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The relationship between psychological distress and impairment of disease-specific quality-of-life compared between liquid sclerocompression therapy and invasive treatments in patients with superficial venous disease during a one-year follow-up

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Abstract

Introduction: Superficial venous disease (SVD) is a very common disease and much research has been done towards finding the ideal treatment and discovering the pathophysiology of SVD. Not much is known about the psychological burden of SVD. Current guidelines and scientific publications tend to focus on clinical and physiological aspects of SVD. The aim of this study was to relate the changes in Quality-of-Life (QoL) after SVD treatment to possible changes in psychological distress (PD).

Methods: A prospective cohort was set up with the assistance of 5 specialized vein clinics in the Netherlands. Inclusion criteria were: 18 years of age or older, fluent in Dutch language, C1 to C6 (CEAP) class intended to be primary treated with either endovenous laser (LA), radiofrequency ablation (RFA) and phlebectomy (PHL) or sclerocompression therapy alone (SCT). Patients were divided in two groups:

1. C1-C3 patients treated by SCT
2. C1-C6 patients treated invasively (LA, RFA and PHL)

Outcomes were a disease specific QoL questionnaire (CIVIQ-20) and a questionnaire to assess PD (Hospital Anxiety and Depression Scales (HADS)). This study was approved by the local institutional review board, following the principles outlined in the Declaration to Helsinki. This trial was registered in the ISRCTN registry with study ID ISRCTN12085308

Results: 442 patients were included in the study and completed the T0 measurements. Mean age of these patients is 54.4 years (s.d. 12.9, 17-90). Number of females: 349 (79.0%), of males: 93 (21.0%). The mean baseline (T-0) HADS depression (0-3) scale scores is 2.54 (s.d. 0.51, n = 412). The mean one-year difference between T-12 HADS depression (0-3) scale scores and baseline T-0 scores is +0.06. The mean baseline (T-0) HADS anxiety (0-3) scale scores is 2.19 (s.d. 0.5, n = 283). The mean one-year difference between T-12 HADS anxiety (0-3) scale scores and baseline T-0 scores is +0.06. Controlled for baseline scores, gender, age, weight and length (BMI), patients in group 2 (receiving invasive treatment) show significantly higher one-year improvement in the QoL of their psychological state of mind than patients in group 1 (receiving SCT and having C1,2,3) (beta 0.158 p = 0.002).

Conclusions: The significant improvement in psychological, QoL and clinical scores that we observe after successful invasive treatment compared to no significant improvement after SCT and the lack of psychological distress in patients

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with “simple” SVD indicates that SCT is mainly performed for cosmetic reasons. One could thus argue that reimbursement of SCT as a stand-alone medical treatment is debatable.

Keywords

Venous reflux, venous medicine, venous disease, venous anatomy, vascular surgery

Background

Superficial venous disease (SVD) is a very common disease, in the Western world up to 60% of adults suffer from different stages of SVD, ranging from simple spider veins to venous ulcers.^{1,2}

Extensive research has been done towards finding the ideal treatment and discovering the pathophysiology of SVD. Only a small percentage of the available literature investigates patient-reported Quality-of-Life (QoL) in relation to SVD. Since the introduction of Patient-reported Outcome Measures (PROMs) in guidelines, protocols and standard care the availability of QoL data regarding SVD has increased.³

Although publications investigating Psychological Distress (PD) in patients suffering from SVD are available,⁴ none has tried to link the PD to the severity of the disease and the according treatment indication. (cosmetic v.s. medical indication) Questions are manifold and unanswered, like: Is PD related to simply the severity of SVD or to disease specific or generic QoL? Do patients with PD, next to the severity of the disease differ according to relevant demographics such as gender and age? Can PD eventually be influenced by interventions for SVD? Do physicians underestimate the burden of SVD? Do we treat a cosmetic nuisance, or do we really improve the QoL of patients? No studies have assessed the intervention effects in SVD with both QoL and PD to answer these questions.

