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10TH ANNUAL MEETING OF THE EUROPEAN VENOUS FORUM - 5-7 JUNE, COPENHAGEN (DEN)

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A PROSPECTIVE EVALUATION OF LYMPHOMYOSOT IN THE MAINTENANCE TREATMENT OF BREAST CANCER-RELATED LYMPHEDEMA

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ABSTRACT

Purpose: To assess the efficacy and tolerability of the combination of Lymphomyosot with compression hosiery in the maintenance treatment of breast cancer-related lymphedema.

Methods: Female patients diagnosed with breast cancer, who had undergone unilateral breast surgery and exhibited stage II-IV arm lymphedema secondary to treatment received oral Lymphomyosot and were monitored over a period of 6 months. Primary outcome measure was the percentage reduction in lymphedema volume.

Results: Thirty-six patients, with a mean age of 60 years and a long (4 years) disease duration were included. The reduction of lymphedema volume was 29.5% (95% CI, 15.0 to 43.9) at month 1, 31.5% (95% CI, 13.2 to 49.9) at month 3, and 41.2% (95% CI, 17.6 to 64.9) at month 6. Lymphomyosot was well-tolerated.

Conclusions: Lymphomyosot combined with compression hosiery might be an efficacious and well-tolerated therapeutic alternative for the maintenance treatment of patients with breast cancer-related lymphedema.

KEY WORDS: Breast cancer, lymphedema, compression hosiery, compression therapy, Lymphomyosot.

INTRODUCTION

Lymphedema is a chronic condition resulting from lymphatic system insufficiency and disrupted lymphatic transport [1]. Lymphedema is commonly classified as primary (eg, congenital lymphatic dysplasia) or secondary (eg, after radical operative dissection, irradiation or from repeated lymphangitis with lymphangiosclerosis) [1]. In breast cancer patients, secondary lymphedema is a relatively common and troublesome treatment sequela. Despite the improvement in surgical procedures, the incidence of lymphedema in recent series is about 30% of women treated [2]. In addition to the type of surgery, breast cancer patients

receiving radiation therapy, aged 60 or over, or who are obese, seem to be at greater risk of developing lymphedema [3]. The occurrence of lymphedema in patients with breast cancer is associated with significant psychological and physical morbidity [4-6] and a negative impact on quality of life [7,8].

Although there is a relative lack of sufficient high-quality evidence on the treatment of lymphedema secondary to breast cancer treatment [9,10], physical therapy is one of the more common and better supported strategies. In this regard, the so-called Complete or Complex Decongestive Therapy has been recommended by a consensus panel. Complete Decongestive Therapy (CDT) generally involves a two-stage treatment program. The first phase consists of skin care, manual lymphatic massage, decongestive exercises, and compression by means of multi-layer bandaging. In the second phase, in addition to continuing with skin care, exercises and massages as needed, compression with a low-stretch elastic stocking or sleeve is applied [1]. Overall, it seems that more intensive therapies such as CDT, manual lymphatic drainage, pneumatic pump and laser therapy are associated with a greater reduction in the volume of lymphedema [11].

A few pharmacological agents have been evaluated for the treatment of lymphedema in randomized clinical trials, including coumarin [12,13], rutosides [14,15] and Daflon [16]. However, there is no evidence to support the use of these medical therapies [9]. Lymphomyosot is a homeopathic combination medication containing components of plant, animal and mineral origin (Table 1), which is thought to be useful for a variety of conditions including the treatment of exudative and lymphatic diathesis. The efficacy and tolerability of Lymphomyosot have been evaluated in several observational studies in patients suffering from a variety of conditions including diabetic peripheral neuropathy [17,18], tonsillitis [19] and patients with lymphedema or other lymphatic disorders [20,23]. However, these studies were run in widely heterogeneous unselected samples with a lack of standardized treatment conditions.

Table 1 - Lymphomyosot Composition (Drops).

Constituents				Finished Goods (grs)	
Nr	Code	Name	Final Potency	100g	Quantity MT (mg)
1.	17111	Myosotis arvensis	D3	5,0	0,015
2.	17360	Veronica officinalis (<i>Veronica</i>)	D3	5,0	0,01
3.	17325	Teucrium scorodonia	D3	5,0	0,015
4.	17182	Pinus sylvestris	D4	5,0	0,0015
5.	16982	Gentiana lutea	D5	5,0	0,00015
6.	16923	Equisetum hiemale (<i>Equisetum hyemale</i>)	D4	5,0	0,001
7.	17274	Smilax (<i>Sarsaparilla</i>)	D6	5,0	0,00005
8.	17240	Scrophularia nodosa	D3	5,0	0,015
9.	17037	Juglans regia	D3	5,0	0,015
10.	16798	Calcium phosphoricum	D12	5,0	5×10^{-12}
11.	17138	Natrium sulfuricum	D4	5,0	0,0005
12.	16965	Fumaria officinalis	D4	5,0	0,001
13.	17071	Levothyroxinum	D12	5,0	5×10^{-12}
14.	16708	Araneus diadematus (<i>Aranea diadema</i>)	D6	5,0	0,00005
15.	16984	Geranium robertianum	D4	10,0	0,002
16.	17120	Nasturtium officinale (<i>Nasturtium aquaticum</i>)	D4	10,0	0,003
17.	16941	Ferrum iodatum (<i>Ferrum iodatum</i>)	D12	10,0	10×10^{-12}
		TOTAL		100g	

MT: Mother Tincture
Contains 35 Vol.% ethanol

The objective of this study was to assess the reduction in arm lymphedema volume resulting from the combination of Lymphomyosot with compression hosiery in the maintenance treatment of breast cancer-related lymphedema.

PATIENTS AND METHODS

Design

This was a unicentre, prospective, noncomparative, 6 month follow up study conducted between May 2005 and August 2005, in the Lymphedema Unit of the Hospital Universitario La Fe.

Patients

Female patients diagnosed with breast cancer who had undergone unilateral breast surgery and exhibited arm lymphedema secondary to treatment were enrolled in this study. To be included, patients also had to show stage II to IV lymphedema, the swollen arm had to show an excess of volume greater than 200 ml as compared to

the contralateral unaffected arm, and lymphedema needed to be considered clinically stable, that is, without significant changes (less than 10%) in the arm volume within the last year using the same type of compression hosiery.

Patients were excluded if: (1) they had active neoplastic disease or there was a lack of information on this regard; (2) there were signs of active lymphangitis; (3) they required prescription of Complete Decongestive Therapy or CDT was applied in the previous year; (4) they were diagnosed as having a psychiatry disorder; (5) there were signs of edema of venous or cardiovascular origin; or (6) they were receiving or requiring treatment with diuretic drugs.

Treatment regimen

Patients were instructed to continue with their flat-knit custom-made compression garment, which exerted a minimum of class II compression (30-40 mm Hg) (Figure 1). All patients received Lymphomyosot, oral drops or tablets, at a dose of 15 drops or 3 tablets three times daily throughout the duration of the study. They were also asked to perform daily kinesiotherapy and skin care.



Fig. 1 - Stable breast cancer-related lymphedema with a flat-knit custom-made compression garment.

Assessments

Patients were followed up for 6 months through 4 visits: at baseline, month 1, month 3 and month 6. At each study visit, the following assessments were performed: physical examination, height and weight, assessment of limb volume, assessment of symptoms and recording of adverse events.

Limb volume was measured by determining multiple circumferences by manual surface measurements using the Kunkhe method. The Kunkhe method requires no special equipment and is quick and easy to use in the clinical practice setting. In this method, circumference measurements are taken with a tape measure at 4-cm intervals along the limb, from wrist to axilla. Limb volume is then calculated using the formula for a cylinder:

$$\text{Volume} = C1^2 + C2^2 + Cn^2 / \pi$$

where C is each of the circumference measurements.

Subjective assessment of symptoms was performed with visual analog scales for pain, heaviness and numbness.

Statistical analysis

Data were analyzed using SPSS version 11.5 (SPSS Inc, Chicago, Illinois). As this study used a noncomparative design, the statistical analyses presented are essentially descriptive. Continuous variables (eg, age, VAS scores) were described using the mean, range and 95% confidence interval, whereas categorical

variables (eg, sex, frequency of adverse events) were described by their absolute and relative frequencies with the corresponding 95% CI where appropriate.

The primary outcome was the percentage reduction in lymphedema volume in the affected arm. Limb volume was calculated by the Kunkhe method as explained above. The percentage reduction in limb volume was calculated as follows:

$$\% \text{ Limb volume reduction} = [(\text{pre-treatment volume} - \text{post-treatment volume}) / \text{pre-treatment volume}] \times 100$$

Lymphedema volume was calculated by subtracting the volume of the affected arm from that of the unaffected arm. The percentage reduction of lymphedema volume was then calculated as follows:

$$\% \text{ lymphedema volume reduction} = [(\text{pretreatment lymphedema volume} - \text{post-treatment lymphedema volume}) / \text{pre-treatment lymphedema volume}] \times 100$$

An exploratory analysis of possible factors predicting treatment response was performed. The variables included in the analysis were: age, sex, proteinaemia, initial limb volume of the affected arm and the limb volume difference, type of surgery, lymphadenectomy, radiotherapy, hormone therapy, dominant or non-dominant limb status, lymphedema stage, presence of fibrosis, body mass index, duration of lymphedema (years), history of hypertension, diminished joint mobility, and associated venous disorders.

We applied Levene's test for the homogeneity of variance and the Kolmogorov-Smirnov test for assessing normality for continuous variables. Wherever possible, parametric hypothesis tests were used for the inferential statistical analysis. In all cases, hypothesis testing was two-tailed, with the application of a 5% level of significance ($p < 0.05$) and a statistical power of 80%. The comparison of non-ordinal categorical variables was made using contingency tables with the chi-square test (χ^2) and Fisher or Yates correction of continuity, where required. The evaluation of an exposure variable with ordinate categories and a binary response variable was carried out using the lineal tendency test (χ^2_{TL}). The association between categorical and continuous variables was explored by analysis of variance (ANOVA test). For studying the relationship among continuous variables, ANOVA was likewise used, since it offers greater power than the t-test (Student-Fisher test) for comparing two means of independent samples. The analysis of the relationship between quantitative exposure variables and quantitative response variables was based on a linear regression model (β coefficient).

RESULTS

Study Participants

A total of 36 patients were included from May to August 2005, of which 35 patients were available for evaluation after one month, 31 patients after 3 months and 17 patients after 6 months.

Baseline patient and illness characteristics are presented in Table 2. The mean patient age was 60 years. They had a long disease duration (4 years), and a majority of patients (80%) had left arm lymphedema. Two thirds of the patients had undergone a modified

Table 2 - Demographics and clinical characteristics.

Characteristic	N=36
Age, mean (95% CI)	59.9 (56.6-63.3)
Affected limb, n (%)	
Right	7 (19.4)
Left	29 (80.6)
Dominant limb, n (%)	
No	28 (77.8)
Yes	8 (22.2)
Disease duration (years), mean (95% CI)	4.3 (3.1-5.5)
BMI, mean (95%CI)	28.9 (27.5-30.2)
Type of surgery, n (%)	
Modified radical mastectomy	24 (68.6)
Quadrantectomy	7 (20.0)
Lumpectomy	4 (11.4)
Axillary lymphadenectomy	35 (97.2)
Type of adjuvant therapy, n (%)	
Chemotherapy	25 (75.0)
Radiotherapy	26 (72.2)
Hormone therapy	30 (83.3)
Lymphedema stage, n (%)	
II	14 (39.9)
III	19 (52.8)
IV (elephantiasis)	3 (8.3)
Fibrosis, n (%)	
No	26 (72.2)
Local	10 (27.8)
Initial limb volume (ml), mean (95% CI)	2950 (2730-3171)
Initial lymphedema volume (ml), mean (95% CI)	492 (393-591)
Patients with pain at baseline, n (%)	18 (50.0)
Patients with heaviness at baseline, n (%)	29 (80.6)
Patients with numbness at baseline, n (%)	16 (44.4)
VAS pain score, mean (95% CI)	2.6 (1.6-3.6)
VAS heaviness score, mean (95% CI)	4.3 (3.2-5.3)
VAS numbness score, mean (95% CI)	2.5 (1.5-3.6)

BMI: body mass index; CI: confidence interval; VAS: visual analog scale.

radical mastectomy, and all but one had undergone axillary lymphadenectomy. The most frequent symptom was heaviness (80%) and, with the exception of heaviness, symptoms were of mild intensity.

Treatment compliance and effectiveness outcomes

Four patients (11%) did not comply with compression hosiery during the study, either because its use was discontinued or because they failed to use the garment as prescribed. Similarly, only few patients did not comply with the Lymphomyosot treatment as prescribed: 1/35 (2.9%) after one month; 2/31 (6.4%) after 3 months; 3/17 (17.6%) after 6 months.

The reduction of lymphedema volume was 29.5% (95% CI, 15.0 to 43.9) at month 1 and was maintained throughout the study (Figure 2). The reduction of limb volume followed the same pattern, with a 4.1% (95%CI, 2.4 to 5.9) reduction at month 1, 5% (95% CI, 3.4 to 6.7) at month 3, and 5.7% (95% CI, 3.2 to 7.9) at month 6. Overall, 87% of the patients showed an improvement of the lymphedema, with 29% of the patients exhibiting a lymphedema reduction over 50% (Table 3). A positive linear association was found between the percentage reduction of lymphedema volume and the number of days of treatment with Lymphomyosot; for each day of treatment the lymphedema volume was reduced 0.4% (β : 0.41; 95% CI, 0.18 to 0.64; $p=0.001$). Although the severity of symptoms was reduced throughout the study (Table 4), these changes were not statistically significant.

