Lymphology 55 (2022) 155-166

MANUAL LYMPHATIC DRAINAGE INCREASES THE NUMBER OF OPENED LYMPHATIC PATHWAYS IN PATIENTS WITH LOWER LIMB LYMPHEDEMAS: A SEQUENTIAL RESEARCH ON 80 PATIENTS

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ABSTRACT

The purpose of this study was to lymphoscintigraphically assess the effect of skin mobilization, nonspecific massage, and manual lymphatic drainage (MLD) on the root of the lower limb in patients with lower limb lymphedema. Lower limb root lymphoscintigraphical exams of 80 patients with lower limb lymphedema were analyzed. All patients underwent our stand 3 phase protocol and then were subjected to the 4th phase which included 3 subphases. Images were taken directly after the injection (subphase 1), after pinching and stretching the injection site (subphase 2), after nonspecific massage was applied to the injected site (subphase 3) and after manual lymphatic drainage of the injected site (subphase 4). The number of opened lymphatic pathways was analyzed and compared after and between each subphase (SP). SP 1 displayed open lymphatic pathways in 22 of the 80 cases (27.5%). SP 2 displayed newly opened lymphatic pathways in 48 of the 80 cases (60.0%). SP 3 displayed newly opened lymphatic pathways in 57 of the 80 cases (71.3%). Only 9 of these 57 cases did not show improvement following the next SP. SP 4 displayed newly opened lymphatic pathways in 60 of the 80 cases (75.1%). MLD improved the visualization of the lymphatic pathways in 48 cases (60%) compared to phase 3. MLD was the only technique to allow visualization of the lymphatic drainage at the level of the root of the edematous limb in 6 cases (7.5%). Physical therapy leads to a greater number of lymphatic collaterals opening in a region where no other complex decongestive therapy technique can be applied.

Keywords: Manual Lymphatic Drainage, lymphedema, lymphoscintigraphy

Lymphedema is a chronic and evolving condition that can cause significant morbidity presenting in various forms depending on its origin and localization. It affects 140 to 250 million people worldwide, and 99% of this population are associated with cancer treatment or parasitic infection (1). According to the 2020 consensus of the International Society of Lymphology (ISL), lymphedema is a superficial (and/or subfascial) indication of lymphatic system insufficiency and disturbed lymph transport (2). The accumulation of extracellular protein-rich fluid due to lymphatic insufficiency leads to swelling of the affected body part and eventually to a chronic inflammatory status (3). Lymphedemas are classified into two types: primary lymphedema (congenital, praecox, or tarda) follow dysplasia of the lymphatic system (lymph vessels or nodes), and secondary lymphedemas following damage to the lymphatic system. Secondary lymphedema can be caused by various factors such as trauma, infection, neoplastic invasion, and parasitic infection however in developed countries, the primary causes are lymphadenectomy, radiotherapy, and chemotherapy for oncological treatment (4,5). In most cases, the physical examination and clinical history are sufficient to diagnose lymphedema. However, in some more complex cases where the clinical history remains unclear, proper imaging is necessary to objectify lymphatic insufficiency (6,7). Several imaging modalities can be used to visualize the lymphatic system (8), such as MRI (9) and lymph fluoroscopy (10). Amongst these, the lymphoscintigraphy is considered to be the gold standard for lymphedema diagnosis and the only imaging modality that can give an approximate quantification of lymphatic flow by tracer quantification (11). Lymphoscintigraphy can offer valuable information about a patient's physiological drainage guiding the patient to an appropriate treatment decision. Physical therapy and particularly manual lymphatic drainage (MLD), plays a significant role in the management of lymphedema according to the 2020 ISL consensus (2,12,13). MLD is a very specific massage technique aimed at improving lymphatic drainage (14) by increasing lymph vessel contractility, facilitating the edema resorption (15-17) or moving the edema from a poorly drained area to a better drained area. Although MLD remains an important part of the physical treatment for lymphedema, its effectivity alone is still debated principally due to a lack of trials with large populations (18,19). To further explore the effects of MLD on physiological drainage in lymphedema patients, this study focuses on the use of lymphoscintigraphy as an evaluation tool of the technique. In some cases, conventional three-phased lymphoscintigraphy (evaluation of lymphatic drainage following a period of rest, following active mobilization and physical activity of the edematous and healthy lower limbs) may not provide sufficient information on the patient's lymphatic drainage, either due to decreased resorption of the injection site or significant dermal backflow. In those cases, a fourth phase can be added by administering another injection at the root of the limb in regards to the greater trochanter. The additional phase helps complete the diagnosis, enabling the physician to guide the patient towards appropriate treatment (physical or surgical). Imaging can be performed following the injection, skin mobilization, a nonspecific massage, and a MLD treatment. The purpose of this study was to analyze the results of the fourth phase lymphoscintigraphical examination of patients with lower limb lymphedema, in order to evaluate the effects of MLD.