In order to relate QoL, PD, clinical severity of SVD, before and after an intervention, prospectively acquired data in a cohort of patients are collected, together with demographics like, age, gender, treatment type, etc., are included with a minimum follow-up of one year. In order to investigate this a predefined conceptual model with hypotheses regarding the underlying relations between the variables is necessary.

Material and methods

A prospective cohort study was set up including patients with SVD in five specialized venous clinics in the Netherlands. Inclusion criteria were: 18 years of age or older, fluent in Dutch language, C1 to C6 (CEAP) class intended to be primarily treated with either endovenous laser (LA), radiofrequency ablation (RFA) and phlebectomy (PHL) or liquid sclerocompression

therapy (SCT) alone. The SCT group includes small varicose veins unfit for phlebectomy.

Patients with previous venous treatment or deep vein thrombosis or deep vein insufficiency in their medical history were excluded.

In the Netherlands treatment of spider, reticular and small varicose veins with SCT is considered cosmetic and not reimbursed by healthcare insurance companies. In order to allow proper statistical analysis of this consideration, patients were divided in two groups:

1. C1-C3 patients treated by SCT
2. C1-C6 patients treated invasively (LA, RFA and PHL)

All patients received a venous Duplex before the treatment, following the clinical practice guidelines of the Dutch Society of Vascular Surgery and Dermatology.

Compression sclerotherapy of spider, reticular and small varicose veins was performed with using polidocanol 0,5% and 1% (Aethoxysklerol®, Kreussler Pharma) in a liquid form.

The patients in group 1 did not have any (Duplex confirmed) signs of deep vein insufficiency or superficial main branch (such as great, small or anterior accessory saphenous vein) insufficiency.

Varicose vein removal was performed with microstab phlebectomy, under local anesthesia.

RFA treatments were performed with the ClosureFast (previously VNUS) (Medtronic) under local anesthesia.

LA treatments were performed with the VenaCure (AngioDynamics) under local anesthesia.

Patients demographics were noted and they were asked to complete, before, 6 and 12 months after treatment (T0, T6, T12) a disease specific QoL questionnaire (the CIVIQ-20)⁵ and a well-established scale to measure PD (Hospital Anxiety and Depression Scales (HADS)).⁶

The HADS consists of a seven-item depression scale (HADS-dep) and a seven-item four-point scale (0-3) anxiety scale (HADS-anx). Higher scores (0-21) are supposed to show higher distress. The HADS instrument is made in such a way that its scores are not influenced by somatic pathology.

The Chronic Venous Insufficiency Quality-of-Life Questionnaire (CIVIQ)⁵ is a disease-specific instrument to measure QoL in SVD patients. It consists of 20 five-point Likert items containing four overall scales: a Pain, Physical Problems, Social Problems and Psychological Problems scale. The four scales are presented as VAS scales (0 (max)-100 (no problems)).

Hypotheses

We hypothesize that an increased clinical severity and impaired QoL in SVD will also increase PD and that an invasive intervention (group 2) will show larger improvements compared to SCT (group 1). The aim of our study is not to prove the effect of the therapy on the psychological burden, but the psychological burden of SVD itself.

We assume that disease-specific QoL impairment has an impact on generic experienced daily-life PD, and not the other way around. For instance, particular perceptions of patients regarding the condition of the veins in their legs are supposed to affect the full range of their feelings of depression or anxiety in everyday life. The conceptual relationship between perceived impairment and generic distress is assumed to be one-way recursive, that is: depression or anxiety will not affect the specific perceptions of impairment.

Statistics

To investigate whether variables show normal distributions the Shapiro-Wilk test is used. If normally distributed, means, standard deviations and numbers of patients are given for metric variables, if not, the minimum and maximum scores are also presented. Categorical variables are shown as frequencies and percentages. Raw outcome variables at baseline (T-0), at 6 months (T-6) and at 12 months (T-12) such as psychic distress and QoL are presented in tables broken down for CEAP (Tables A1–A4) and treatment group (Tables A5–A8). Tables A1–A8 are presented in the Appendix.