In the exploratory analysis of factors predicting treatment response (Table 5), the only factors associated with treatment response were the lymphedema stage at baseline and a positive history of previous treatment with decongestive therapy. The less the lymphedema severity, the greater the reduction in lymphedema volume; thus, in patients with stage II lymphedema the reduction was 67.4% (95% CI, 43.1 to 91.7) while the reductions in stages III and IV lymphedema were 15.8% (95% CI, 0.5 to 31.1) and 8.6% (95% CI, -24.6 to 41.8) ($F=9.733$; $p=0.001$). Patients who had not received previous decongestive therapy showed a 48.8% (95% CI, 28.1 to 69.5%) reduction in lymphedema volume compared to a 17.6 (95% CI, -2.6 to 38.0) reduction in patients who had a previous history of treatment with decongestive therapy ($F=4.646$; $p=0.040$).

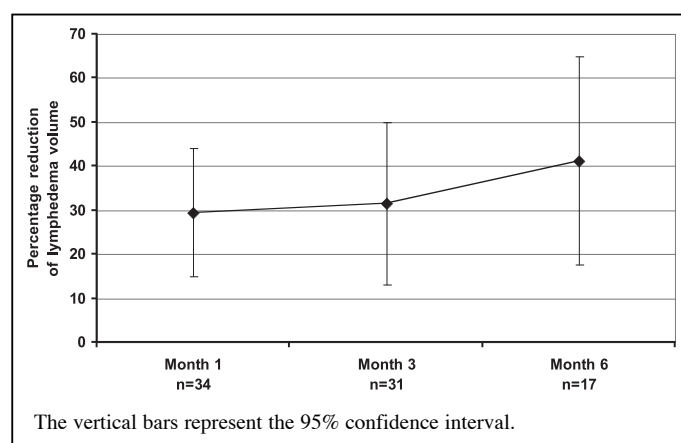


Fig. 2 - Percent reduction in lymphedema volume in patients treated with Lymphomyosot over a 6 month treatment period.

Table 3 - Degree of improvement according to lymphedema reduction.

Degree of improvement	n	%
Worsening or no improvement	4	12.9
Mild improvement (<i>lymphedema reduction <25%</i>)	10	32.3
Good improvement (<i>lymphedema reduction 25-50%</i>)	8	25.8
Excellent improvement (<i>lymphedema reduction >50%</i>)	9	29.0

Table 4 - Effect of Lymphomyosot on lymphedema symptoms over time.

VAS score	Baseline n=36	Month 1 n=35	Month 3 n=31	Month 6 n=17
Pain, mean (95% CI)	2.6 (1.6-3.6)	2.0 (1.0-3.0)	1.8 (0.6-2.9)	1.6 (0.1-3.0)
Heaviness, mean (95% CI)	4.3 (3.2-5.3)	2.8 (1.8-3.8)	2.5 (1.3-3.9)	3.1 (1.3-4.8)
Numbness, mean (95% CI)	2.5 (1.5-3.5)	1.8 (0.9-2.7)	1.5 (0.5-2.5)	1.7 (0.4-3.0)

CI: confidence interval; VAS: visual analog scale.

Table 5 - Exploratory analysis of possible factors predicting treatment response at month 3.

No. of patients	31
Age	β : -0.264 (95% CI -2.6-0.4) (p=0.152)
Body mass index	β : -0.196 (95% CI -5.7-1.7) (p=0.290)
Disease duration	β : -0.104 (95% CI -5.5-3.1) (p=0.576)
Lymphedema stage, mean (95% CI)	
II (13 cases)	67.4% (43.1-91.7)
III (15 cases)	15.8 % (0.5-31.1)
IV Elephantiasis (3 cases)	8.6% (-24.6-41.8)
	(F=9.733; p=0.001)
Fibrosis, mean, (95% CI)	
No	40.9% (22.6-59.3)
Local	19.2% (-0.6-39.0)
	(F= 1.344; p=0.256)
Type of surgery, mean (95% CI)	
Modified Radical Mastectomy (22 cases)	24.4 (7.5-41.2)
Quadrantectomy (5)	61.6 (8.1-115.1)
Lumpectomy (3)	63.8 (10.8-116.7)
	(F=2.956; p=0.069)
Initial lymphedema volume (ml)	β : -0.261 (95% CI -0.1-0.0) (p=0.157)
No. of lymph nodes removed	β : 0.034 (95% CI -3.3-3.7) (p=0.902)
Adjuvant chemotherapy	
No (8)	44.9 (13.2-76.7)
Yes (23)	33.8 (15.3-52.5)
	(F=0.414; p=0.525)
Adjuvant radiotherapy, mean (95% CI)	
No (9)	51.4 (13.1-89.8)
Yes (22)	30.7 (14.2-47.2)
	(F=1.632; p=0.212)
Arterial hypertension, mean (95% CI)	
No (21)	43.3 (23.6-63.0)
Yes (10)	23.0 (-2.4-48.3)
	(F=1.666; p=0.207)
Previous CDT, mean (95% CI)	
No (19)	48.8 (28.1-69.5)
Yes (12)	17.6 (-2.6-38.0)
	(F=4.646; p=0.040)

CDT: complete decongestive therapy; CI: confidence interval.

Adverse events

Treatment-emergent adverse events were experienced by 8 (22%) patients. Reported adverse events were nycturia (n=4), anxiety (n=2), hypertensive crisis (n=1), right hypochondrial pain (n=1), constipation (n=1), heartburn (n=1), and dry mouth (n=1).

Adverse events leading to treatment discontinuation were nycturia, hypertensive crisis, hypochondrial pain, and heartburn, with one case each.

DISCUSSION

Our results suggest that the addition of Lymphomyosot to compression hosiery in the maintenance treatment of breast cancer-related lymphedema reduces lymphedema volume to a significant extent and is well tolerated. However, our study has several limitations that should be kept in mind. Although our primary outcome, the percentage reduction of lymphedema volume, is an objective measure, the uncontrolled and unmasked design might have led to overestimation of treatment results. In addition, sample size was relatively small and the 6-month follow up could only be completed in half of the original sample.

Previous studies with Lymphomyosot in patients with lymphedema have shown that this homeopathic medication is efficacious and well tolerated [20-23]. However, as mentioned before, these studies were run in widely heterogeneous unselected samples with a lack of standardized treatment conditions. In addition, two of them were retrospective [20-22] and only used subjective outcome measures. Kirchhoff prospectively studied a cohort of patients with post-mastectomy lymphedema who received Lymphomyosot (n=60), lymphatic drainage (n=10) or both (n=10) [23]. Although disease duration was not reported, it seems that patients received this treatment as part of the acute phase of lymphedema treatment. Overall, Kirchhoff reported that the use of Lymphomyosot improved the subjective complaints of the patients [23]. Our study represents the first evaluation of the efficacy of Lymphomyosot using an objective and standardized measure such as the percentage reduction in lymphedema volume. The reduction in lymphedema volume observed in our study, about 30% at month 1 and at month 3, seems to be clinically significant since an important proportion of patients (55%) exhibited a lymphedema reduction classified as either excellent (over 50% of volume reduction) or good (25-50% of volume reduction). Noteworthy, this improvement was observed during the warmest months of the year (the mean summer temperature in Valencia in 2005 was 24°C, with mean maximum 30°C and minimum 19°C). However, although numerically we observed an improvement in the symptoms evaluated, this improvement was not statistically significant. This could be due to the relatively small sample or, more importantly, to the fact that the patients of our sample had only mild symptoms as reflected by the low scores in the corresponding VAS.

We found that the reduction of lymphedema volume was associated with its initial severity, with stage II lymphedema showing a much greater reduction (67%) than stage III or IV lymphedema. This finding is consistent with previous results in other studies in similar populations. McNeely et al., in a

randomized clinical trial, compared the efficacy of the combination of manual lymph drainage with compression bandaging to that obtained with compression therapy alone in patients with breast cancer related lymphedema [24]. They found that, in the group receiving the combined treatment, the reduction in lymphedema volume, assessed by the measurement of the circumference or displacement volumetry, was also much greater in patients with mild lymphedema (ie, an affected arm volume of up to 15% larger than the unaffected arm) compared to that of patients with moderate or severe lymphedema [24]. It is possible, as these authors argue, that in patients with less severe lymphedema, the lymphatic system is still working to a greater extent than that of the patients with greater severity, thus allowing a better lymphatic flow and treatment result.

Lymphomyosot was well tolerated as demonstrated by the low proportion of patients who experienced adverse events. These results are consistent with previous studies with Lymphomyosot in several populations.

In conclusion, despite the limitations of our study, it seems that Lymphomyosot combined with compression hosiery might be an efficacious and well tolerated therapeutic alternative for the maintenance treatment of patients with breast cancer-related lymphedema. However, these promising results should be confirmed in randomized clinical trials.

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REFERENCES

- 1 International Society of Lymphology (2003). *The diagnosis and treatment of peripheral lymphedema. Consensus document of the International Society of Lymphology*. Lymphology, 36: 84-91.
- 2 Williams A.F., Franks P.J., Moffatt C.J. (2005): *Lymphoedema: estimating the size of the problem*. Palliat. Med. 19: 300-13.
- 3 Sakorafas G.H., Peros G., Cataliotti L., Vlastos G. (2006): *Lymphedema following axillary lymph node dissection for breast cancer*. Surg. Oncol., 15: 153-65.
- 4 Tobin M.B., Lacey H.J., Meyer L., Mortimer P.S. (1993): *The psychological morbidity of breast cancer-related arm swelling. Psychological morbidity of lymphoedema*. Cancer, 72: 3248-52.
- 5 Passik S.D., McDonald M.V. (1998): *Psychosocial aspects of upper extremity lymphedema in women treated for breast carcinoma*. Cancer, 83 (12 Suppl American): 2817-20.
- 6 Ververs J.M., Roumen R.M., Vingerhoets A.J., Vreugdenhil G., Coebergh J.W., Crommelin M.A., Luiten E.J., Repelaer van Driel O.J., Schijven M., Wissing J.C., Voogd A.C. (2001): *Risk, severity and predictors of physical and psychological morbidity after axillary lymph node dissection for breast cancer*. Eur. J. Cancer, 37: 991-9.

- ⁷ Velanovich V., Szymanski W. (1999): *Quality of life of breast cancer patients with lymphedema*. Am. J. Surg., 177: 184-7.
- ⁸ Ridner S.H. (2005): *Quality of life and a symptom cluster associated with breast cancer treatment-related lymphedema*. Support Care Cancer, 13: 904-11.
- ⁹ Kligman L., Wong R.K., Johnston M., Laetsch N.S. (2004): *The treatment of lymphedema related to breast cancer: a systematic review and evidence summary*. Support Care Cancer, 12: 421-31.
- ¹⁰ Badger C., Preston N., Seers K., Mortimer P. (2004): *Physical therapies for reducing and controlling lymphoedema of the limbs*. Cochrane Database Syst Rev 4: CD003141.
- ¹¹ Moseley A.L., Carati C.J., Piller N.B. (2007): *A systematic review of common conservative therapies for arm lymphoedema secondary to breast cancer treatment*. Ann. Oncol., 18: 639-46.
- ¹² Casley-Smith J.R., Morgan R.G., Piller N.B. (1993): *Treatment of lymphedema of the arms and legs with 5,6-benzo-[alpha]-pyrone*. N. Engl. J. Med., 329: 1158-63.
- ¹³ Loprinzi C.L., Kugler J.W., Sloan J.A., Rooke T.W., Quella S.K., Novotny P., Mowat R.B., Michalak J.C., Stella P.J., Levitt R., Tschetter L.K., Windschitl H. (1999): *Lack of effect of coumarin in women with lymphedema after treatment for breast cancer*. N. Engl. J. Med., 340: 346-50.
- ¹⁴ Piller N.B., Morgan R.G., Casley-Smith J.R. (1988): *A double-blind, cross-over trial of O-(beta-hydroxyethyl)-rutosides (benzo-pyrones) in the treatment of lymphoedema of the arms and legs*. Br. J. Plast. Surg., 41: 20-7.
- ¹⁵ Mortimer P.S., Badger C., Clarke I., Pallett J. (1995): *A double blind randomized, parallel-group, placebo-controlled trial of O-(beta-hydroxyethyl)-rutosides in chronic arm edema resulting from breast cancer treatment*. Phlebology, 10: 51-5.
- ¹⁶ Pecking A.P., Février B., Wargon C., Pillion G. (1997): *Efficacy of Daflon 500 mg in the treatment of lymphedema (secondary to conventional therapy of breast cancer)*. Angiology, 48: 93-8.
- ¹⁷ Dietz A.R. (2000): *Möglichkeiten einer Lymphtherapie bei diabetischer Polyneuropathie. Matrixtherapie bei Typ-II-Diabetikern – eine Praxisstudie*. Biol. Med., 29: 4-9.
- ¹⁸ Eiber A., Klein P., Weiser M. (2003): *Periphere diabetische Polyneuropathie. Adjuvante homöopathische Behandlung verstärkt den Therapieerfolg*. Der Allgemeinarzt, 25: 610-4.
- ¹⁹ Rinneberg A.L. (1988): *Behandlung und Rezidivprophylaxe der Tonsillitis mit Lymphomyosot*. Biologische Medizin, 4: 179-182.
- ²⁰ Küstermann K., Weiser M. (1997): *Behandlung lymphatischer Erkrankungen mit einem Homöopathikum*. Biologische Medizin 26: 110-4.
- ²¹ Zenner St., Metelmann H. (1989): *Therapeutischer Einsatz von Lymphomyosot – Ergebnisse einer multizentrischen Anwendungsbeobachtung an 3512 Patienten (I)*. Biologische Medizin, 5: 548-64.
- ²² Zenner St., Metelmann H. (1989): *Therapeutischer Einsatz von Lymphomyosot – Ergebnisse einer multizentrischen Anwendungsbeobachtung an 3512 Patienten (II)*. Biologische Medizin, 6: 658-66.
- ²³ Kirchoff H.W. (1982): *Ein klinischer Beitrag zur Behandlung des Lymphödems*. Der praktische Arzt, 21: 621-33.
- ²⁴ McNeely M.L., Magee D.J., Lees A.W., Bagnall K.M., Haykowsky M., Hanson J. (2004): *The addition of manual lymph drainage to compression therapy for breast cancer related lymphedema: a randomized controlled trial*. Breast Cancer Res. Treat., 86: 95-106.