METHODS

Data Sources and Searches

This was a retrospective sequential study. Eighty lymphoscintigraphical clinical imaging exams (LyScs) of patients presenting primary (n=44) or secondary (n=36) lower limb lymphedema were analyzed at the Jules Bordet Institute, Brussels, Belgium (*Table 1*). All medical data and information regarding the patients included in this study were used in compliance with the rules of conduct dictated by the institution and in agreement with the ethics committee of the Jules Bordet Institute (ethics committee number 2048). Every LySc was performed by the same investigator following a lower limb LySc protocol approved by the Belgian Society of Nuclear Medicine and recognized by the Belgian National Health Insurance System (Institute National Assurance Maladie Invalidité or INAMI) (20,21). Patients with a painful hip due to inflammation, an osteoarticular disorder, or pain following trauma of the lower limb did not undergo MLD to avoid painful manipulation during imaging.

TABLE 1
Demographic Information of Patients Enrolled in the Study

Total number of subjects	80
• Women	61
• Men	19
Primary Lymphedema	44
Secondary Lymphedema	36
Age (mean +/- SD)	53 ± 16.2
• Min	13
• Max	88

Before every lymphoscintigraphy, patients were required to be aware of the protocol and the clinical importance of following it. Patients were advised to go to the bathroom prior to examination, and any elastic stockings were removed before the injection. Patients remained in a dorsal decubitus position on the examination bed, and the injections were administered at least 5 min after positioning the patient. The lymphoscintigraphy apparatus used in this study was an SMV ST-XLi instrument from GE Healthcare, Little Chalfont, United Kingdom. The injected solutions were made by adding 30 mCi (1110 MBq) of 99mTcO4 in one ampoule of Human Serum Albumin nanosized colloids Nanocoll® (GE Healthcare, Little Chalfont, United Kingdom) and saline 0.9% up to a final volume of 2.0 ml. Injections consisted of 0.2 cc (3 mCi per syringe) of tracer solution. The LySc injections were administered subcutaneously in the first

TABLE 2
Imaging Protocol Describing the Three-phase Lymphoscintigraphy Investigations Utilized to Examine Lower Limb Superficial Lymphatic System. General Parameters: Collimator, Low Energy with High Resolution, 140 keV

	Superficial lymphatic system lymphoscintigraphy investigation of lower limb edema	
Phase n°	**Description**	**Acquisition parameters**
0	Camera centred on the injection sites as well as the syringes for radioactivity measurement	Anterior static imaging: Word mode, Matrix 128x128, 60 sec
1	Patient at rest for 30 min in the dorsal decubitus position Dynamic imaging centred on the inguino-iliac lymph nodes for 30 minutes, followed by entire-body scanning from the feet to the head	Antero-posterior dynamic imaging: Matrix 64x64, 90 frames of 20 sec Antero-posterior whole-body scanning: Continuous mode, 1024x256, 40 cm/min
2	Same position as the previous phase; the patient is required to stand tiptoed for 5 minutes. Dynamic imaging centred on the inguino-iliac lymph nodes for 15 minutes, followed by whole body scanning from head to toe.	Anteroposterior dynamic imaging: Matrix 64x64, 90 frames 10 sec Antero-posterior whole-body scanning: Continuous mode, 1024x256, 40 cm/min
3	The patient is required to walk for one hour. After that, the patient returns on the table to undergo the final imaging. Static imaging camera centred on the injection sites and syringes followed by whole body scanning from the feet to the head.	Anterior static imaging: Word mode, Matrix 128x128, 60 sec Antero-posterior whole-body scanning: Continuous mode, 1024x256, 40 cm/min

