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OUTCOME OF LYMPHEDEMA AFTER MICROSURGICAL TREATMENT

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Running title: Microsurgery in lymphedema patients

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INTRODUCTION

Lymphedema is a chronic disease with accumulation of water and proteins in the tissue, secondary to impairment of the lymphatic transport capacity. Nowadays, probably millions of persons worldwide are suffering from the disease. Lymphedema can be primary (congenital) or secondary (acquired after e.g. lymph node excision, radiotherapy, recurrent episodes of lymphangitis). The extremities are mostly affected although it can be present at every part of the body. Clinical parameters of lymphedema vary from swelling and recurrent infections (erysipelas) up to disability in end-stage disease because of inflammation and fibrosis in the affected limb.

Although lymphedema is a chronic disease, the severity of the edema can be reduced by conservative treatment in many patients. The conservative approach comprises the association of manual lymph drainage, multilayer bandaging (short stretch bandages), physical exercises and skin care. Lifelong use of elastic stockings is mandatory. In patients that respond suboptimally to conservative treatment, one can find benefits associating surgical treatment. The aim of surgery in those cases is to reduce the size of the affected limb, to minimize recurrent episodes of lymphangitis and to improve limb function. A variety of surgical procedures have been applied. Currently, three types of surgical options exist. In reconstructive microsurgery, the interrupted lymphatic system is repaired by the interposition of a homologous vein or lymphatic collector [1,2]. In contrast, derivative microsurgical procedures [3,4,5,6,7] aim to deviate the excess of lymphatic flow towards the venous system. A second type of surgery is the liposuction/lipectomy procedure [8] where the excess of fat accumulation after chronic tissue moderation is removed. As third option, the surgical resection of excess skin and subcutaneous tissue can be mentioned [9].

The aim of the study was to investigate the clinical outcome of the derivative lympho-venous microsurgical procedure in patients with stadium II, III and IV lymphedema.

MATERIAL AND METHODS

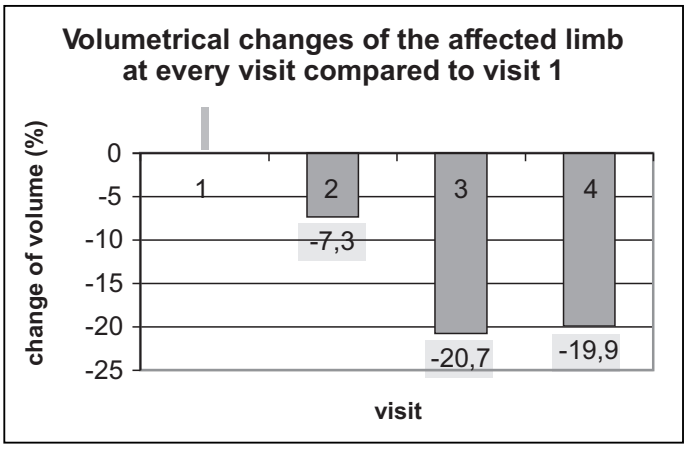
Study design and Patient selection

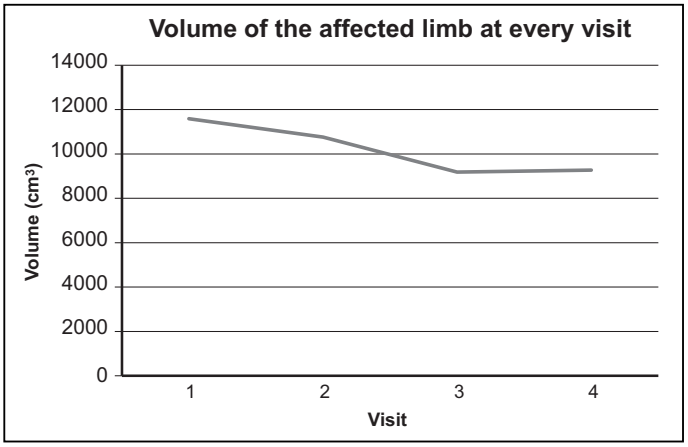
The study was set-up to investigate the effect of surgical therapy in addition to maximal conservative treatment. The study population consisted of lymphedema patients (stadium II, III or IV according to Campisi [2]) with unsatisfactory reduction of the volume of the affected limb after maximal conservative treatment (manual lymph drainage, multilayer compressive bandage) for at least 2 months. In addition, patients had to be eligible for surgical treatment and hence to fulfil the following criteria: (1) functional impairment of movements of the affected limb and (2) recurrent episodes of erysipelas and (3) scintigraphic evidence of lymphatic obstruction and evidence of lymphatic back-flow. Patients with bilateral lymphedema were not excluded. Exclusion criteria were age restrictions (< 20 years and > 80 years), recurrent malignancy (metastatic disease), no compliance of the patient to wear compressive stockings post-operatively or contraindication to general anaesthesia. All patients gave written informed consent. Patients were recruited at two regional hospitals in Belgium between January 2007 and August 2009. At visit 1 (intake), the diagnosis of lymphedema was established (clinically and