LYMPHATIC DAMAGE IN VENOUS SURGERY

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ABSTRACT

Purpose: Before a lower limb surgical operation due to venous disease, it is necessary to immediately evaluate the presence and seriousness of the concurrent lymphatic deficiency.

Methods: Besides objective test that can reveal a clinically evident lymphatic deficiency, it is helpful to investigate family and remote pathological anamnesis to identify possible risk factors or specific family propensities. As far as instrumental tests are concerned, it is advisable to perform both a doppler ultrasonographic examination and a limb segmentary Lymphoscintigraphy. The most risky area is the inguinal one, where lymphatic collector vessels join main lymph-nodal structures. Obviously, lesions of these structures may start a lymphatic deficiency, but it is also important to underline that scar reactions and relevant fibrosis, that may characterize an even normal post-operation period, may create a further obstacle to normal lymphatic drain.

Results and Conclusions: Special attention has to be paid to precise indications and venous surgery technique in mixed clinical situations, when both venous and lymphatic systems are involved, to avoid potential clinical state worsening. Finally, diagnostic and therapeutical prevention modalities for possible lymphatic injuries in CVI affected limbs have to be kept into consideration, up to microsurgical technique application. Hopefully therefore, with the purpose of a correct preventive and not invasive surgical operation, more and more attention will be paid regarding potential lymphatic impairment derived from venous surgery.

INTRODUCTION

Venous and lymphatic circulation can be considered as strictly correlated and it is often necessary, during the analysis of a physio-pathological process, to contextually check them as if they were a single functional unit.

They do have a common embryonic genesis: as a matter of fact, lymphatic sacs, that represent lymphatic circulation primordial structures, take origin from primordial venous formations.

From an anatomical standpoint, both circulations have a supra- and sub-fascial course and are equipped with anti reflux valvular devices.

As far as functional profile is concerned, lymphatic and venous systems cooperate in maintaining correct interstitial liquids and extracellular matrix homeostasis, thus guaranteeing a centripetal transportation of organic materials and molecules originated by cellular metabolism.

AN OUTLINE OF PHYSIOPATHOLOGY

Whenever a clinically evident edema or an inflammatory-infectious manifestation affecting lower limbs is detected, it is possible to highlight a concurrent lymphatic circulation direct involvement.

This latter can adequately compensate the "load" increase or, even in advance, reveal symptoms of functional insufficiency, "de facto" worsening involved subject's clinical-prognostic aspect. Getting into more details, the appearance of lymphatic edemas affecting lower limbs in the course of venous disease can be schematically due to:

- 1) low output failure, when an insufficient lymphatic drain is already present, and a paraphysiological increase is therefore sufficient to create a circulatory incompetence (i.e. primary and secondary lymphatic edemas – stage 1a, or pre-existing functional deficiencies)
- 2) high output failure: while, as for instance with post-thrombophlebitic syndrome and CVI, the rise of lymphatic load can be initially offset by circulatory functional reserve, in case of further overloading or lympho-nodal lymphatic structures lesions, an oedema display can show up.

While first hypothesis represents a less common situation, the second condition, where lymphatic system insufficiency is subordinate to venous circulation alteration, is frequently met. In clinical practice it is pretty common to detect lymphatic edemas without any evidence of venous system alteration; with

fleboedemas, on the contrary, a concurrent involvement of lymphatic system always exists and, “ab initio” already, it can show clinical symptoms of dynamic or mechanical deficiency (Lympho-Fleboedema o Flebo-Lymphoedema). Moreover, lymphatic circulation involvement in CVI is worsened by the appearance of dystrophic-ulcerative lesions and lipodermatosclerosis.

O. Eliska, with reference to the above mentioned subject, has demonstrated lymphatic involvement around venous ulcers and, through aimed biopsies, has confirmed that perilesional edemas are very frequent as well.

During phlebitis events, often pathognomonic “rubra” stria only represents a “linfangitic stria”, satellite of the vein that has been affected by inflammatory/thrombotic process.

CLINICAL/DIAGNOSTIC ELEMENTS

Before a lower limbs surgical operation due to venous disease, it is necessary to immediately check presence and seriousness of the concurrent lymphatic deficiency. It has to be outlined that transitory edemas may already mean an early indication of lymphatic involvement (stage 1b).

Besides objective test that can reveal a clinically evident lymphatic deficiency, it is helpful to investigate family and remote pathological anamnesis to identify possible risk factors or specific family propensities.

As far as instrumental tests are concerned, when someone is considered at risk, it is advisable to run both a doppler ultrasonographic examination and a limb segmentary Lymphoscintigraphy, being this latter considered as the “gold standard” in lymphatic circulation insufficiency care and classification by stages.

LYMPHATIC DAMAGE WITH VENOUS SURGERY

With reference mainly to above-mentioned anatomic-functional contiguity, it is almost impossible, even during a perfectly performed surgical operation, not to damage lymphatic structures. These ones, usually superabundant, are sometimes affected to such an extent that a vascular deficiency can show up.

The most risky area is the inguinal one, where lymphatic collector vessels join main lympho-nodal structures.

Obviously, lesions of these structures may start a lymphatic deficiency (as well known, ipoplastic lympho-nodal structures often generate primary lymphoedemas) but it is important to underline that cicatrization reactions and relevant fibrosis, that may characterize an even normal post-operation period, may create a further obstacle to normal lymphatic drain.

Inguinal “debridement” represents a standard during lymphatic microsurgery operations when lower limbs are concerned.

If the patient reveals a clinically evident concurrent deterioration of the lymphatic system since the beginning of the symptoms, it is recommended that surgery is planned only whenever ascending phlebitis and/or bleeding are highly probable, according to a recent Lymphology article by Prof. M. Foeldi. This article highlights as in 90% of venous surgery with concurrent lymphoedema or lipo-lymphoedema, symptomatology defined as “varicogenic” and

characterized by tiredness, heaviness, cramps or itching didn’t regress at all.

Whenever there’s a high probability of potential lymphatic deficiency (for instance having to deal with an evident drain slowing down during an aimed lymphoscintigraphic test), considerable caution in adopted technique (low traumatic operative techniques, measuring devices use during stripping etc.) is highly recommended.

Furthermore, visual aids are helpful for a direct analysis of lympho-nodal lymphatic structures: this can be accomplished through an injection of Blue Patent Violet (BPV) vital dye in foot interdigitals spaces and in the upper 1/3 of the antero-medial thigh surface, in order to avoid unintentional damage to collecting structures, not clearly distinguishable during crossectomy, saphenic stripping and ligation of incompetent collateral and perforating veins (Figs. 1, 2).

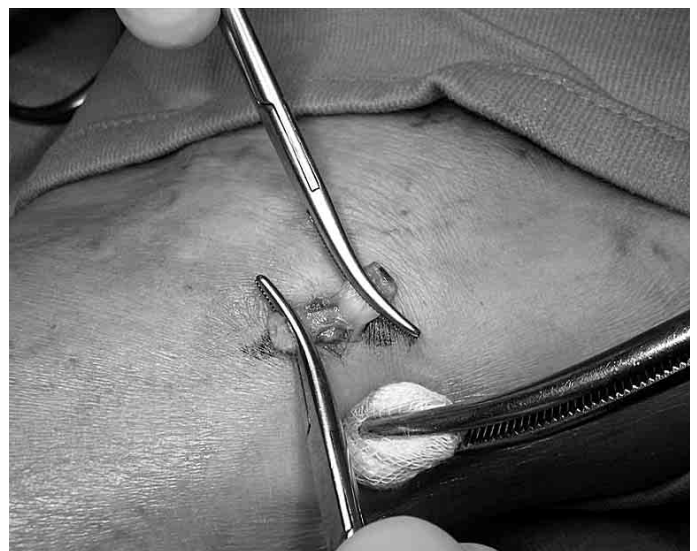


Fig. 1 - Lymphatic collectors pointed out by the blue dye near the great saphenous vein at the malleolus.

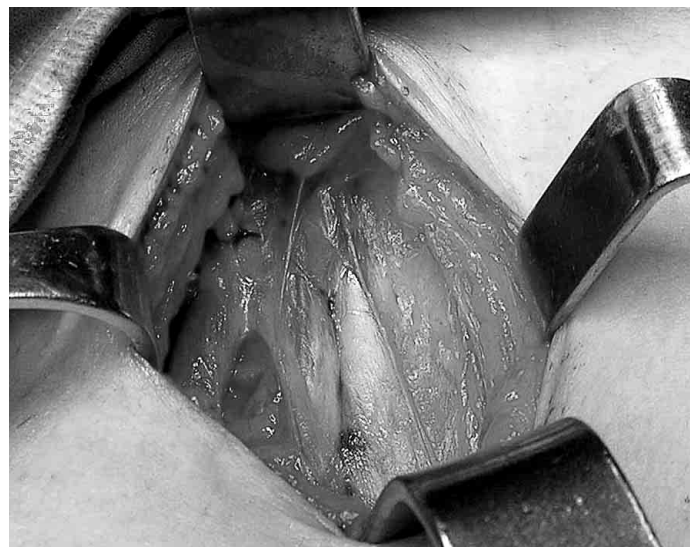


Fig. 2 - Blue lymphatic collectors near the great saphenous vein at the groin.

Lymphatic-Venous derivative microsurgical anastomoses represents by now a consolidated reality in lymphoedema therapy and in mixed conditions, when a concurrent venous insufficiency is present as well, it is possible to co-ordinate, in the same session, both surgical operations in order to get a final solution for both jeopardized vascular systems.

Whenever it's not possible to find continent and lymphatic anastomoses suitable venous vessels, it is viable to carry out a valvuloplasty. As above underlined, prevention is fundamental for correct venous and lymphatic surgical approach, but it's necessary to remember that, after surgery, a correct follow up and an eventual rehabilitation therapy, aimed at keeping under control potential worsening of clinical picture (mainly from a lymphatic standpoint) are equally important.

CONCLUSIONS

Several investigations have demonstrated lymphatic system involvement in an CVI context. Literature evidence demonstrates as lymphatic involvement includes low output failure and high output failure context.

A lymphatic circulatory involvement is always associated with a chronic edema of lower limbs with CVI signs.

Diagnostic framing of these mixed pathologies always has to be complete an integrated.

Special attention has to be paid to precise indications and venous surgery technique in mixed clinical situations, when both venous and lymphatic systems are involved, to avoid potential clinical state worsening – “Primum non nocere”.

Finally, diagnostic and therapeutical prevention modalities for possible sequences of lymphologic order in CVI affected limbs have to be kept into consideration, up to microsurgical technique application.

Hopefully therefore, with the purpose of a correct preventive and not intrusive surgical operation, more and more attention will be paid regarding potential lymphoangiologic sequences derived from a not careful, reckless venous surgery.

REFERENCES

1. Eliska O., Eliskova M.: *Morphological changes in lymphatic vessels from edema to venous leg ulcer*. Phlebolympology 2003; 41: 177-182.
2. Bollinger A., Isenring G., Franzeck U.K.: *Lymphatic microangiopathy: a complication of severe chronic venous incompetence (CVI)*. Lymphology, 1982 Jun;15(2): 60-5.
3. Allegra C. et al.: *Morphological and functional characters of the cutaneous lymphatics in primary lymphoedemas*. Europ. J. Lymphol. Rel. Probl., 1996; 6: I, 24.
4. Olszewski W.: *Clinical efficacy of micronized purified flavonoid fraction (MPFF) in edema*. Angiology, 2000 Jan; 51(1): 25-9.
5. Földi M., Idiazabal G.: *The Role of Operative Management of Varicose Veins in Patients with Lymphedema and/or Lipedema of the Legs*. Lymphology 2000; 33 (4): 167-171.
6. Campisi C., Boccardo F.: *Lymphedema and Microsurgery (Invited Review)*. Microsurgery 2002; 22: 74-80.
7. Mortimer P.S.: *Implications of the lymphatic system in CVI-associated edema*. Angiology, 2000 Jan; 51(1): 3-7.
8. Michelini S.: *Dove va la Linfologia Italiana*. Linfologia Italiana, 1/2004, Edit. pag 3.
9. Macciò A., Campisi C.: *Dizionario di Linfologia*. Ed. Minerva Medica, 2003.
10. Visitin A.: *La linfologia nella pratica quotidiana del MMG*. Workshop: “La Linfologia nella cultura medica attuale”, 7° Congresso Nazionale IFC, 2003, Udine.
11. Foeldi E.: *The treatment of lymphedema*. Cancer, 1998 Dec. 15; 83(12 Suppl American): 2833-4. Review.
12. Campisi C., Michelini S., Boccardo F.: *Guidelines of the Societa Italiana di Linfangiologia: excerpted sections*. Lymphology, 2004 Dec; 37(4): 182-4.
13. Campisi C., Zilli A., Macciò A., Schenone F., da Rin E., Eretta C., Boccardo F.: *Prevention of lymphoedema secondary to the treatment of breast cancer: a case report and proposal for a prevention protocol*. Chir. Ital. 2004 May-Jun; 56(3): 419-24.