TABLE 3
Imaging Protocol Describing the Fourth Phase of the Lymphoscintigraphy Investigation Utilized to Examine the Lower Limb Superficial Lymphatic System in Selected Patients Following Three-phase Protocol (Table 2) . General Parameters: Collimator, Low Energy with High Resolution: 140 keV]

Fourth phase of superficial lymphatic system lymphoscintigraphy investigation		
Subphases n°	**Description**	**Acquisition parameters**
1	Intradermal injection in front of the greater trochanter of the oedematous lower limb. Static imaging centred on the injection site.	Anterior-posterior static imaging: Byte mode, Matrix 256x256, 60 sec
2	Pinching of the injected site for 5 min. Static imaging centred on the injection site.	Anterior-posterior static imaging: Byte mode, Matrix 256x256, 60 sec
3	Five-minute period of deep muscular tissue massage of the injection site. Static imaging centred on the injection site.	Anterior-posterior static imaging: Byte mode, Matrix 256x256, 60 sec
4	Ten-minute period of manual lymphatic drainage of the shoulder and injected site. Static imaging centred on the injection site	Anterior-posterior static imaging: Byte mode, Matrix 256x256, 60 sec

interdigital space of each lower limb for the classical 3-phase LySc and intradermally at the level of the greater trochanter of the edematous lower limb for the fourth phase. Both LySc protocols were subdivided into 4 phases, as described in *Table 2* for the classical 3-phase LySc and in *Table 3* for the fourth phase LySc. Every LySc was analyzed by the same expert investigator and verified by a second investigator. Each phase of the protocol was set to evaluate one physiological aspect of the patient's lymphatic drainage, and additional acquisitions provided the possibility to further quantify the tracer extraction following each phase, as follows (*see Fig. 1*):

- Classical 3 phase lymphoscintigraphy:

1. Phase 1: Evaluation of lymphatic drainage after a period of rest (30 minutes),
2. Phase 2: Evaluation of lymphatic drainage after a period of moderate physical activity (5 minutes of tiptoeing), and
3. Phase 3: Evaluation of lymphatic drainage after a longer period (one hour) of activity, similar to that used in daily activities (patients were requested to walk and not to remain seated without movement).

- Fourth phase LySc:

1. Subphase (SP) 1: Evaluation of lymphatic drainage after injecting the tracer.
2. SP 2: Evaluation of lymphatic drainage after skin mobilization of the injected site.
3. SP 3: Evaluation of lymphatic drainage after nonspecific massage.
4. SP 4: Evaluation of lymphatic drainage after manual lymphatic drainage following Leduc's method (22).

Data Extraction and Quality Assessment

Data analysis was performed by analyzing the number of lymphatic vessels and lymph nodes visualized after each subphase of the fourth phase LySc (*see Fig. 2*).

Data Synthesis and Analysis

Statistical analysis was performed with GraphPad using linear regression to observe the global reaction to the fourth phase LySc and Friedman test with Dunn's post-test to verify the possible significant differences

