EFFECTIVENESS OF MANUAL LYMPH DRAINAGE FOR THE TREATMENT OF BREAST CANCER-RELATED LYMPHEDEMA: EFFORT-BCRL TRIAL

Tessa De Vrieze PhD, PT – post doctoral research fellow FWO
Annual meeting Benelux Society of Phlebology 2022, Leuven
17% (n = 2169) develops lymphedema of the arm
Diagnosis and treatment for cancer: lymph node dissection, radiotherapy → damage to lymphatic system

- reduced transport capacity of the lymphatic system

Incidence BCRL (DiSipio et al 2013)
SLNB: 5%
ALND: 20%
TREATMENT OF LYMPHEDEMA

Decongestive Lymphatic Therapy (International Society of Lymphology)

Intensive phase
Aim: reduction of lymphedema volume

Methods:
- Skin care
- MLD
- Exercises
- Bandaging

Maintenance phase
Aim: stabilisation of lymphedema volume

Methods:
- Skin care
- (MLD)
- Exercises
- Compression stocking
Purpose of manual lymph drainage (MLD):

- To stimulate lymphatic transport
- To reduce swelling
- To soften potential hardened skin

Effect of MLD?
• Almost every patient with BCRL: MLD as a treatment modality
  o No consensus on clinical effectiveness (but physiological)

• Possible reason: "traditional" MLD applied in an inefficient way
  o Currently: mostly relative low pressure, mostly pumping manoeuvres
  o But above all: according to a 'normal' anatomy
    → lymphatic ducts damaged due to the treatment
    → fibrosis of the superficial system
    (Kwon 2016)
MORE EFFECTIVE?
To improve the efficiency of MLD:
- Gliding (vs. pumping) and relatively higher (vs. lower) pressure → enhanced lymphatic transport (Belgrado 2016)
- On areas with dermal rerouting as well as functional lymphatic collectors, visualized by lymph fluoroscopy

= fluoroscopy-guided MLD (Belgrado et al 2016)
OBJECTIVE

• One session of fluoroscopy-guided MLD improves the lymphatic transport (Belgrado 2016, Tan 2011)

• **Effect of multiple sessions of fluoroscopy-guided MLD on clinical parameters?**

  ➔ **EFforT-BCRL trial**

  “**Effectiveness of fluoroscopy-guided manual lymph drainage for the treatment of breast cancer-related lymphedema**”

Aim =
To investigate, through a multi-center, double-blinded, randomized controlled trial, the effectiveness of fluoroscopy-guided MLD vs. traditional MLD vs. placebo MLD on clinical parameters in patients with chronic BCRL.
**METHODOLOGY**

**N= 201, study centers:**
- 1. UZ Leuven, Centre for Lymphoedema, Leuven
- 2. UMC Sint-Pieter Brussel, Lymphedema Clinic, Brussel
- 3. UZ Antwerpen, Multidisciplinary Breast Clinic, Antwerpen
- 4. AZ Groeninge Kortrijk, Centre for Oncology, Kortrijk
- 5. UZ Gent, Centre for Radiotherapy, Gent

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Women/men with unilateral BCRL</td>
<td>- Allergy for (sodium)iodine; ICG</td>
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<tr>
<td>- Chronic lymphedema (&gt;3 months), stage I to IIb</td>
<td>- Increased activity of the thyroid gland</td>
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<tr>
<td>- Pitting edema</td>
<td>- Age &lt;18y</td>
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<tr>
<td>- ≥5% difference between both arms and/or hands, corrected for arm dominance</td>
<td>- Edema due to other reason</td>
</tr>
<tr>
<td>- Written informed consent</td>
<td>- Lymph node transfer, lymphovenous shunt</td>
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<td></td>
<td>- Not able to participate the entire study period</td>
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<tr>
<td></td>
<td>- Mentally or physically impossible to participate</td>
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</tbody>
</table>
METHODOLOGY

Study design

201 patients with unilateral arm/hand lymphedema

Standard treatment:
Education, skin care, compression therapy, exercises

Intensive phase: 3w intensive (14 sessions)
Maintenance phase: 6M maintenance (18 sessions)
Follow-up phase: 6M follow-up