Flow Chart

Venous Surgery Candidate Patient

- ❶ Lymphatic insufficiency manifested
(Clinical Examination)
 - a. Limited indications
 - b. Mini-Invasivity, use of Blue Dye
 - c. Simultaneous L-V Microsurgery
- ❷ Not clinical evidence of Lymphatic Insufficiency
(Anamnesis, Risk Factors, Lymphoscintigraphy)
 - a. Mini-Invasivity, use of Blue Dye
 - b. Selective surgery
 - c. Lymphologic Follow-up

ADEQUATE POST-SURGERY PHYSIOTHERAPY FOR WOMEN WITH BREAST CANCER IN EVIDENCE BASED MEDICINE. **REVIEW.**

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INTRODUCTION

In the last 20 years important medical and surgical innovations have been done about treatment of breast cancer. Reduced shoulder range of movement (ROM) and function has been recognised as a problem after breast cancer surgery for many decades.

Choices of surgical procedures, from modified radical mastectomy (MRM) to breast conservative treatment (BCT) followed by radiation therapy and to sentinel node biopsy, need a review about post surgical rehabilitation treatment.

Wound seroma and shoulder dysfunction are the most frequent complications of a mastectomy. To prevent the development of a frozen shoulder it seems justifiable to recommend post-operative exercises. However, early shoulder exercises may have a deleterious effect on wound healing and seroma formation.

Early discharge of patients, who had surgery for breast cancer, is a routine practice; in Italy women are usually discharged at the third day post surgery with wound drains still in place.

Thanks to these innovations and referring to Evidence Based Medicine, the aim of the study is to identify the best therapeutic approach for women with breast cancer in post-surgical phase.

RESEARCH STRATEGY

We have done two different researches in Medline/PubMed. The first one on the 5 of May 2006 with these key-words: #1 (breast neoplasm); #2 (breast cancer); #3 (breast tum*); #4

(rehabilitation); #5 (physical therapy); #6 (exercise therapy); #7 (movement therapy); #8 (physiotherapy); #9 (#1 OR #2 OR #3); #10 (#4 OR #5 OR #6 OR #7 OR #8); #11 (#9 AND #10).

Limits: All Adult: 19+ years, Randomized Controlled Trial, Humans.

The second one on the 14 of January 2008 with the same key-words to find new publications. These researches let us find 15 studies.

CHARACTERISTICS OF THE STUDIES

Randomized clinical trials published from 1989 to August 2007 in English/French language.

All the studies included women who have undergone breast cancer surgery (Breast Conserving Treatment or Modified Radical Mastectomy) followed by physical therapy within three months from surgery.

4 studies compared an early rehabilitation group vs a delayed one.

7 studies compared a sperimental treatment group vs a control one.

1 study compared a movement + massage group vs only movement or only massage or no treatment ones.

1 study compared an early discharge group vs a standard one.

1 study compared a clinical and volumetric evaluation group vs a clinical and lymphoscintigraphic one.

1 study compared a latissimus dorsi "quilting" procedure group vs a control one.

PATIENTS AND METHODS

Tab. 1

Authors/Years	Treatment Group 1 (patients randomized number)	Control Group 2 (patients randomized number)
DAWSON <i>et al.</i> 1989	Early rehabilitation (51 pt): the exercise group started to exercise on the 1 st day after-surgery	Delayed rehabilitation (49 pt): in the delayed rehabilitation group the ipsilateral arm was immobilized in a sling for 5 days after-surgery; then the same shoulder exercises of early rehabilitation group were started
PETREK <i>et al.</i> 1990	Early rehabilitation group (27 pt): 2 nd day after-surgery. Graduate range of motion exercises were begun under the supervision of a physical or occupational therapist	Delayed rehabilitation group (30 pt): 5 th day after-surgery. The same standard exercises of early rehabilitation were begun
GANZ <i>et al.</i> 1992	Treatment Group. One month after surgery Experimental case management intervention included initial provision of information, reassurance, and referrals for specific problems identified in the needs assessment, and on-going telephone monitoring for continuing and new rehabilitation problems during the subsequent year	Control Group. One month after surgery Minimal intervention group received a dictated consultation generally describing the woman's rehabilitation needs
SCHULTZ <i>et al.</i> 1997	Early group (89 pt): 1 st day after surgery The physiotherapist assessed shoulder mobility preoperatively and postoperatively. The pt were instructed to do active shoulder exercises to regain full range of motion. Ante-flexion, abduction and rotation three times daily, pain being the limiting factor for the extent of motion	Delayed group (74 pt): 7 th day after surgery The physiotherapist assessed shoulder mobility preoperatively and postoperatively. Started the full exercise program one week postoperatively, after instructions from the physiotherapist
LE VU <i>et al.</i> 1997	The authors compared different modes of treatments: rehabilitation alone, massage alone, both or neither Treatment group rehabilitation and massage (64 pt): Like rehabilitation and massage treatment * for all four groups treatment began the day after breast surgery and continued for 7 days. Afterwards, all patients had massage and shoulder movements until the end of hospitalisation. Treatment efficacy was evaluated at day 7 by the volume of lymph drained, and by degree of shoulder movement	Delayed group (74 pt): 7 th day after surgery The physiotherapist assessed shoulder mobility preoperatively and postoperatively. Started the full exercise program one week postoperatively, after instructions from the physiotherapist
BUNDRED <i>et al.</i> 1998	Early discharge (49 pt) two days after surgery (before removal of drain). Shoulder movement was assessed preoperatively and at one and three months postoperatively. Patients were asked about functional shoulder movements and the degree of abduction, adduction, internal or external rotation, flexion and extension were measured. Pt were instructed how to manage the wound drain and given information sheets on wound care and advice on shoulder exercises. They were asked to measure the volume of fluid draining from the wound and were telephoned daily by specialist breast nurses and visited by them every other day	Standard discharge (51 pt) five/ten days after surgery (after removal of drain) Shoulder movement was assessed preoperatively and at one and three months postoperatively. Patients were asked about functional shoulder movements and the degree of abduction, adduction, internal or external rotation, flexion and extension were measured. Pt were instructed on wound care and advice on shoulder exercises

Authors/Years	Treatment Group 1 (patients randomized number)	Control Group 2 (patients randomized number)
SHIMOZUMA <i>et al.</i> 1999	Treatment Group. Experimental case management intervention like Ganz <i>et al.</i> 1992	Control Group. Minimal intervention like Ganz <i>et al.</i> 1992
BOX <i>et al.</i> 2002 - I	Treatment Group (32 pt): assessments were completed preoperatively, at day 5 and at 1 month, 3, 6, 12 and 24 months postoperatively. TG received the Physiotherapy Management Care Plan (PMCP). It includes a thorough preoperative assessment and explanation with inpatient and outpatient postoperative reviews to monitor shoulder ROM, progress exercise programmes, provide lymphedema awareness education and individualised intervention as required. The exercise protocol used in this current study incorporated the gradual progression of shoulder movements from the second postoperative day. All movements of the OA were assisted initially by the unoperated arm, with the introduction of further progressions from day 14 or once the axillary drain had been removed with the limiting factor for all exercises being each woman's own level of discomfort Exercises started 2 nd day post-surgery	Control group (33 pt): assessments were completed preoperatively, at day 5 and at 1 month, 3, 6, 12 and 24 months postoperatively. The CG only received an exercise instruction booklet with no instruction or supervision provided by the physiotherapist. Exercises started 2 nd day post-surgery
BOX <i>et al.</i> 2002 - II	Treatment Group (32 pt): Like Box <i>et al.</i> 2002 - I The physiotherapy intervention programme included principles for lymphedema risk minimisation and early management of this condition when it was identified. Three measurements were used for the detection of arm lymphoedema: arm circumferences (CIRC), arm volume (VOL) and multi-frequency bio-impedance (MFBIA). Early intervention with a self-management programme (manual lymph drainage, compressive bandage, arm's elevated posture and skin care) is implemented when secondary lymphedema is identified as persistent, or progressive, from 3 months postoperatively	Control group (33 pt): Like Box <i>et al.</i> 2002 - I
CAMPISI <i>et al.</i> 2002	Lymphoscintigraphy group (25 pt) clinical follow-up (objective valuation and volumetry) and lymphoscintigraphy before operation and after 1-3-6 months and 1-3 years from the treatment. Patients who presented lymphoscintigraphic alterations (dermal back flow, diffused or delayed transit of the tracer, etc.), before edema appeared clinically, underwent physical and rehabilitative therapy (bandages, manual lymphatic drainage, mechanical lymph drainage, elastic garments, etc.) and microsurgery (lymphatic-venous anastomoses at the arm), performed early (stages Ib and II) in patients not responsive to physical therapy.	Control group (33 pt): Like Box <i>et al.</i> 2002 - I
WYATT <i>et al.</i> 2004	Lymphoscintigraphy group (25 pt) clinical follow-up (objective valuation and volumetry) and lymphoscintigraphy before operation and after 1-3-6 months and 1-3 years from the treatment. Patients who presented lymphoscintigraphic alterations (dermal back flow, diffused or delayed transit of the tracer, etc.), before edema appeared clinically, underwent physical and rehabilitative therapy (bandages, manual lymphatic drainage, mechanical lymph drainage, elastic garments, etc.) and microsurgery (lymphatic-venous anastomoses at the arm), performed early (stages Ib and II) in patients not responsive to physical therapy	I° Control group (64 pz): participants received surgeon-ordered agency home nursing care. The nature of the agency home nursing care was that of a generalist. Nursing care was provided by standard visiting nurse services in the various communities II° Control group (55 pz): participants received no-post surgical home nursing care

Authors/Years	Treatment Group 1 (patients randomized number)	Control Group 2 (patients randomized number)
LAURIDSEN <i>et al.</i> 2005	<p>Group A (72 pz): Standard treatment of the ward and in addition, team instructed physiotherapy consisting of 12 sessions of 60 min., two sessions a week. The treatment was instituted during the sixth to eight postoperative weeks.</p> <p>* Standard treatment of the ward included daily demonstrations and instructions in shoulder and vein pump exercise during the first postoperative week. Instructions were given by a physiotherapist and the patient were encouraged to continue exercising when discharged from the hospital</p> <p>** Additional treatment: the exercise program consisted of exercises based on extension and relaxation, strength training, vein pump therapy and instruction in stretching of scar tissue in order to increase the mobility of the skin above the pectoral major muscle and in the area of axilla. The pt were encourage to perform the exercises on a regular basis at home</p>	<p>Group B (67 pz): Standard treatment of the ward and in additions the same additional treatment of group A but after the 26th postoperative week</p>
DALTREY <i>et al.</i> 2006	<p>Quilting Group (54 pz) Closure of the donor site dead space with “quilting technique”</p>	<p>Control Group (54 pz) Routine closure of the back skin wound</p>
LEE <i>et al.</i> 2007	<p>Stretch group (31 pz) were recruited 1 week prior to the commencement of radiotherapy. Skin care + lymphedema advice + pectoral muscle stretching program (low-load, prolonged, passive stretching of pectoralis major and minor while in supine-lying). Weekly visit during all radiotherapy treatment All pt were encourage to continue stretching until follow-up 7 months after radiotherapy</p>	<p>Control Group (30 pz) were recruited 1 week prior to the commencement of radiotherapy. Skin care + lymphedema advice. Weekly visit during all radiotherapy treatment follow-up 7 months after radiotherapy</p>
BEURSKENS <i>et al.</i> 2007	<p>Treatment Group (15 pz) Specific physiotherapy treatment started 2 weeks after surgery (9 treatments number)</p> <p>Follow up at 3 and 6 months after surgery</p>	<p>Control Group (15 pz) Leaflet flyer with advice and exercises for the arm/shoulder for the first weeks following surgery and no further contact with physiotherapist.</p> <p>No physiotherapy Follow up at 3 and 6 months after surgery</p>

Concerning to the objectives, fixed at the beginning of our study, results obtained from literature’s review are inhomogeneous . To evaluate adequately the results, we compare articles about the same outcomes. The evaluated outcome measures are:

- Shoulder functional valuation
- Seroma incidence
- Secondary lymphedema
- Quality of life

Shoulder Functional Valuation

DAWSON *et al.*, SHULTZ *et al.* and LAURIDSEN *et al.*: in the long term, all patients do not show significant differences in shoulder functional motion.

LAURIDSEN *et al.*: the best results happen in subjects who do not receive radiotherapy and/or undergo conservative surgery. Patients with breast-conserving therapy showed less severe and less frequent sholder problems than patients with modified radical

mastectomy. Besides the type of surgery the effect of physiotherapy was influenced by adjuvant radiation therapy. BOX *et al.*, BEURSKENS *et al.*: the best and fastest functional recovery happens in treatment groups.

BOX *et al.*: factors related to recovery are previous shoulder’s problems, compliance to the treatment and post-surgery complication.

LEE *et al.*: pectoral stretching program during radiotherapy do not influence shoulder ROM because the symptoms reported by patients are not a consequence of contracture.

DALTREY *et al.*: breast reconstruction with Latissimus Dorsi “quilting technique” do not compromise shoulder mobility.

Quilting the LD donor side shown that All patients recovered full shoulder abduction within 3 months.

BUNDRED *et al.*: early discharge home facilitates shoulder movement and reduce subsequent would pain. Patients suitable for early discharge must have support from a relative at home and be in good physical health.

Seroma Incidence

DAWSON *et al.*, PETREK *et al.*, SHULTZ *et al.*: in early treatment groups (1-2 days post-op.) there is a bigger incidence of seroma formation and wound infections.

SHULTZ *et al.*: there is a significant correlation between seroma formation, older age and increase of surgical time.