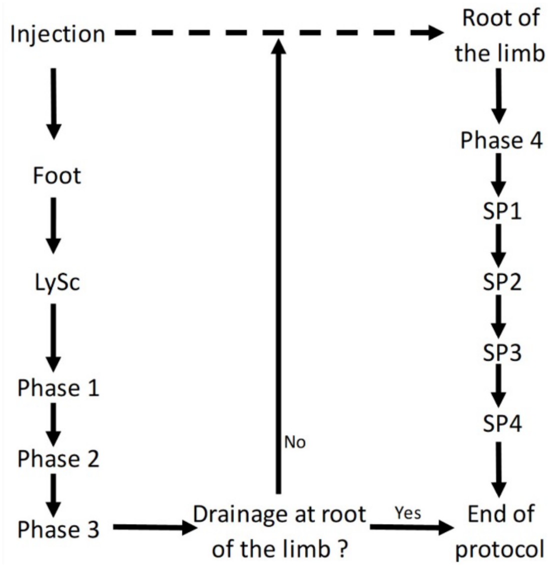

Fig. 1. Clinical imaging protocol for patients undergoing a lymphoscintigraphical (LySc) procedure. The first three phases are sequenced on the left and if no drainage to the root of the limb is seen, patients then undergo the fourth phase with sub-phases on the right.

between the different SPs. Possible data normality was rejected using the D'Agostino & Pearson test, Anderson-Darling test, Shapiro-Wilk test and Kolmogorov-Smirnov test. Data were then compiled into a tree diagram to objectify every reaction possible following the fourth phase. Statistical significance was determined as follows:

A p value greater than or equal to 0.05 indicated that no significance was reached, and the null hypothesis was not rejected. A p value between 0.05 and 0.01 or equal to 0.01 indicated that significance was reached, and the null hypothesis was rejected. A p value between 0.01 and 0.001 or equal to 0.001 indicated that high significance was reached, and the null hypothesis was rejected.

A p value lower than 0.001 indicated that the highest significance was reached, and the null hypothesis was rejected.

RESULTS

Linear Regression for the Number of Lymphatic Structures Visualized

The linear regression for the number of lymphatic structures visualized according to the different subphases shows almost a perfect fit with an R^2 equal to 0.97 (*Fig. 3*). This shows that there is a dependency between the number of lymphatic structures visualized and the different physical techniques used.

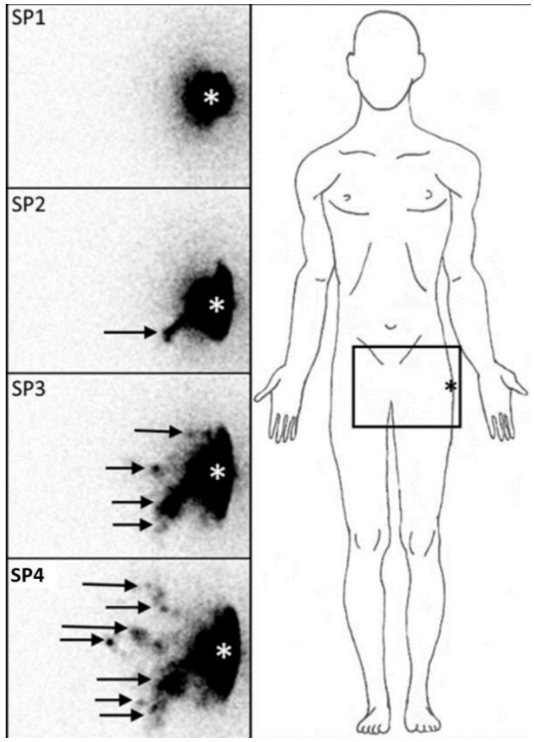

Fig. 2. Example images from a 4 phase 4 lymphoscintigraphic examination depicting subphases 1 to 4. The injected site is localized at the level of the white star laterally to the trochanter major. Every black arrow is directed towards a lymphatic structure that can be observed on imaging. This gives a total count of no lymphatic structure observed following SP1, 1 lymphatic structure observed following SP2, 4 lymphatic structures observed following SP3 and 7 lymphatic structures observed following SP4. In this case, SP2, SP3 and SP4 all increased the number of newly opened lymphatic collaterals compared to the previous subphase. MLD led to the maximum number of newly opened lymphatic collaterals.

