise versus deconditioning for breast cancer survivors. *Exerc Sport Sci Rev* 38(1): 17–24

Schmitz KH, Ahmed RL, Troxel A et al (2009) Weight lifting in women with breast cancer–related lymphedema. *N Engl J Med* 361(7): 664–73

Schmitz KH, Ahmed RL, Troxel AB et al (2010) Weight lifting for women at risk for breast cancer-related lymphedema: a randomized trial. *JAMA* 304(24): 2699–705

RW When treatment effects are modest and not statistically significant: would it be better to consider the net benefit?

In the RCT conducted by Stuiver et al (2013), the investigators concluded that given there were no significant differences between the control and intervention groups in any of the primary outcomes assessed, "the routine prescription of class II graduated compression stockings after inguinal lymph node dissection (ILND) should be questioned and alternative prevention strategies be considered".

In considering their findings, the authors were careful to also discuss the possibility of a 'Type 2' error. That is, that they perhaps failed to detect a real treatment effect when one truly exists due to an insufficient number or participants or events. The chosen *a priori* specification of the treatment effect for the powering of the study was based on an anticipated absolute reduction in the incidence of lymphoedema from 40% to 10%, given that "this represented a number needed to treat (NNT) of approximately three patients, which would be clinically meaningful".

The effects that were actually observed in the RCT were, in the end, much closer to an alternate treatment effect estimate cited by the authors themselves and based on available observational data where there was a 17.9% absolute risk reduction from a 45.8% incidence (39% in relative terms) for a compression stocking treatment group compared to an unexposed group. However, on the basis of their pre-specified treatment effect margin, the investigators concluded that the absolute and unadjusted reduction in risk of lymphoedema of 16% at 6 months (81% *vs* 65%) and the unadjusted relative risk reduction of 31% (HR=0.69, 95% CI=0.38 to 1.26, p=0.23) did not show adequate evidence of benefit to the patient to recommend its use.

The question of whether or not the investigators were justified in powering their study on an effect that they themselves judged to be clinically meaningful and one that was larger than that seen in observational studies, raises the issue of whether or not there exists better ways of declaring a treatment as useful or not.

In addition to the treatment effect itself, other factors to consider are those of individual patient risk and the risk of unnecessary harm to the patient. In basing their power calculation on NNT, and their interpretations on the statistical significance of the absolute treatment effect alone, the investigators do not consider individual patient risk or whether or not there exists a 'net benefit' (Steyerberg et al, 2012); i.e. the treatment effect adjusted for the harm caused to those patients who would not end up having lymphoedema even without treatment.

Were the negative effects of compression stocking treatment, including discomfort, concerns over appearance, costs, and a reduction in quality of life to be considered as relatively harmless then we could justify treating all patients assuming that there is at least some benefit of treatment. Given, however, that such effects are not considered harmless, we need to try and quantify a risk threshold for the treatment of patients. This is done by deciding at what level of lymphoedema risk the benefits of treatment start to outweigh treatment harm (Dorresteijn et al, 2013). If the benefit of treatment is only 15% (rather than the arbitrarily chosen 30%), but this benefit still exceeds the risk of treatment harm when the lymphoedema risk is say 40% (the average patient's risk in this trial), then treatment could be justifiably provided to patients at this level of lymphoedema risk and beyond.

For patients at higher lymphoedema risk, there is less risk of treatment harm (particularly unnecessary treatment) and, therefore, even greater chance of seeing a net benefit. A further statistical aspect of this particular trial that influences interpretation concerns the small number of events that had the capacity to impact heavily on the statistical significance because of the trial's relatively small size. In such circumstances, a frailty index to help interpret the reliability of results has recently been proposed (Walsh et al, 2014).

Rather than determining whether the trial reached statistical significance in terms of an arbitrarily chosen effect size — or whether the study was underpowered to detect a smaller, more realistic, effect that was indeed observed — a more holistic look at the various aspects of the trial suggests that this is a treatment that may well be of benefit, particularly in higher risk patients. A larger RCT that also allows for the development of individual risk prediction might be the next step in providing more definitive evidence for establishing compression stocking treatment guidelines after ILND.

References

Dorresteijn JA, Boekholdt SM, Van Der Graaf Y et al (2013) High-dose statin therapy in patients with stable coronary artery disease: Treating the right patients based on individualized prediction of treatment effect. *Circulation* 127(25): 2485–93

Steyerberg EW, Pencina MJ, Lingsma HF et al (2012) Assessing the incremental value of diagnostic and prognostic markers: A review and illustration. *Eur J Clin Invest* 42(2): 216–28

Stuiver MM, De Rooij JD, Lucas C et al (2013) No evidence of benefit from class-ii compression stockings in the prevention of lower-limb lymphedema after inguinal lymph node dissection: Results of a randomized controlled trial. *Lymphology* 46(3): 120–31

Walsh M, Srinathan SK, Mcauley DF et al (2014) The statistical significance of randomized controlled trial results is frequently fragile: A case for a fragility index. *J Clin Epidemiol* 67(6): 622–8