BUNDRED *et al.*: early discharge does not affect rate of post-surgery complications if it is supported by wound care instructions, relative support and specialist breast care nurses.

DALTREY *et al.*: breast reconstruction with "quilting technique" significantly reduce the incidence of symptomatic dorsal seroma, its volume and frequency of aspirations.

Quilting the donor side after LD-flap harvesting significantly reduced total wound drainage and the risk of seroma after drain removal, with proportionately fewer aspirations required

Secondary Lymphedema

SHIMOZUMA *et al.*: patients who undergo conservative breast surgery and radiotherapy have more incidence to develop secondary lymphedema.

CAMPISI *et al.*: lymphoscintigraphy allows to point out alterations of lymphatic drainage before the clinical appearance of edema and to identify the risk of development of arm secondary lymphedema. Microsurgical operation performed precociously, at the early stages of the disease, permits to obtain the complete regression of the pathology thanks to the repair of preferential lymphatic pathways before of fibro-sclerotic tissutal alterations occur, which cause progressive worsening of clinical conditions, together with recurrent attacks of acute lymphangitis.

BOX *et al.*, WYATT *et al.* and LAURIDSEN *et al.*: informational and educational supports are fundamental to prevent secondary lymphedema. Risk factors related to the development of lymphedema are: elevate BMI, wound complications and radiotherapy.

Quality of Life

GANZ *et al.*, SHIMOZUMA *et al.*: one year after surgery most women report high levels of functioning and QOL, with no relationship between type of surgery and QOL; younger working women obtain the best results; predictive variables: mood disturbance, body image discomfort and number of positive lymph nodes.

WYATT *et al.*: improvement of QOL, already in short term, can be reached with an adequate home-care support, knowledge and education about post-surgery period.

BEURSKENS *et al.*: adequate rehabilitative treatment, began 15 days after surgery, significantly improve QOL.

DISCUSSION

Studies about rehabilitation treatments show that there is a strong relation between seroma formation and the beginning of shoulder rehabilitation.

Early treatments cause more frequently formation of seroma in comparison with the delayed ones.

In the long term, however, both treatments allow patients to reach pre-surgery functional shoulder levels.

Only two authors try to individuate the anatomical structures determining limited shoulder ROM:

LEE *et al.*: "The pectoral stretching program, during radiotherapy, did not influence the outcomes measured because the symptoms reported by patients were not consequence of contracture.

Radiotherapy to the breast did not cause contracture or loss of shoulder range: objective measurements of range did not correlate with local symptoms reported by women during radiotherapy".

DALTREY *et al.*: "Quilting of the latissimus dorsi donor site had no apparent effect on shoulder movement. All patients recovered full shoulder abduction within 3 months".

The incidence of seroma (Schultz) could be reduced using less traumatic surgical techniques and minimizing shoulder motions in the immediate post surgery.

Clinical assessments of shoulder function and measurement of omolateral upper limb, pre and post-surgery, allow to identify early lymphedema. Lymphoscintigraphy performed preoperatively, permitted to find lymphatic impairment (absence of deltoid way, reduced axillary lymph nodal tracer uptake, delayed transit of the tracer) at the upper limb.

Pre-surgery lymphoscintigraphy allows to find alterations of lymphatic circulation and the risk of development of lymphedema. In these cases preventive physical and rehabilitation measures allows to reduce the clinical appearance of lymphedema.

Even if there is no scientific evidence, many authors (Földi, Cohen, Harris, ...) support that meticulous skin care is fundamental to reduce the risk of infections as a potential trigger factor for lymphedema.

Patients' knowledge and education about secondary lymphedema symptoms give support to treatment and produce best outcomes. Physical assessment by a clinician and patient self-report are both important measures, and are likely to be complementary.

Further investigations may need to assess the actual incidence of latent subcutaneous fibrosis caused by radiotherapy to assess the need for preventative exercise (Lee)

REFERENCES

- Dawson I, Stam L, Heslinga JM, Kalsbeek HL (1989) [1] Effect of shoulder immobilization on wound seroma and shoulder dysfunction following modified radical mastectomy: a randomized prospective clinical trial. *Br. J. Surg.*, 76: 311-2.
- Petrek JA, Peters MM, Nori S, Knauer C, Kinne DW, Rogatko A (1990) [2] Axillary lymphadenectomy. A prospective, randomized trial of 13 factors influencing drainage, including early or delayed arm mobilization. *Arch Surg*, 125(3): 378-82.
- Ganz PA, Schag Ac, Lee JJ, Polinsky MI, Tan Sj (1992) [3] Breast Conservation Versus Mastectomy. Is there a difference in Psychological Adjustment or Quality of Life in the year after surgery? *Cancer*, 69(7): 1729-38.
- Schultz I, Barholm M, Grondal S (1997) [4] Delayed Shoulder Exercise in Reducing Seroma Frequency after Modified Radical Mastectomy: A Prospective Randomized Study. *Ann Surg Oncol*, 4(4): 293-7.

Le Vu B, Dumortier A, Guillaume MV, Mouriesse H, Barreau – Pouhaer L (1997) [5] Efficacité du massage et de la mobilisation du membre supérieur après traitement chirurgical du cancer du sein. *Bull Cancer*, 84(10): 957-61.

Bundred N, Maguire P, Reynolds J, Grimshaw J, Morris J, Thomson L, Barr L, Baidam A (1998) [6] Randomised controlled trial of effects of early discharge after surgery for breast cancer. *BMJ*, 317: 1275-9.

Shimozuma K, Ganz PA, Petersen L, Hirji K (1999) [7] Quality of life in the first year after breast cancer surgery: rehabilitation needs and patterns of recovery. *Breast Cancer Research and Treatment*, 56:45-57.

Box RC, Reul-Hirche HM, Bullock-Saxton JE, Furnival CM (2002) [8] Shoulder movement after breast cancer surgery: results of a randomised controlled study of postoperative physiotherapy. *Breast Cancer Research and Treatment*, 75: 35-50.

Box RC, Reul-Hirche HM, Bullock-Saxton JE, Furnival CM (2002) [9] Physiotherapy after breast cancer surgery: results of a Randomised controlled study to minimise lymphoedema. *Breast Cancer Research and Treatment*, 75: 51-64.

Campisi C, Boccardo F, Zilli A, Maccio A, Napoli F, Ferriera Azevedo W Jr, Fulcheri E, Taddei G (2002) [10] Linfedema secondario al trattamento del cancro mammario: possibilità prevenzione diagnostica e terapeutica. *Ann Ital Chir*, 73(5): 493-8.

Wyatt GK, Donze LF, Beckrow KC (2004) [11] Efficacy of an In-Home Nursing Intervention Following Short-Stay Breast Cancer Surgery. *Research in Nursing & Health*, 27: 322-31.

Lauridsen MC, Christiansen P, Hessev I (2005) [12] The effect of physiotherapy on shoulder function in patients surgically treated for breast cancer: A randomized study. *Acta Oncologica*, 44: 449-57.

Daltrey I, Thomson H, Hussien M, Krishna K, Rayter Z, Winters E (2006) [13] Randomized clinical trial of the effect of quilting latissimus dorsi flap donor site on seroma formation. *Br J Surg*, Jul 93(7): 825-30.

Lee TS, Kilbreath SL, Refshange KM, Pendlebury SC, Beith JM, Lee MJ (2007) [14] Pectoral stretching program for women undergoing radiotherapy for breast cancer. *Breast Cancer Res Treat*. 2007 May; 102(3): 313-21.

Beurskens CH, Van Uden CJ, Strobbe LJ, Oostendorp RA, Wobbes T (2007) [15] The efficacy of physiotherapy upon shoulder function following axillary dissection in breast cancer, a randomized controlled study. *BMC Cancer*. Aug 30; 7: 166.

[*] Harris SR, Hugi MR, Olivetto IA, Niesen-Vertommen SL, Dingee CK, Eddy F, *et al.*: Upper extremity rehabilitation in women with breast cancer after axillary dissection: clinical practice guidelines. *Crit Rev Phys Rehab Med*, 2001, 13: 91-103.

[**] Casley-Smith J, Casley-Smith JR: Modern treatment for lymphoedema. 5th edition, Adelaide. S.A. Lymphoedema Association of Australia; 1997.

IMMUNE-STIMULATION AND REDUCTION OF INFECTIVE COMPLICATIONS IN PATIENTS WITH LYMPHEDEMA

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ABSTRACT

In primary and secondary lymphoedema the lymphangitis are very frequent and above all in particular subjects they may occur 3 or more times a year. Every new phlogistic episode alters the anatomical-functional state with a general clinic worsening. In patients with primary and secondary lymphoedema in order to reduce the phlogistic recurrences, and the consequent antibiotic treatment, we used an immune-stimulating vaccine (*staphylococcus*, *streptococcus*, *haemophilus* and *klebsiella*) in patients that had almost two lymphangitic episodes in their clinical history. The results show a reduction of lymphangitic recurrences and also the use of the antibiotic-treatment.

KEY WORD: lymphedema prevention, immunostimulation.

INTRODUCTION

Lymphangitis are a very frequent complication of lymphoedema (Fig. 1). Often the inflammatory disease is due to skin saprophytic bacteria such as *staphylococcus* and *streptococcus*. Ethel Földi asserts that lymphoedema is a good ground for a sterile chronic inflammatory disease. The *streptococcus* bacteria easy infect this compromised area and so can give a particular clinical state, called erysipelas, which involves all the organism, compromising the general-health state: high fever, asthenia and pain focused on interested body part. The pathognomonic sign of erysipelas is represented by an evident step between infected and normal skin. Each new lymphangitic event get worsen the anatomical-pathological local state and also the general-health state. Regardless they had primary or secondary lymphoedema, some patients are subject to lymphangitis several time a year: the treatment is based on antibiotic and anti-inflammatory therapy or corticosteroids. Often it is possible to do a diagnostic mistake, due to a not-real etiological classification, confusing with a venous inflammatory disease, so that patients would be treated with heparin for a long time without benefits. Because the high incidence of infection and its related complications, the authors evaluated the use of an antimicrobial vaccine in a group of patients which had two or more lymphangitic events in their clinical history, in order to prevent the complications by an immune-system stimulation.



Fig. 1 - Acute lymphangitis.

MATERIALS AND METHODS

We observed 316 patients affected by lymphoedema from over one year (201 female and 115 male, age between 19 y and 76 years old). Two hundred thirty two were affected by a secondary lymphoedema of upper and lower limbs and 84 by a primary lymphoedema. One hundred twelve (35.4%) had in their clinical history lymphangitic events, 43 of these had only one event and 69 two or more. The female/male ratio is about 2:1 (the incidence per sex was 66.6% for female and 33.4% for male). The secondary lymphoedema was more frequent than primary.

Our inclusion criteria was:

- at least two lymphangitic episode in the past 12 months;
- a complete compliance from patients.

Our exclusion criteria was:

- a recent or acute inflammatory disease;
- a concomitant antibiotic therapy;
- continuous steroid therapy;
- primary immunodeficiency.

To all patients a vaccination nasal spray has been administered with a mixture containing bacterial stocks (*Staphylococcus*,

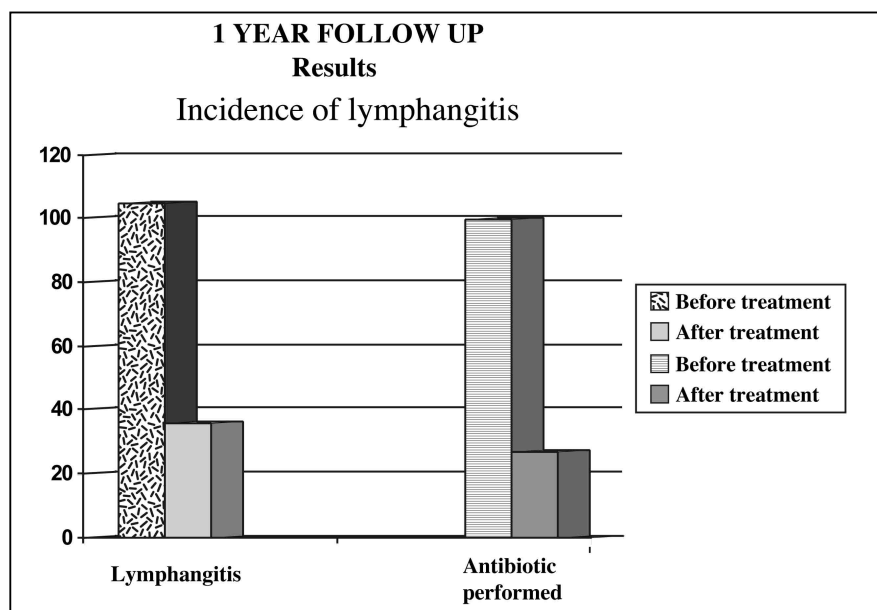


Fig. 2 - Incidence of lymphangitis in 1 year follow up.

Streptococcus, Klebsiella and Hoemophilus) deprived of their pathogenic power.

In the vaccine the percentages of the bacterias were fairly distributed (25% each) and as excipients was used NaCl, phenol and glycerine.

The immunostimulating treatment consisted of an initial phase and one of maintenance. The initial phase was composed of four bottles of 5ml each. The first bottle contain 10 millions of bacterias per ml; the second 30 millions bacterias/ml; the third 100 millions bacterias/ml; the fourth 300 millions bacterias/ml.

The maintenance phase was composed of three bottles of 5 ml with 300 millions bacterias/ml each.

In the first week patients used the first bottle making one breathed per nostril every day (about 2 millions of bacterias/die), during the second week, using the second bottle with the same way of administration (one breathed per nostril/die), the patients take about 6 millions of bacterias/die; in the third week, using the third bottle in the same way, the patients take about 20 millions of bacterias/die; from the fourth week instead, using the fourth bottle, patients made one breathed per nostril on alternate days (about 60 millions of bacterias each administration) until exhaustion of bottle.