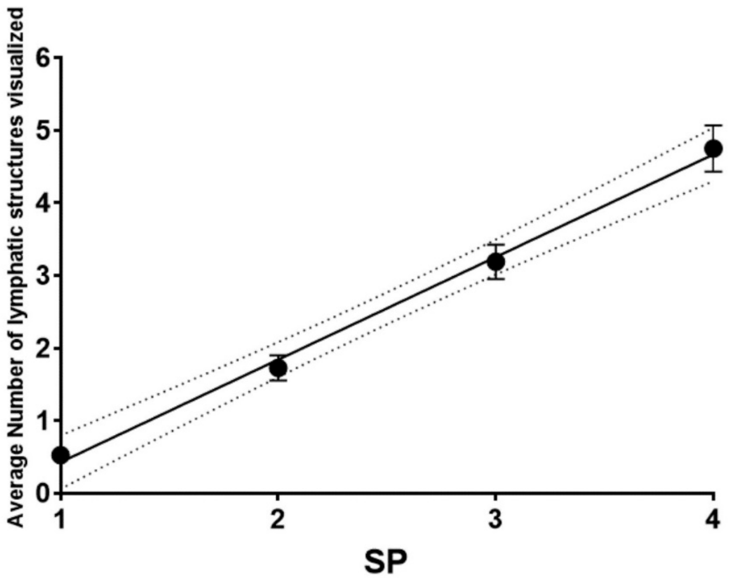

Fig. 3. Chart demonstrating linear regression results of the average number of observed lymphatic structures identified following each subphase (SP).

TABLE 4
Sub-phase Results from the 4th Imaging Phase for the Number of Lymphatic Structures Visualized for Patients with LLLE of All Types and Both Primary and Secondary Origin. Data Is Mean and Standard Error (Se), P Value Determined Using Friedman

Sub-phase	All Patients	Primary Lymphedema	Secondary Lymphedema
SP 1	0.53 ± 0.11	0.68 ± 0.16	0.33 ± 0.16
SP 2	1.73 ± 0.17	1.80 ± 0.21	1.64 ± 0.29
SP 3	3.19 ± 0.24	3.09 ± 0.31	3.31 ± 0.38
SP 4	4.75 ± 0.32	4.50 ± 0.41	5.06 ± 0.51
	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$

The slope of 1.372 shows that each consecutive SP tends to show 37% more lymphatic structures than the previous SP.

Fourth Phase LySC Analysis for LLLE.

For the patients in total, results show a statistically increased number of new lymphatic pathways (LyPs) following each SP (*Table 4*). This means that SP2, SP3, and SP4 significantly increased the number of newly opened LyPs compared to the previous LyP (*Fig. 4*). In examining patients with either primary or secondary LLLE, results globally show a statistically increased number of new LyPs following each SP (*Table 4*). This means that SP3 and SP4 significantly increased the number of newly opened LyPs compared to the previous LyP (*Fig. 4*).

Tree Diagram

All imaging results were put into a tree diagram to observe each type possible result following each subphase of the fourth phase. Visualization of the LyP after the first sub-

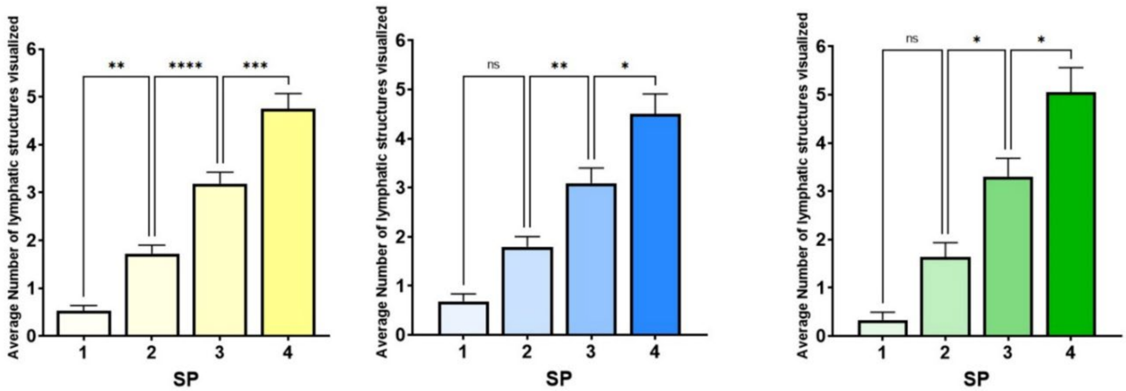

Fig. 4. Statistical analysis of the average number of lymphatic structures visualized during the 4 phase lymphoscintigraphical clinical imaging exam (LySc) for patients with LLLE. All patients (yellow) are included on the left, patients with primary lymphedema (blue) are in the middle, and patients with secondary lymphedema (green) are on the right.