Intervention group (n=67)
Fluoroscopy-guided MLD

Control group (n=67)
Traditional MLD

Control group (n=67)
Placebo MLD
## METHODOLOGY

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Fluoroscopy-guided</th>
<th>Traditional</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>On areas with dermal rerouting and draining lymphatic routes, visualized by fluoroscopy</td>
<td>• Comparable with MLD on ‘healthy’ lymphatic system (“blind”)</td>
<td>• No influence on lymphatic system</td>
<td></td>
</tr>
<tr>
<td>Hand movements:</td>
<td>• Hand movements:</td>
<td>• Hand movements:</td>
<td></td>
</tr>
<tr>
<td>• Higher pressure</td>
<td>• Lower pressure</td>
<td>• Across the muscles</td>
<td></td>
</tr>
<tr>
<td>• Gliding movements on skin</td>
<td>• Pumping movement on skin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
METHODOLOGY

Assessments

Intensive phase
- Baseline: Fluoroscopic investigation
- 3w: Fluoroscopic investigation
- 1M: Fluoroscopic investigation
- 3M: Fluoroscopic investigation

Maintenance phase
- 6M: Fluoroscopic investigation

Follow-up
- 12M: Fluoroscopic investigation
<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lymphedema volume at level of the hand <em>(inter-limb ratio)</em></td>
<td>Valgrado volumetry</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Accumulation of lymph at level of the shoulder/trunk <em>(mean of both inter-limb ratios)</em></td>
<td>Tissue dielectric constant <em>(Delfin MoistureMeterD compact®)</em></td>
</tr>
</tbody>
</table>
Hypotheses:

Patients receiving the fluoroscopy-guided MLD additional to decongestive lymphatic therapy, will have:

1) a significantly greater reduction in volume at the level of the arm/hand;

2) significantly less accumulation of fluid at the level of the shoulder/trunk;

than patients receiving traditional MLD or placebo MLD after three weeks of intensive treatment (P)
<table>
<thead>
<tr>
<th>Secondary outcomes</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Local tissue water at the level of the arm/hand and shoulder/trunk (\text{inter-limb ratio PWC}%)</td>
<td>Tissue dielectric constant (Delfin MoistureMeterD compact®)</td>
</tr>
<tr>
<td>2. Extracellular fluid in the upper limb (L\text{-Dex score})</td>
<td>BioImpedance Spectrosopy (Impedimed U400®)</td>
</tr>
<tr>
<td>3. Thickness of the cutis and subcutis at the level of the arm/hand and shoulder/trunk (\text{inter-limb ratio mm, presence of thickened skin})</td>
<td>Ultrasound and palpation</td>
</tr>
<tr>
<td>4. Skin elasticity at the level of the arm/hand and shoulder/trunk (\text{inter-limb ratio Newton, presence of fibrotic skin})</td>
<td>SkinFibrometer®</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Method</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>5. Problems in functioning</td>
<td>Lymph-ICF-UL questionnaire</td>
</tr>
<tr>
<td>6. Quality of Life</td>
<td>McGill QOL questionnaire</td>
</tr>
<tr>
<td>7. Amount of episodes of erisypelas</td>
<td>Interview</td>
</tr>
<tr>
<td>8. Superficial lymphatic architecture</td>
<td>Fluoroscopy</td>
</tr>
</tbody>
</table>
RESULTS: PARTICIPANTS

- 391 patients screened
- 194 patients included and randomized
- 197 patients excluded
  - not meeting inclusion criteria (n=115)
  - declined to participate (n=82)

Baseline characteristics were comparable between all groups

<table>
<thead>
<tr>
<th>n</th>
<th>Fluoro</th>
<th>Traditional</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>65</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>P</td>
<td>63</td>
<td>63</td>
<td>64</td>
</tr>
<tr>
<td>P6</td>
<td>62</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>P12</td>
<td>60</td>
<td>61</td>
<td>61</td>
</tr>
</tbody>
</table>

- After intensive treatment: 5 drop-outs of which 4 lost to follow-up
- After maintenance treatment: 3 additional patients lost to follow-up
- After follow-up: 5 additional patient lost to follow-up

During 12 months: 12 patients (6%)
RESULTS: PRIMARY OUTCOMES

(1) Volume arm/hand:

![Graph showing volume arm/hand outcomes for different treatment groups.]