After one months form the end of initial phase the maintenance phase started. During this phase patients made one breathed per nostril on alternate days until exhaustion of three bottles.

RESULTS

At one year follow-up we observed an average increase, compared to initial values, of: IgG (about 27%), IgM (about 34%) and IgA (about 40.5%). We also observed an average reduction of: lymphangitic events (about 59%), antibiotic therapy assumption (about 64%) by patients (Fig. 2). The duration of lymphangitic new events, after immunostimulating therapy, were significantly shorter and the symphoms were eased. [Clinically the new lymphangitic events were eased and the flogistic disease cleared up faster].

The appearance interval between consecutive lymphangitic events, in patients who had before multiple recurrences per year, lengthened of about 3.2 months.

No adverse or intolerance reactions was observed in all patients.

CONCLUSION

This preliminary study suggests that the use of a specific vaccine, which increases the self-immunotimulation in patients with lymphoedema who had multiple lymphangitic recurrences, can be useful to avoid this complication (without putting aside from the respect of the hygienic norms and style of life) and also the antibiotic therapy.

Actually we're looking for the possibility to personalize the bacterias dose in the single bottle adjusting by the patients weight and also for using the sublingual way of administration.

The preliminary study introduced intends to study in depth the effects during long time follow-up, taking into consideration the cyclic repetition of maintenance phase.

REFERENCES

1. Olszewski W.: *Recurrent bacterial dermatolymphangioadenitis (DLA) is responsible for progression of lymphoedema*. Lymphology 1996; 29 (Suppl): 331.
2. Olszewski W.: *Bacteriological Studies of skin, tissue fluid and lympho in filarial lymphedema*. Lymphology 1994, 27 (Suppl), 345-348.
3. Campisi C., Boccardo F., Tacchella M.: *Lymphangitis and lymphedema: new personal method of thermotherapy*. Lymphology 1994, 27 (Suppl), 639-643.
4. Michelini S., Failla A., Moneta G., Cardone M., Rubeghi V., Zinicola V.: *Immunostimulation and decrease of phlogistic complications in lymphedema patients: preliminary study*. The European Journal of Lymphology. Vol. 19, N. 54, pag. 19, 2008.
5. Witte C.L., Witte M.H.: *Consensus and dogma*. Lymphology 1998 Sep; 31(3): 98-100.

THE SURGICAL MANAGEMENT OF CHRONIC PENOSCROTAL LYMPHEDEMA

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ABSTRACT

Chronic penoscrotal lymphedema is not as frequent a symptom of lymphatic insufficiency as the lymphedema of lower extremities; however, people suffering from it have significant problems. Regarding the problems connected with the use of compression, the complex decongestive therapy has only limited possibilities. The authors demonstrate their experience with surgical treatment of chronic penoscrotal lymphedema - elephantiasis, call attention to indications for surgery, particular steps performed during surgery and post-operative care.

KEY WORDS: penoscrotal lymphedema, surgery, lymphatic insufficiency, proteolytic enzymes.

INTRODUCTION

For those who are concerned with the long-term care of patients with chronic lymphedema, irrespective of the specific etiologies causing the problem, after a certain period of time, they may notice that in a certain number of patients treated by conservative procedures, the volume of the afflicted part of their body slowly increases, and even when the treatment is performed properly, they are not able to attain the required reduction in volume nor is the resulting improvement in the patient's quality of life achieved. Among these patients are also individuals with chronic lymphedema of the scrotum and penis (penoscrotal lymphedema). As they often cannot find adequate medical aid, they resolve this handicap by merely tailoring their trousers to a greater width. A far greater impediment to their lives is the problem associated with personal hygiene, sexual function, and mobility. The incidence of penoscrotal lymphedema is much lower than lymphedema of extremities. In Europe, one can usually find it as a result of lymphadenectomy and/or radiotherapy of inguinal or pelvic lymphatics. Its progression is passed through the same stadiums as the lymphedema of the upper or lower extremities. In

many cases, lymphedema progresses to the lipohypertrophy (Fig. 1) and/or elephantiasis (Fig. 2), even in the case of very well done CDT^{1,2}.



Fig. 1 - Chronic lymphedema with the scrotum lipohypertrophy occurring after "trivial surgery" in the inguinal area.



Fig. 2 - Penoscrotal elephantiasis.



Fig. 3 - Chronic penoscrotal lymphedema with lymphorrhea in combination with lymphedema of the lower limb.

In the literature, surgical procedures resulting in reduction of soft tissues of scrotum and penis are discussed^{3,4,5,6,7}. It is very important to consider the lymphatic drainage of scrotum and penis. It is generally agreed that posterior and posterolateral areas of scrotum are not usually largely afflicted by fibrotic changes and they can be used for the formation of “neoscrotum”. This fact is probably caused by partially separated lymphatic drainage of the penis and scrotum. This also explains why the lymphedema of penis and the scrotum does not necessarily appear together. The efferent collectors originate in the vicinity of the raphe and contralateral branches anastomose with each other. Those lymph vessels near the root of the penis continue together with the cutaneous collectors of the penis to the superomedial inguinal nodes. Those lymph vessels originate in the middle and posterior part of the scrotal skin continue through the genitofemoral sulcus to the inferomedial inguinal nodes. The collectors of the penile skin that originate in the inner and outer cutaneous network of the prepuce and the efferent cutaneous lymph vessels of the penis terminate in the superomedial superficial inguinal nodes (but can also lead to other node groups). The cutaneous lymph vessels of the scrotum anastomose with the cutaneous collectors of the penis, cutaneous rectal zone, perineum, and medial surface of the thigh⁸.



Fig. 4 - Penoscrotal elephantiasis in a patient with Down's Syndrome.



Fig. 5 - Chronic penoscrotal lymphedema post oncosurgery and radiotherapy of regional lymph nodes.

MATERIAL AND METHODS

The chronic penoscrotal lymphedema and elephantiasis is rare in areas without endemic filiriasis. Its aetiology in Europe includes the following:

- primary causes* - this is often found in combination with lymphedema of the lower limbs (Fig. 3) or occurs in the context of another syndrome, for example Down's Syndrome (Fig. 4)
- secondary causes* - this frequently follows the series of treatments for malignancies (Fig. 5) or as the result of complex treatment of lymphedema of the lower limbs⁹ (Fig. 6). Sometimes, it may follow “trivial surgeries”, such as operations near the inguinal area (Fig.1).



Fig. 6 - Chronic penoscrotal lymphedema as a result of complex decongestive treatment of secondary lymphedema of the lower limb.

As part of the *preoperative assessment*, we recommend to perform an MRI examination to precisely identify the corpora cavernosa with the urethra and the testes and ductus deferrens, along with their vascular supply (Fig. 7). Soft tissues must be non-pitting. This means that only pure lipohypertrophy is involved. The surgery is performed under general anaesthesia with antibiotic prophylaxis.

Individual surgical steps:

- the selected incision is purely up to the individual patient and is based on the clinical finding (Fig. 8);
- preparation of the penis glans (Fig. 9);
- installation of a permanent urinary catheter (Fig. 9);
- preparation of the penis, making sure to preserve the foreskin so as to prevent injury to the neural and vascular supply (Fig. 9);
- preparation of both testes with the ductus deferens and its vascular supply (Fig. 9);
- resection of the hypertrophic soft tissues (Fig. 10);
- formation of the “neoscrotum” with testicular pexy (Fig. 11);
- performance of a circumcision (Fig. 11);
- drainage with Redon drains (Fig. 11);
- suture of the resulting defect (Fig. 11).



Fig. 9 - Preparation of the penis, both testes, installation of a permanent urinary catheter.



Fig. 10 - Resection of the hypertrophic soft tissues.

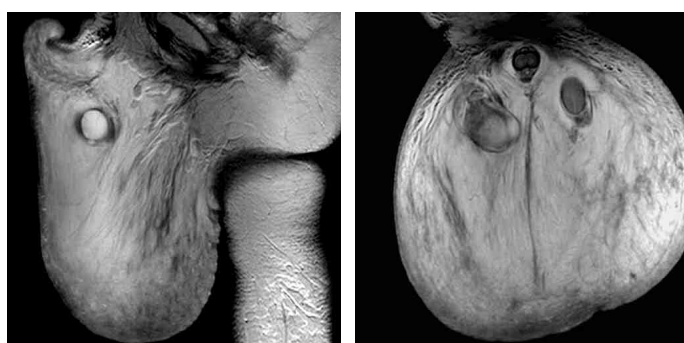


Fig. 7a, b - MRI examination to precisely identify the corpora cavernosa with the urethra and the testes.



Fig. 11 - Formation of the “neoscrotum”, installation of Redon drains, suture of the resulting defect and performance of a circumcision.

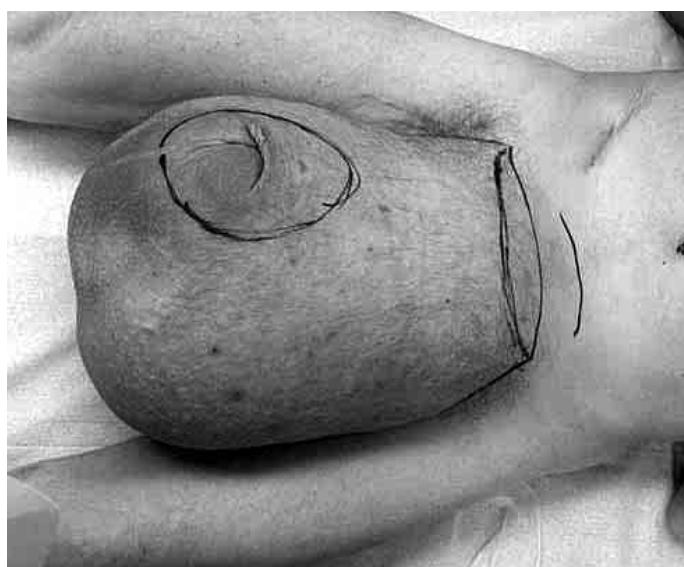


Fig. 8 - The selected incision is purely up to the clinical finding.

Postoperatively, at first intravenous, and then later peroral penicillin antibiotics are given. High doses of proteolytic enzymes are given perorally. By combining antibiotics and proteolytic enzymes, we reduce the risk of infectious complications in the cut and we considerably reduce postoperative lymphedema¹⁰. We have improvised on the technique of compression of the soft tissues of the neoscrotum and penis. Patients are mobilised early. The urinary catheter is usually left in place for a period of 3 weeks and is removed at the same time as surgical sutures. In certain cases, we have performed small corrections to the residual soft tissues of the hypertrophic foreskin in the out-patient department under local anaesthesia.

RESULTS

In last 20 months we have operated on a total of 5 patients. The hospitalisation lasted for 7-10 days. In all cases, the wounds were healed *per primam intentionem* (Fig. 12). The cosmetic and functional results are satisfactory in all cases; however, considering the short observation time, it would not be objective to talk about possible recurrence of lymphedema and/or lipohypertrophy with growth of the size of scrotum and/or penis.



Fig. 12 - Result one year after the surgery.

CONCLUSION

At present, patient feedback from these surgeries has been unanimously positive from the aspect of: assisting with their personal hygiene, solving this social handicap, and from the perspective of improved sexual function; however, it is necessary to reach a better cosmetic effect, especially in the case of young individuals.

REFERENCES

- ¹ Dumaini S., Schubert J.: *Chronic lymphedema in the genital area. Etiology and therapeutic possibilities.* Arztl Fortbild Qualitatssich 1997 Sep; 91(6): 537-41.
- ² Ross J.H., Kay R., Yetman R.J., Angermeier K.: *Primary lymphedema of the genitalia in children and adolescents.* J. Urol., 1998 Oct;160(4): 1485-9.
- ³ Vaught S.K., Litvak A.S., McRoberts J.W.: *The surgical management of scrotal and penile lymphedema.* J. Urol., 1975 Feb;113(2): 204-6.
- ⁴ Altchek E.D., Hecht H.: *A modification of the standard technique for repair of scrotal elephantiasis: case report.* Plast. Reconstr. Surg., 1977 Aug; 60(2): 284-6.
- ⁵ Ollapallil J.J., Watters D.A.: *Surgical management of elephantiasis of male genitalia.* Br. J. Urol., 1995 Aug; 76(2): 213-5.
- ⁶ Garaffa G., Christopher N., Ralph D.J.: *The management of genital lymphoedema.* BJU Int., 2008 Aug;102(4): 480-4.
- ⁷ Stokes T.H., Follmar K.E., Silverstein A.D., Weizer A.Z., Donatucci C.F., Anderson E.E., Erdmann D.: *Use of negative-pressure dressings and split-thickness skin grafts following penile shaft reduction and reduction scrotoplasty in the management of penoscrotal elephantiasis.* Ann. Plast. Surg., 2006 Jun; 56(6): 649-53.
- ⁸ Földi M., Földi E., Kubik S.: *Textbook of Lymphology.* Urban and Fischer Verlag, 2003, Munich.
- ⁹ Boris M., Weindorf S., Lasinski B.B.: *The risk of genital edema after external pump compression for lower limb lymphedema.* Lymphology, 1998 Mar; 31(1): 15-20.
- ¹⁰ Dušková M., Wald M.: *Orally Administered Proteases in Aesthetic Surgery.* Aesth. Plast. Surg., 1999; 23: 41-44.