scintigraphically) and conservative treatment was optimized. At visit 2, the result of maximal conservative treatment was assessed and in case of unsatisfactory result, patients were eligible for surgical treatment. Microsurgical intervention, performed between September 2007 and August 2009, occurred on average 5.2 (range 2-12) months after visit 1. Three patients suffering for more than 10 years of lymphedema were operated 1 month after visit 1 because of a history of recurrent erisypelas complicated by sepsis. Visit 3, the first postoperative consult, took place on average 2.5 (range 1-8) weeks after the intervention. Visit 4, at follow-up, occurred between 2 months and 13 months postoperatively.

Measurements

Limb volumes were based on circumferential measurements, performed every 10 cm, which is proven to be a reliable measurement of lymphedema [10,11]. Approximation of the volume (cm^3) of the limb was performed by the formula of truncated cones (summation of a sequence of segments of conical frustrums) [10]. Measurements were performed on admission (visit 1), after maximal conservative treatment (visit 2), postoperatively (visit 3) and at follow-up (visit 4). Both, affected and unaffected limb volumes were calculated at each visit. However, since patients with bilateral affected limbs were not excluded, ipsilateral volume changes were assessed. Changes in volume of the affected limb (Δ volume) between two visits were expressed as:
[(initial volume - present volume)/ initial volume] x 100





Surgical procedure

A derivative lympho-venous anastomosis (LVA) was performed in all patients by one experienced vascular surgeon, trained in lymphatic microsurgery. The anastomosis was performed with Prolene 8/0 and with the help of a microscope (Pentero, Zeiss, magnification 40 x). The patients were operated under general anaesthesia.
In case of lymphedema of the arm, the incision was made at the medial third of the volar surface of the arm. Patent lymphatics were identified by intradermal injection of Blue Patent V dye (2 ml). All visible lymphatics (were used to perform the anastomosis). The vein used for the anastomosis was normally a branch of one of the omeral veins.
In case of lymphedema of the leg, the incision was made at the inguinal region. In parallel to the upper limb, the lymphatics were visualised after injection of Blue Patent V dye (2 ml). The vein used for the anastomosis was normally a branch of the Vena Saphena Magna.
All the veins were tested to insure the continence of the valves. In case of incontinence of the valve, an external valvuloplasty was carried out to avoid blood reflux and consequent trombosis of the anastomosis .
The mean time to perform a LVA of the arm is 2 hours and for a leg 3,5 hours. Antibiotics were give peri-operatively. Postoperatively, the limb was bandaged and elevated. The use of elastic stockings was maintained in the follow-up phase.