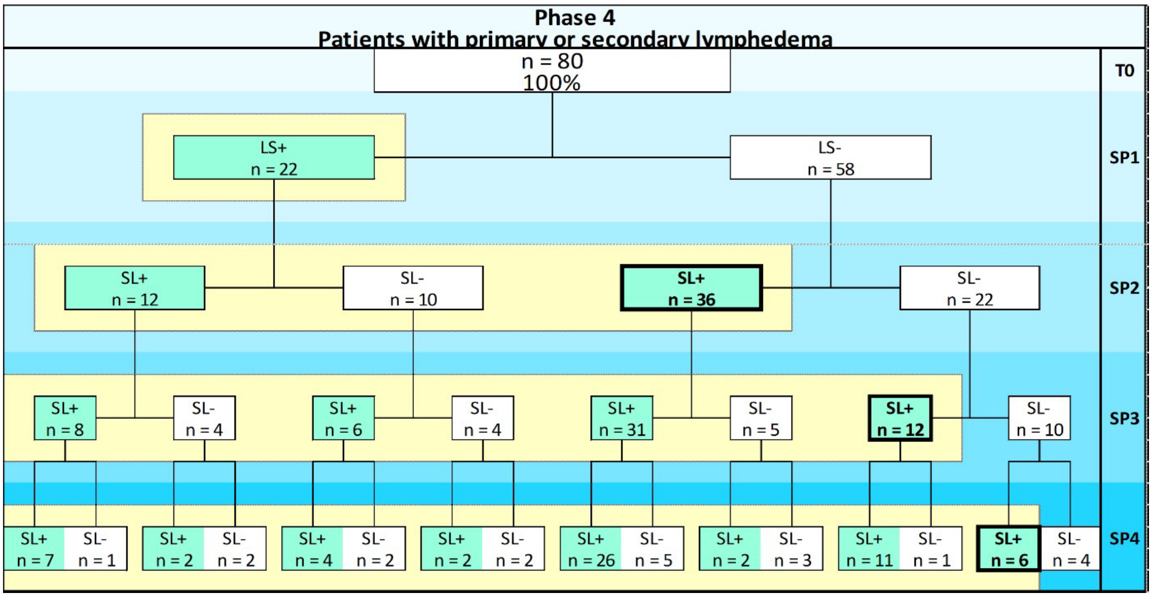

Fig. 5. Tree diagram of the different results possible following each subphase (SP) of the fourth phase lymphoscintigraphical clinical imaging exam for all patients with LLLE. A result marked "+" shows an increased number of lymphatic structured (LS) visualized. On the contrary, a result marked "-" shows that the number of lymphatic structured visualized did not change after the last SP.

phase was considered spontaneous migration of the tracer (*Fig. 5*).

The tree diagram can be analyzed along three major categories:

- Cases showing several LyPs after each SP.
- Cases developing new LyPs for the first time after each SP
- Cases improving the number of LyPs after each SP

<u>First category (depicted in yellow): Cases showing several LyPs after each SP:</u>

The results indicate that only 27.5%

(22/80) of the patients spontaneously (SP1) showed several LyPs. Of these patients, 72.5% (58/80) showed several LyPs after injection site stimulation; 87.5% (70/80), after nonspecific massage; and 95% (76/80), after an MLD session. This means that each SP is increasing the number of cases showing LyP. Only 5% of the cases (4/80) in total showed no spontaneous or forced lymphatic drainage at the root of the limb after the totality of the SP.