A CASE OF CHYLOUS DYSPLASIA CAUSING A SERIOUS CONDITION IMMUNODEFICIENCY

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ABSTRACT

Background: Among primary immunodeficiencies, common variable immunodeficiency (CVID) is defined by an impaired production of immunoglobulins, characterized by low levels of plasma immunoglobulins and altered antibody response. The case reported was initially interpreted as a CVID.

Clinical Case: A male, 20 years old, suffered from diarrhoea (2-4 times a day), weight loss (8 kilos in 5 years), and malnutrition (hypogammaglobulinemia, hypoalbuminemia, leukocytopenia with lymphocytopenia). Accurate diagnostic assessment allowed to diagnose a protein-losing enteropathy. Conventional oil contrast lymphangiography allowed to accurately assess the case and to establish a proper therapeutic approach. The operation consisted in multiple antigravitational ligatures of dilated and incompetent chylous vessels and chylous vessel-mesenteric vein microanastomoses.

Results: Parameters concerning albumin and leukocytes normalized in 1 week after operation and remained stable with time, there were no more episodes of diarrhoea and the patient recovered weight.

Conclusions: An accurate diagnostic assessment and above all lymphangiography allow to diagnose properly difficult cases of immunodeficiency due to intestinal protein dispersion and to plan a correct therapeutic functional approach.

INTRODUCTION

Among primary immunodeficiencies, common variable immunodeficiency (CVID) is defined by an impaired production of immunoglobulins, characterized by low levels of plasma immunoglobulins and altered antibody response. The case reported was initially interpreted as a CVID. But, clear information about the patient's medical history and accurate clinical examination allowed to reach the correct diagnosis and perform a proper treatment.

In case of chylous disorders, from the immunological point of view, it is important to avoid the leakage of immunoglobulins and

lymphocytes in order to maintain immunologic competence. Lymph in the thoracic duct contains from about 2,000 to 20,000 lymphocytes per mm,³ i.e., a concentration of lymphocytes 2-10 times higher than in the blood. This lymphocytosis varies according to the number of lymph nodes, temperature, digestive phase and endocrine conditions. It is, therefore, easy to understand the importance of restoring normal drainage of the intestinal lymph circulation. In the majority of cases, malnutrition is present, with significant hypoproteinemia – specially affecting the albumin fraction – and weight loss. Respiratory problems and steatorrhea are also often present in Protein Losing Enteropathy associated forms.

In case of chylous dysplasias, patients should not undergo operation prematurely until at least a proper diagnosis has been made as to the nature and site of the likely chyle leak. During this period, the patient should be properly metabolically compensated through an appropriate diet with protein integration and limited lipid input confined only to medium chain triglycerides (MCT). MCTs, rather than being absorbed through intestinal chyliferous lymphatic roots, use the portal venous pathway. The addition of water-soluble vitamins (ADEKs tablet) should also be considered. From the etiopathological point of view, a malformation affecting the thoracic duct, Pecquet cyst, and/or chyliferous vessels can cause a significant obstacle to lymph drainage and, in particular, to intestinal drainage. Therefore, chyliferous vessels along the walls of the small intestine and of the mesentery become significantly dilated and abnormally stretched due to chylous stasis. The disease also features lymphatic megacollectors with more or less extensive chylous lymphangiectasia, often associated with lymphangiomyomatosis.¹⁻⁵ In some cases, the chyliferous vessel at the centre of the villus breaks into the intestinal lumen, thus causing the loss of proteins, lipids, lipoproteins, and even calcium and glucose, which lead to metabolic disorders that are typical of so called "Protein Losing Enteropathy" (PLE).

CLINICAL CASE

A male, 20 years old, suffered from diarrhoea (2-4 times a day), weight loss (8 kilos in 5 years), malnutrition (BMI 16,6),

hypogammaglobulinemia, hypoalbuminemia, leukocytopenia and lymphocytopenia, associated with diarrhea.

After a first interpretation of the clinical feature as CVID, an accurate diagnostic assessment allowed to diagnose a protein-losing enteropathy.

High resolution ultrasonography demonstrated a certain quantity of intrabdominal free fluid, markedly dilated (43 mm diameter) ileal intestinal loops full of intraluminal liquid, thickened intestinal wall (4,5 mm diameter) with rich vascularisation of the wall.

The test of protein dispersion with ^{99m}Tc labelled albumin proved an intestinal protein dispersion probably at the ileal region.

Lymphoscintigraphy was not indicative of the kind and site of the chyle leakage.

Conventional oil contrast lymphangiography allowed to accurately assess the case. Lymphographic phase showed markedly dilated lymphatic pathways at the iliac-lumbar-aortic region, mainly at the right side, with dysplastic vessels and gravitational reflux. Cisterna chyli and thoracic duct were normal.

At first, a total parenteral nutrition and protein integration were performed for about a week, but without obtaining any improvement as concerns the metabolic alterations.

Hypoalbuminemia and lymphocytopenia persisted.

Therefore, it was decided to operate the patient and a proper surgical approach was established. Chylous vessels were pointed out thanks to a fatty meal (60 gr. of butter eaten at 4 o'clock in the morning before operation). They appeared dilated and full of chyle. The operation consisted in multiple antigravitational ligatures of dilated and incompetent chylous vessels and chylous vessel-mesenteric vein microanastomoses (Fig.1).

In less than a week, biochemical parameters improved and reached almost normality. Post-operative course was favourable and drains could be removed after 5 days, without the appearance of chylous ascitis. After a week of total parenteral nutrition, the patient started eating, following a diet regimen with medium chain triglycerides. Presently, at over 1 year from operation, the metabolic conditions are stable, there no signs of malnutrition and the patient could conduct a normal life, gathering also in weight. Since the chylous dysplasia is very extensive, he is still following a proper diet regimen. But, before microsurgical operation this diet was not sufficient to allow him to be in discrete conditions. Thus, the association of surgical approach and diet were able to help him in reaching stable conditions of a proper metabolic situation and a normal intestinal function without diarrhea.

DISCUSSION

In this case the intestinal loss of chyle with proteins and lymphocytes were higher than what it could be administered, thus the surgical approach was necessary and aimed at reducing this leak. The alternative of a right colectomy should have been considered, but this would have been a symptomatic solution not a causal one. This would have brought in this case towards the formation of other areas of gravitational reflux because the dysplasia was more extensive. Instead, performing lymphatic ligatures and deriving the chyle into the blood stream, the reduction of chylous hypertension allowed to obtain a positive and stable result.

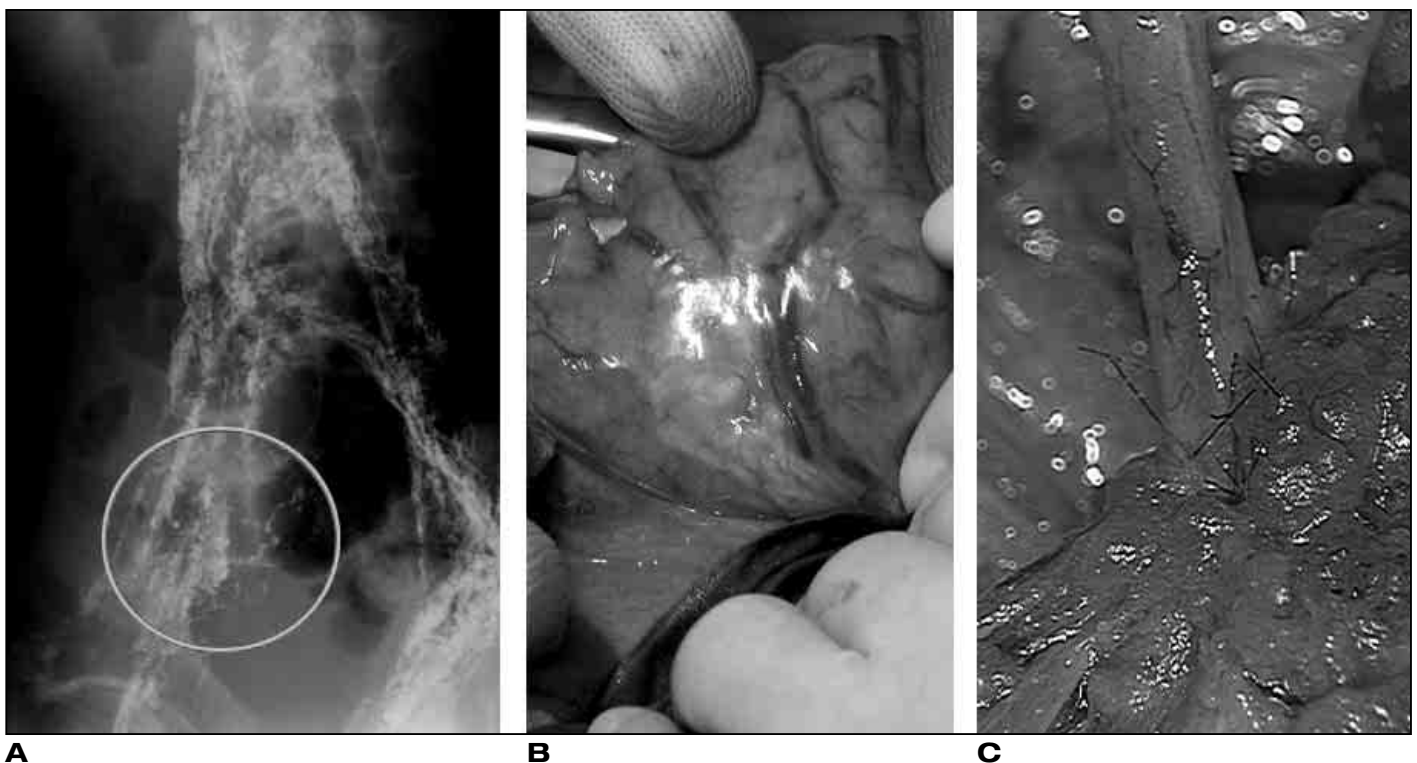


Fig. 1 - Lymphographic phase showed markedly dilated lymphatic pathways at the iliac-lumbar-aortic region, mainly at the right side, with dysplastic vessels and gravitational reflux (A); Chylous vessels are pointed out thanks to a fatty meal, dilated and full of chyle (B); Chylous vessel-mesenteric vein multiple microanastomosis (C).

The wide ranging extension of the chylous malformations and the complexity of their association with dysplasia of chylo-lymphatic vessels, thoracic duct, and chylous cyst explain why, especially in the newborn, sometimes these conditions affecting multiple-districts are incompatible with life. Further, upon clinical onset of the most severe cases, effective treatment may be difficult to achieve later in life, thus leading to more or less complex prognostic implications involving “*quoad valetudinem*” as well as “*quoad vitam*” issues.⁶⁻¹¹

In conclusion, considering the etiopathogenesis as well as the nature and complexity of chylous dysplasias, the treatment of these difficult pictures and the outcome significantly depend on the skills of the physicians/surgeons and on the available technology and equipment. For this reason, it is highly recommended that these patients be referred to the few centers that have a specific surgical experience in the treatment of this disease.

REFERENCES

1. Browse N., Burnand K.G., Mortimer P.S.: *Diseases of the lymphatics*. Arnold, London, 2003.
2. Servelle M., Noguès C.: *The chyloiferous vessels*. Expansion Scientifique Francaise, Paris, 1981.
3. Tosatti E., Cariati E., De Mauro D., Ricco G.: *Linfonodi, cisterna di Pecquet e dinamica antigravitazionale linfatica*. Gazz. Sanit., 3: 83, 1964.
4. Casaccia M., Campisi C.: *Chyloedèmes*. Journal des Maladies Vasculaires, 13:145-153, 1988.
5. Witte M.H. et al.: *Lymphangiogenesis: mechanisms, significance and clinical implications, in Regulation of Angiogenesis*, edited by ID Goldberg, EM Rosen EM. Basel/Switzerland, Birkhuser Verlag, 1996, p. 65.
6. Campisi C., Boccardo F.: *Lymphedema and microsurgery*. Microsurgery, 2002; 22: 74-80.
7. Aalami O.O., Allen D.B., Organ C.H. Jr.: *Chylous ascites: a collective review*. Surgery 2000; 128:761-78.
8. Kinmonth J.B.: *The lymphatics. Surgery, lymphography and diseases of the chyle and lymph systems*. E. Arnold, London, 1982.
9. Gruwez J.: *Lymphoedema, basic mechanism, clinical problems, indications for therapy*. Chylous reflux. ISL Congress, Tucson, Arizona, 1973.
10. Press O.W., Press N.O., Kaufmann S.D.: *Evaluation and management of chylous ascites*. Annals of Internal Medicine 1982; 96: 358-64.
11. Campisi C., Boccardo F., Zilli A., Borrelli V.: *Chylous reflux pathologies: diagnosis and microsurgical treatment*. Int. Angiol. 1999 Mar; 18(1): 10-3.

THE URETERAL STENTING IN THE RAT: A SIMPLE TECHNIQUE FOR STUDYING THE INTERACTION BETWEEN THE UROTHELIUM AND BIOMATERIALS

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SUMMARY

In Urology the employment of the biomaterials needs some compatibility surveys through experimental easy and reliable models. Suturing the ureter of the rat, we have planned our model to analyse the tissular reaction to several materials. In this paper we are going to show our preliminary outcomes.

KEY WORDS: Stent, biocompatibility, ureter, urothelium.

INTRODUCTION

In Urology and in almost the whole Urinary System, stents are employed to allow the urinary down flow across the stopped tracts (stones, tumours, stenosis) or when the Urinary Tract needs a preferential drain. An ideal stent should be a biocompatible, chemically inert and made in scale proof material. The Polyurethane and the Silicone are properly endured and they show well known features of resistance and flexibility [1]. But especially with the Polyurethane, these stents usually develop several reactions of encrustation (Fig.s 1, 2, 3).