Statistical analysis

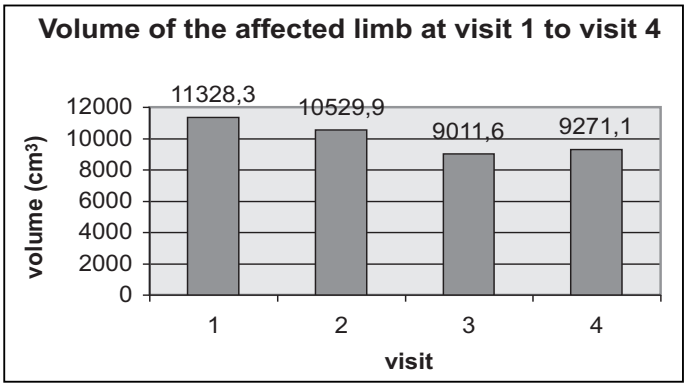
Means and standard deviations (SD) are given. Multivariate analysis (Wilks' lambda) was performed if the p-value was less than 0.05 in univariate analysis. SPSS 17.0 software was used for all statistical analysis. Limb volumes at every visit were compared using a multivariate analysis (general linear model) with post-hoc Bonferroni tests for multiple comparisons.

RESULTS

A total of 26 LVA interventions in 26 patients are described in this study.
Patient characteristics are given in Table 1. Mean age was 53.2 years (SD 11.9). Mean BMI was 27.1 kg/cm^2 (SD 5.8).
The major part of the patients did not require a valvuloplasty (25/26; 96.2%). Postoperative complications (2/26; 7.7%) were minimal: one patient suffered from a pneumonia and one patient had a transitory leakage of lymph in the operated limb.
Application of previous treatment (surgical or conservative) did not affect the volume at any visit (data not shown).
The mean volume of the affected limb at admission (visit 1) was 11 584.7 (SD 5 192.1) cm^3. After maximal supportive therapy (visit 2) the mean volume of the affected limb reduced to 10 758.8 (SD 4 789.9) cm^3 which is a decrease of 7.3%. A further decrease in mean volume up to 9 181.5 (SD 3 902.7) cm^3 at visit 3 and up to 9271.1 (SD 4091.8) cm^3 at visit 4 was found.
Overall, the volumetrical change of the affected limb was statistically significantly different across the 4 visits ($p < 0.001$).
Optimizing conservative treatment (visit 2 versus visit 1) resulted

Table 1. Patient characteristics (n=26)

Characteristics	N	(%)
Sex		
Male	4	(15.4)
Age (mean in years)	53.2	(11.9)
BMI (mean in kg/m^2)	27.1	(5.8)
Educational level		
High	11	(42.3)
Medium	12	(46.2)
Low	3	(11.5)
Co-morbidities		
Yes	9	(34.6)
No	17	(65.4)
Lokalisation of lymphedema at		
Arm	7	(26.9)
Leg	19	(73.1)
Suffering since		
<10 years	14	(53.8)
>10 years	12	(46.2)
Type		
Congenital	15	(57.7)
Acquired	11	(42.3)
Stadium		
II	7	(26.9)
III	15	(57.7)
IV	4	(15.4)
Pitting		
Yes	5	(19.2)
No	21	(80.8)
Previous invasive treatment for lymphedema		
None	14	(53.8)
Superficial shunt	8	(30.8)
Liposuction	1	(3.9)
Combination	3	(11.5)
Previous conservative treatment for lymphedema		
None	1	(3.8)
Lymphatic drainage	19	(73.1)
Lymphatic drainage plus compression	6	(23.1)
History of recurrent erysipelas		
Yes	14	(53.8)
No	12	(46.2)



in a statistically significant volume decrease of 7.3% of the affected limb ($p = 0.014$). Furthermore, the decreases in volume of 20.7% and 19.9% between visit 1 and visit 3 and between visit 1 and visit 4 respectively, were highly statistically significant ($p < 0.001$). There was no additional volumetrical change between visit 3 and visit 4.

Factors as lokalisation (leg), duration of suffering from lymphedema (more than 10 years), type (congenital) and stadium of lymphedema explained the volumetrical changes across the 4 visits in the univariate analysis (Table 2).

However, in multivariate analysis only localization and stadium at diagnosis were responsible for the volumetrical decrease of the affected limb across the 4 visits (Table 2). Since all patients who were suffering from lymphedema for more than 10 years and who had congenital lymphedema, all had lymphedema lokalised at the lower limb, these two factors probably did not contribute to the volume reduction of the affected limb across the visits after multivariate analysis.

The mean volume of the unaffected limb attenuated significantly between visit 3 and visit 1 ($p= 0.042$) and between visit 4 and visit 1 ($p= 0.036$). Overall, the decrease in volume of the unaffected limb across the 4 visits was borderline significant ($p= 0.055$).