Second category (in bold): Cases developing new LyP for the first time after each SP

After injection site stimulation, lymphatic drainage was observed in 60% (36/58) of cases, for which no spontaneous drainage was observed after injection. After nonspecific massage, lymphatic drainage was observed in 54% (12/22) of the cases, for which no lymphatic drainage was observed. Finally, a session of MLD such as SP4 seemed necessary to observe lymphatic drainage in 60% (6/10) of the remaining cases for which there was still no lymphatic drainage observed. If the injection site stimulation can be considered representative of the natural stimulus of the skin during daily activity compared to SP3 and SP4 as manual interventions, nonspecific massage and MLD are proven necessary to show LyPs in 82% of the cases (18/22) that did not show any lymphatic drainage.

Third category (in green): Cases improving the number of LyPs after each SP:

Following injection site stimulation, 60% of the cases showed a greater number of LyPs, as compared with 71.3% after nonspecific massage and 75.1% after the MLD session. This means that each phase can improve the result obtained after the previous phase, adding value to each technique.

When considering only the cases that showed spontaneous LyP opening (22 cases), we can see that 54.5% (12/22) of the cases showed a greater number of LyPs after injection site stimulation and that 63.6% (14/22) of the cases showed a greater number of LyPs following nonspecific massage, as compared with 68.2% (15/22) following the MLD session.

When considering only the cases which showed no subsequent spontaneous LyP opening (i.e., 58 cases), we can see that 62.1% (36/58) of the cases showed a greater number of LyPs after injection site stimulation and that 74.1% (43/58) of the cases showed a greater number of lymphatic collaterals opening following nonspecific massage, as compared with 77.6% (45/58) following the MLD session. Again, if the SP2 can be considered representative of the natural stimulus of the skin during daily activity and SP3 and SP4 as manual interventions, nonspecific massage and MLD sessions are necessary to increase the number of LyPs in 86.5% of the cases (69/80).

Finally, we observed at the end of the protocol that 2.5% (2/80) of the cases spontaneously showed the maximum number of LyPs, that 6.3% (5/80) of the cases showed the maximum number of LyPs after injection site stimulation, that 11.3% (9/80) showed the maximum number of LyPs after SP3, and that 75% (60/80) showed the maximum number of LyPs after SP4. This data indicates that MLD is the most efficient technique to open the maximal number of LyPs.

DISCUSSION

In the 18th century, Vodder described alternate lymphatic routes by injecting cadavers with dye. These routes were later confirmed through scientific examination and with more physiological techniques, such as lymphoscintigraphy (23). These trials began in the early seventies, notably with research conducted by A. Leduc and his team. They demonstrated, using Knisely's technique (transillumination with tracer injection) that resection of the retropectoral lymph node in mice led to new methods of lymphatic drainage (24). In 1996, Ferrandez et al (25) noted the visualization of new lymphatic pathways following the application of an MLD session, which is consistent with all of the results that we observed as therapists whose purpose is to stimulate the lymphatic system or move edema from a poorly drained area to a better-drained area.

The effectivity of MLD has been

questioned for several years. Although the trials of numerous authors, including Williams et al (26), McNeely et al (27), Ezzo et al (18), and Ferrandez et al (25), showed the beneficial effects of MLD, some authors, such as Martin et al (28), Tambour et al (29), or Müller et al (30), reported fewer encouraging results. This can be partly explained by the fact that even if physical therapy for lymphedema treatment is well understood, it remains a complex treatment that requires patience, rigor, and proper formation to obtain better results. The visualization of new lymphatic pathways following the application of an MLD session, as noted by Ferrandez in 1996, supports this hypothesis. Stimulating the opening of new lymphatic pathways and moving edema towards those collaterals may be a solution through which physical therapists can obtain greater outcomes for their patients. According to our results, it seems clear that some points can be raised in the interest of patients suffering from lymphedema.