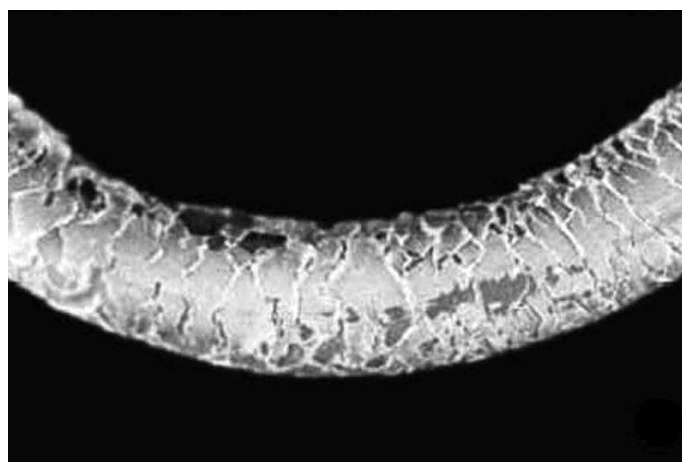


Fig. 2 - Developed encrustations on ureteral stent.



Fig. 3 - An encrusted ureteral stent.

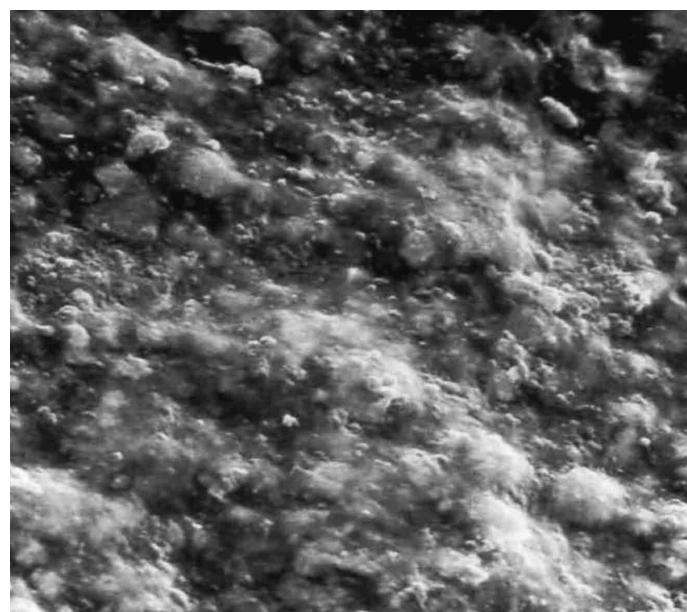


Fig. 1 - Scanning electron microscopy of a Polyurethane ureteral stent shows a very irregular and encrusted surface.

For many years some biodegradable stents have been introduced in the clinical medicine, such as the Polilactic Acid and the Poliglycolic Acid, whose degradation takes place slowly, without releasing any inert or toxic products [2]. To test the biocompatibility, several experimental researches have been performed in some large – size animals or with human endoscopic biopsies [3]. We offer a very easy repeatable model, to value the biomaterials in the rat.

MATERIALS AND METHODS

After inducing the general anesthesia in asepsis, the surgical approach has been done by a median laparotomy, being able to free and to isolate the ureters of both the sides. Under the enlargement of the operator microscope, we have cannulated the proximal ureter with a fine needle (26 Gouge) to function of guide, for the anterograde sliding of the thread. We have introduced and sutured stents with each of three kinds of biomaterials for every of three groups, in which nine rats have been divided (Tab. I). Then we have sutured the small break of the ureteral wall with one or two 10/0 Nylon stitches. We have used some 30 mm about and 5/0 threads, made of Polipropylene, Polidioxanone and Silicone covered Nylon (Tab. I). The abdominal wall has been closed by a layer suture.

Surgery mean length was about forty minutes on average. The awakening of all the rats has carefully been followed.

Moreover we have planned some hematochemical analysis, to examine the renal function at the starting time and after ending the surgery. After drawing the ureters, we have performed their fixation in paraffin, so they have turned hematosyline – eosine or Azan – Mallory and at last we have been able to study them. The follow up has been for three months.

Tab. I - Materials and histological reactions.

Group	Ureters	Material	Histology (mucosa/tunics)
A	1	Silicone®	atrophy/ fibrosis
	2	Silicone®	Integral
	3	Silicone®	Integral
B	4	PDS	atrophy/ fibrosis
	5	PDS	Atrophy
	6	PDS	Atrophy
C	7	Prolhene®	Integral
	8	Prolhene®	Integral
	9	Prolhene®	Integral

RESULTS

The survival rate was excellent, but only one belonging rat to the group B, out of nine ones, has died after two days, due to an ureteral perforation. The eighth leftover rats have ended the forecast follow up.

Two belonging rats to group B have presented Hidroureteronephrosis: after ending the surgery we have examined their creatininemia, which has lightly increased (1,5 mg/dl and 1,6 mg/dl as to 1,0 mg/dl on average).

During the sample, the stent has never been out of seat.

We have analysed the histological examination of nine appreciable ureters, so we have been able to point out several epithelial and subepithelial lesions in the samples, belonging to the tissular areas, in contact with the suture (“contact areas”).

The dead rat and its histological lesions have been examined with an autopsy: so we have considered it in our study.

Four case have presented an atrophic and thinning epithelium, due to the loss of the most of surface cellular layers, with flaking and vacuolated intraepithelial areas. Three of these cases belong to the group B and the leftover one belongs to the group A.

Two cases have shown fibrosis of the lamina propria with disposition to envelope a submucosa tunic, that doesn't usually belong to the ureter of the rat. One of these cases belongs to the group B and the other one belongs to the group A. Both the cases have also presented an atrophic pattern (Fig. 4 A).

These histological lesions also involve the vascular microstructures of lamina propria.

The process of fibrosis develops several thrombuses and clots above all in the venous and arterial capillaries. Besides this changing process concerns the vascular both lymphatic and blood walls with penetration of fibroblasts and collagen fibers (Fig. 5 B, C).

The superficial lesions involve the group B and only in one case they belong to the group A. Only the belonging cases to the group B have been associated with the using of a slowly reabsorbable material: this is the monofilament Polidioxanone and its degradation is due to a slow hydrolysis.

Instead the Polipropylene stent holder ureters haven't presented any histological lesions. This outcome agrees with the well-known tissular reactivity of the same materials. These five leftover rats belong to the group C (three cases on five) and to the group A (two cases on five).

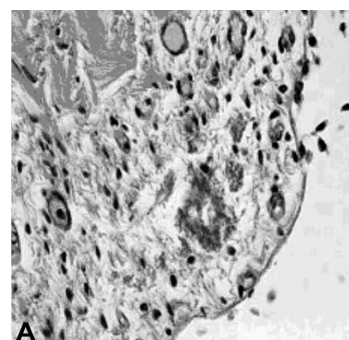


Fig. 4 (A) - Fibro-sclerosis ureteral wall (hematosyline - eosine).

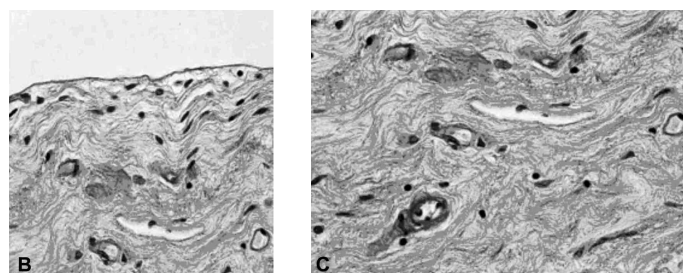


Fig. 5 (B, C) - Ureter: fibro-sclerosis of capillaries (hematosyline - eosine).

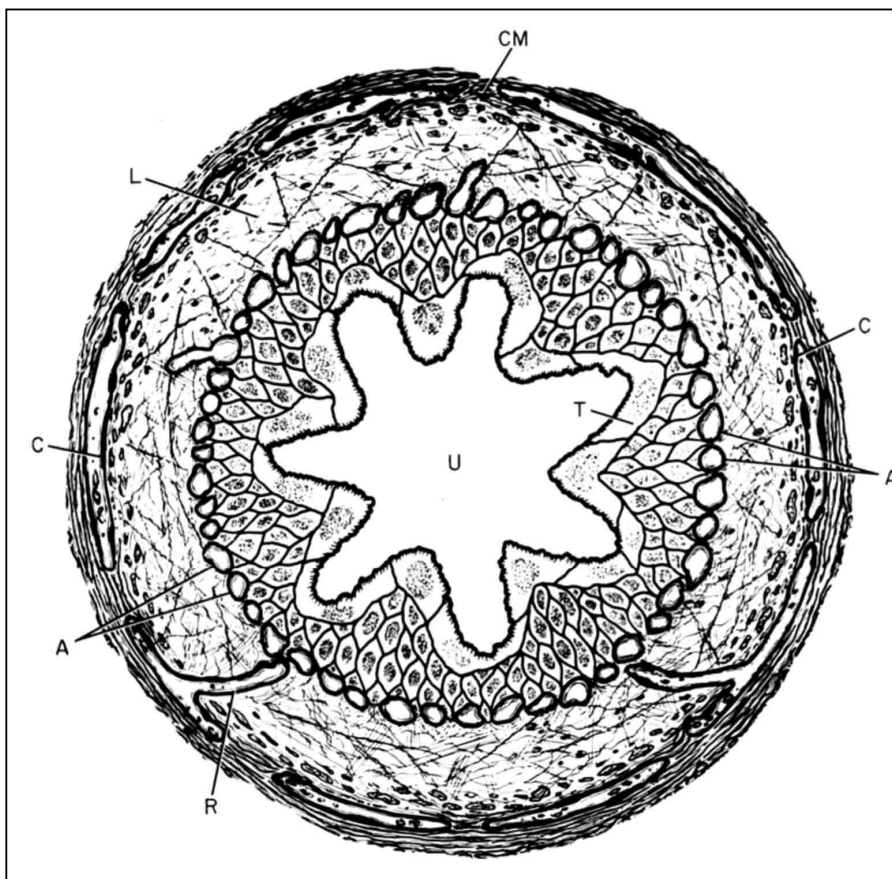


Fig. 6 - A cross section through the rat ureter: the stellate lumen (U) is surrounded by the ridged and fissured transitional epithelium (T), which is three to four cells deep. Below this epithelium there are axially arranged blood and lymphatic vessels (A); only blood ones connect through occasional radial vessels (R) with large, more peripheral, circular blood vessels. Supporting the blood and lymphatic vessels and filling most of the area between them is the lamina propria (L), a connective tissue layer composed of collagen fibers, fibroblasts and few myelinated nerve fibers; at its periphery lamina propria carries longitudinally arranged smooth muscle cells, which set up a compact circular layer of smooth muscle (CM). Surrounding the whole ureter there is a fibro-adipose adventitia, which carries other blood and lymphatic vessels, and nerve fibers. The adventitia isn't represented in this figure.

DISCUSSION AND CONCLUSIONS

The ureter of the rat spreads out along the ventral surface of the Sublombar Muscle, corresponding to the human Psoas Muscle. Then it dorsally and laterally gets into the bladder. Due to the renal collocation, the left ureter is shorter (45 mm about) than the right one (50 mm about). The calibre of the left ureter is 0,7 mm about. The mucosa is made of four – eight layers of epithelial cells and a lamina propria, that presents collagen, elastic fibers and blood and lymphatic capillaries [4]. On the outside there's a muscular tunic, covered by a fibro - adipose adventitia, whom blood and lymphatic vessels and nerves belong to. Besides there isn't the submucosa tunic.

These anatomic features can be compared to the human ones, so they allow to study certainly the urinary tract of the rat, in spite of its slight proportion [5].

The two belonging rats to the group B with idroureteronefrosi therefore show a worsening of the renal functionality, perhaps due to the employment of the same material, PDS. But any statistical contribution assists this consideration.

This model doesn't claim to prove the significance of the statistics, due to the slightness of presenting data. We want to propose an easy and repeatable model to analyse the biocompatibility and to be able to employ for greater studies, in numerical terms, with a more statistical significance. As exactly proposed in such study, these searches could exploit smaller animals than the employed ones by the usual researches.

Besides, without being able to draw meaningful conclusions for

the aforesaid motives, we can observe as the Propylene is a very biocompatible material. It presents the best output of three materials, in terms of biological tissular reactivity and probably in terms of efficiency of the suturing resistance.

The research about the biocompatibility of the materials has to value the toxicity, to study the decay curve of products and the immuno- allergic analysis, but also the histological survey of the "contact areas" can obtain a clinical meaning [6].

We believe the performed model is achievable and easily feasible and it can lead to cheap and long term researches.

BIBLIOGRAFY

- ¹ Yachia D.: *Overview: Role of stents in Urology*. J. Endourol., 1997; 11: 379-382.
- ² Taglja M., Valimaa T., Tammela T., Petas A., Tormala P.: *Bioabsorbable and biodegradable stents in Urology*. J. Endourol., 1997; 11: 391-397.
- ³ Ramsay J.W. et al.: *Urothelial reaction to ureteric intubation. A clinical study*. Br. J. Urol., 1987; 60(6): 504-505.
- ⁴ Hebel R., Stromberg M.W.: *Anatomy of the Laboratory Rat*. Baltimore, The Williams & Wilkins Company, 1976.
- ⁵ Carmignani G. et al.: *A new technique for the end-to-end ureterostomy in the rat, using an indwelling reabsorbable stent*. Microsurgery, 1983; 4: 229-232.
- ⁶ Pariente J.L., Bordenave L., Bareilli R., Baquay C., Le Guillon M.: *The biocompatibility of catheters and stents used in Urology*. Prog. Urol. 1998; 51(6): 927-931.

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