<table>
<thead>
<tr>
<th></th>
<th>B0</th>
<th>P</th>
<th>P1</th>
<th>P3</th>
<th>P6</th>
<th>P12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroscopy-guided MLD (N)</td>
<td>65</td>
<td>63</td>
<td>63</td>
<td>61</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>Traditional MLD (N)</td>
<td>64</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>62</td>
<td>61</td>
</tr>
<tr>
<td>Placebo MLD (N)</td>
<td>65</td>
<td>64</td>
<td>64</td>
<td>63</td>
<td>63</td>
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</table>
## RESULTS: PRIMARY OUTCOMES

### (1) Volume arm/hand:

Relative change compared to baseline

<table>
<thead>
<tr>
<th></th>
<th>FLUO MLD</th>
<th>TRADITIONAL MLD</th>
<th>PLACEBO MLD</th>
<th>P-values for comparison of change between the groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ratio (95%CI)</td>
<td>P-value</td>
<td>ratio (95%CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>P vs B0</td>
<td>0.957 (0.946;0.968)</td>
<td>&lt;.0001</td>
<td>0.958 (0.947;0.969)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>P1 vs B0</td>
<td>0.946 (0.934;0.957)</td>
<td>&lt;.0001</td>
<td>0.939 (0.927;0.950)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>P3 vs B0</td>
<td>0.939 (0.924;0.953)</td>
<td>&lt;.0001</td>
<td>0.941 (0.927;0.956)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>P6 vs B0</td>
<td>0.947 (0.931;0.964)</td>
<td>&lt;.0001</td>
<td>0.947 (0.931;0.964)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>P12 vs B0</td>
<td>0.948 (0.930;0.966)</td>
<td>&lt;.0001</td>
<td>0.961 (0.943;0.979)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Alpha = 0.0125 (due to 2 Bonferroni corrections)
RESULTS: PRIMARY OUTCOMES

(2) Accumulation shoulder/trunk:
RESULTS: PRIMARY OUTCOMES

(2) Accumulation shoulder/ trunk:

Relative change compared to baseline

<table>
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<td><strong>ratio (95%CI)</strong></td>
<td><strong>P-value</strong></td>
<td><strong>ratio (95%CI)</strong></td>
<td><strong>P-value</strong></td>
</tr>
<tr>
<td>P vs B0</td>
<td>1.042 (1.023;1.062)</td>
<td>&lt;.0001</td>
<td>1.007 (0.989;1.026)</td>
</tr>
<tr>
<td>P1 vs B0</td>
<td>1.029 (1.010;1.049)</td>
<td>0.0037</td>
<td>1.009 (0.989;1.029)</td>
</tr>
<tr>
<td>P3 vs B0</td>
<td>1.008 (0.988;1.028)</td>
<td>0.4245</td>
<td>0.990 (0.971;1.010)</td>
</tr>
<tr>
<td>P6 vs B0</td>
<td>0.999 (0.981;1.017)</td>
<td>0.9320</td>
<td>0.990 (0.972;1.008)</td>
</tr>
<tr>
<td>P12 vs B0</td>
<td>1.008 (0.989;1.029)</td>
<td>0.4046</td>
<td>0.991 (0.972;1.011)</td>
</tr>
</tbody>
</table>

Alpha = 0.0125 (due to 2 Bonferroni corrections)
Interpretation results (hypotheses)

Patients having received fluoroscopy-guided MLD during the intensive treatment phase of the DLT:

- (1) did not show a significant greater reduction in lymphedema volume at the level of the arm/hand than patients who received traditional MLD \((p=0.890)\) or placebo MLD \((p=0.826)\);
- (2) did not show a significant lower accumulation of fluid at the level of the shoulder/trunk than patients who received traditional MLD \((p=0.0130^*)\) or placebo MLD \((p=0.101)\).

\(*\text{Alpha} = 0.0125\)
RESULTS: SECONDARY OUTCOMES

Interpretation results (hypotheses)

Patients receiving the fluoroscopy-guided MLD additional to decongestive lymphatic therapy:

Did not show a

1) significantly greater reduction in amount of local tissue water; extracellular fluid; thickness of the skin (cutis and subcutis); episodes of erisypelas

2) significantly greater improvement in elasticity of the skin; problems in functioning; quality of life; lymphatic
functioning

than patients receiving traditional MLD or placebo MLD after three weeks of intensive treatment (P) and after one (P1), three (P3), six (P6) and twelve (P12) months of maintenance treatment (M6-M12 = follow-up)
CONCLUSION

Fluoroscopy-guided MLD (and traditional MLD) did NOT show an added benefit in terms of:

- Lymphedema volume reduction at level of the arm/hand
- Reduction in fluid accumulation at level of the shoulder/trunk
- Reduction in local tissue water at level of the arm/trunk
- Reduction in extracellular fluid at level of the upper limb
- Reduction in skin thickness and episodes of erisypelas
- Improvement in skin elasticity, problems in functions, QoL, lymphatic functioning in patients with chronic BCRL.

Challenges to Developing Practice

“"The greatest difficulty in the world is not for people to accept new ideas, but to make them forget their old ideas!""

John Maynard Keynes
thank you