First, 75% of the patients assessed in this study only needed a 15 min MLD (SP4) period to open new lymphatic collateral pathways. This shows the importance of applying pressure on the root of the limb because it acts like an intersection: MLD led to an average of 4.75 new lymphatic vessel openings at the root of the limb in 75.1% of the patients. The results of this trial correlate with Medina-Rodriguez et al (31) who observed recently in 19 patients with secondary upper limb lymphedemas using the same MLD technique (Leduc's method). This suggests that the findings of the trial not only support the use of MLD in treating lymphedema, but also suggest that by adapting the treatment to the patient's physiology and anatomy, therapists may be able to improve treatment outcomes. Following these results, the physical therapist could be advised to drain the root of the limb at the start of the treatment or when the patient is wearing a multilayered bandage. By doing so, MLD could increase the efficiency of physiological drainage and edema resorption at the root of the limb for which we do not have any other decongestive technique applicable. This would then increase the efficiency of the physical treatment applied directly to the edema by increasing the lymphatic drainage upstream. While a 15-minute session of MLD can open new lymphatic pathways, it should be noted that this is not sufficient for a complete treatment session. To achieve optimal results, the physiotherapist must also focus on opening collateral pathways upstream and increasing lymphatic resorption at the level of the edema. Therefore, the patient would need to be treated for at least 30 minutes, depending on the extent of the affected area. The second point worth noting is that while nonspecific massage can result in some collateral openings, it does not achieve the same level of effectiveness as the MLD method, as supported by statistical evidence presented in this study. This means that the two techniques are not interchangeable for the physical therapist to obtain the best outcomes for his or her patients. However, if a nonspecific massage cannot be considered an appropriate treatment for lymphedema, it could be a way to involve the patient in his or her own treatment. It could then be the responsibility of the physical therapist to explain how to perform it properly if the patient wishes to participate actively in the therapy. Third, skin mobilization can also lead to a greater number of lymphatic collateral openings in 60% of patients. This means that movement is crucial for the patient and that the patient is advised to stay active and/or to practice physical activity but always under the supervision and advice of the physical therapist in order to control the swelling.

A phase 4 LySc can also provide information on the patient's physiological and anatomical drainage at the root of the limb. For example, Roman et al (32) showed in 2017 that some upper limb lymphedemas can be drained through paravertebral or intercostal lymphatic pathways, meaning that alternate lymphatic pathways can be an important part of the lymphatic system anatomy. This can be correlated with our results. Some of the cases assessed in this trial showed unexpected lymphatic pathways, suggesting that some patients could benefit from adapted physical treatment. Lymphoscintigraphy then gives the opportunity for the physical therapist to adapt his or her treatment not to the pathology, but rather to the patient in order to stimulate the functional lymphatic pathways. Moreover, in 2016, a study by Robert Weiss showed that proper physical treatment for lymphedema resulted in lower medical costs and fewer hospitalizations (33).

Although the results from this research are promising, it would be interesting to evaluate the durability of lymphatic collateral openings to know when and where MLD techniques should be applied to the patient. The aim of this study was to include a wide range of patients with lymphatic insufficiency, regardless of the severity, stage, or age of the lymphedema. Future studies should also consider these factors as they can potentially impact the effectiveness of physical treatments. It is important to note that in this study, each phase was conducted consecutively, with the last intervention always being a session of MLD. While this approach may have resulted in a cumulative effect for each intervention, it is unlikely that this would have significantly affected the results. The purpose of the tree diagram was to demonstrate that every type of reaction can occur following each intervention. If the cumulative effect or time effect were significant, there would not have been such notable differences between the cases. Additionally, some cases only responded to one intervention, further indicating that the cumulative effect was not the sole contributing factor. It is worth noting that a cumulative effect may have given an advantage to the non-specific massage intervention, as its maneuvers involve pressure with a skin mobilization effect such as the ones involved in the MLD session. However, even with this potential advantage, the MLD session was still able to open lymphatic collaterals that were not seen following the non-specific massage intervention.

CONCLUSION

As the efficiency of MLD has been questioned for several years, this study provides information to validate, improve, and adapt physical treatment to the patient. MLD is the sole physical therapy technique from the complex decongestive treatment that can be applied to any body part. This study is important in validating and improving the efficacy of Manual Lymphatic Drainage (MLD), which has been questioned for several years.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

ACKNOWLEDGMENTS

The authors would like to thank Magda Langlais for her contribution in creating the image outline of the human body.

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