Table 2. Factors influencing the volumetrical changes across the 4 visits in univariate and multivariate analysis.

	Univariate analysis p-value	Multivariate analysis p-value
Sex	0.258	
Age	0.281	
Educational level	0.287	
BMI	0.075	
Smoking	0.066	
Co-morbidities	0.969	
Lokalisation (arm or leg)	<0.001*	0.009
Suffering since < or > 10 years	0.006*	0.648
Type (congenital or acquired)	0.005*	0.741
Stadium	0.031*	0.018
Pitting	0.022*	0.035

DISCUSSION

This pilot study was set-up to investigate the effect of microsurgical treatment for lymphedema in addition to initiated maximal conservative treatment. A statistically significant decrease in volume of 20.7% of the affected limb after surgical treatment was found ($p<0.001$). Optimizing conservative treatment (visit 2 versus visit 1) resulted already pre-operatively in a statistically significant volume reduction of 7.3% of the affected limb, which is in accordance with the extensive literature on the beneficial effect of conservative therapy [12,13]. Furthermore, the volume reduction continued postoperatively. Probably due to the short follow-up time no further decrease in volume could be documented between visit 3 and visit 4. Localization of lymphedema at the upper or lower limb and the lymphedema stadium were responsible for the volumetrical decrease of the affected limbs across the different visits, independently of each other.

Volume reduction of the affected limb was at every visit more manifest for stadium IV lymphedema patients than for stadium II lymphedema patients. A notable reduction in volume after surgery is obtained when lymphedema is in a more advanced stadium. Ideal indications for lymphatic microsurgery, according to Campisi [7] are stadium I, II and early stadium III. For advanced stadium III and IV, the authors suggest reduction of the limb with non-operative methods prior to microsurgery. In our study, all patients received irrespective of the stadium, maximal conservative therapy before the surgical intervention.

Our findings show a more pronounced reduction of volume if surgery is performed in the lower limb compared to microsurgery at the upper limb. Although comparative studies between upper and lower limb outcome are lacking in literature, anatomical differences in the lymphatic system may explain the results. In the lower limb, more lymphatic vessels are present compared to the upper limb, hence providing a better restoration of the lymphatic flow.

Our data on the clinical outcome of patients with lymphedema treated by microsurgery, are in accordance with data from the literature [4,14,15,16]. However, methodological differences such as small sample size, differences in patient selection, differences in localization (upper or lower limb) and type (congenital or acquired) of the lymphedema, diagnostic assessment (scintigraphic and/or clinical examination), timing of surgery, type of intervention (reconstructive, derivative or others), make it difficult to compare clinical results between different studies [17].

Although this study describes only a limited number of cases, a significant reduction in volume of the affected limb after microsurgery which was performed after optimizing conservative treatment, was found. Even though non-operative multidisciplinary treatment is the keystone of treatment for lymphedema, as many as 30-40% do not respond to conservative therapy [18] and may benefit from surgical intervention. Nowadays, surgery is indicated for selected patients when physiotherapy has clearly proven unsuccessful [19]. Moreover, as shown by this series, the derivative lympho-venous anastomosis is a safe procedure with few complications. Since patients with an established diagnosis of lymphedema (both scintigraphically and clinically) suffering from acquired or congenital lymphedema, localized at the lower or upper limb and undergoing microsurgery after optimal conservative therapy, were included, our results point to an effective therapeutic option for a wide range of lymphedema patients.

Interestingly, a favourable change in volume in the unaffected limb after performing the microsurgical intervention for the affected limb was found. One can hypothesize that through means of the lympho-venous anastomosis the lymph drainage pathways are optimised.

In conclusion, the clinical outcome in terms of volume reduction after microsurgery in patients with stadium II, III and IV lymphedema was evaluated. A significant decrease in volume of the affected limb after the lympho-venous intervention was observed. The localization and stadium of the lymphedema attributed to this decrease independently of each other. To monitor the beneficial effect of microsurgery, long term follow-up of the treated patients is mandatory.

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