To overcome problems of missing data at T-12 the Last-Observation-Carried-Forward (LOCF) technique is performed using data from T-6. Imputed data for T-12 are also displayed in the tables.

Scale constructions with observed items scores usually result in Visual Analogue Scales (VAS) ranging from 0 to 100 (no problems) with exception to the HADS, which ranges from 0 to 3 (no problems).

A p-value of less than 0.05 was considered statistically significant. All data-analysis is performed with IBM SPSS Statistics, version 25.

Results

Descriptive statistics

442 patients were included in the study and completed the T0 measurements. Mean age of these patients is 54.4 years (s.d. 12.9, 17-90). Number of females: 349 (79.0%), of males: 93 (21%).

Males are statistically significantly older than females: 57.8 (12.5) vs. 53.4 (12.9), Student t-test $p = 0.004$.

Out of the 442 patients 288 (65.2%) were included from Zuyderland Medisch Centrum (ZMC), 57 (12.9%) from Phlebology Centre Oosterwal (FCO), 45 (10.2%) from Westfriesgasthuis (WFG), 44 (10.0%) from Braam Clinic (BC) and 8 (1.8%) from Phlebology Centre Grave (FCG).

The frequencies of baseline CEAP classification categories are: C1 29 (6.6%), C2 43 (9.7%), C3 294 (66.5%), C4 54 (12.2%), C5 6 (1.4%) and C6 11 (2.5%). For 5 (1.1% of the total) patients the CEAP class score is missing. Eleven (2.5%) of the 442 patients eventually did not get treated (patients who withdrew themselves from the scheduled therapy or clinic visits).

The remaining 431 patients were treated by the following interventions: laser 72 (16.7%), RFA 153 (35.5%), PHL 111 (25.8%) and SCT 84 (19.5%), Miscellaneous (2.5%) being: compression 6 (1.4%), crossectomy 4 (0.9%) and stripping 1 (0.2%).

33.49% of the included patients was lost at 6 months and 50.69% at 12 months (patients who did not respond to mailed questionnaires or on invitations to visit the clinic). LOCF technique was performed using data from T-6, therefore the amount of analyzed responses were higher, than the actual amount of responsive patients at T-12.

CEAP classes per treatment are shown in Table 1. Including center and respective treatment modalities are shown in Table 2.

Overall

The mean baseline (T-0) HADS DEPRESSION (0-3) scale scores is 2.54 (s.d. 0.51, $n = 412$).

The mean one-year difference between T-12 HADS depression (0-3) scale scores and baseline T-0 scores is +0.06, so there is a statistically significant, one-year positive change (one-sample t-test $P < 0.05$).

The mean baseline (T-0) HADS ANXIETY (0-3) scale scores is 2.19 (s.d. 0.50, $n = 413$).

The mean one-year difference between T-12 HADS anxiety (0-3) scale scores and baseline T-0 scores is +0.06, so there is an overall statistically significant, one-year positive change (one-sample t-test $P < 0.05$).

Table 1. CEAP C-class cross-tabulated with treatment type.

		Treatment							Total	
		Compression	Crossectomy	Laser	Muller	No treatment	SCT	Strip		VNUS
Diagnosis		0	0	2	0	1	0	0	3	6
	C1	0	0	1	0	0	25	0	1	27
	C2	0	0	1	8	0	27	0	6	42
	C3	0	2	49	93	4	29	1	111	289
	C4	0	2	17	5	1	1	0	28	54
	C5	1	0	2	1	1	0	0	1	6
	C6	5	0	0	1	4	0	0	0	10
Total		6	4	72	108	11	82	1	150	434

SCT: liquid sclerocompression therapy; Strip: Stripping; VNUS: radiofrequency ablation.

Table 2. Treatment center cross-tabulated with treatment type.

		Treatment							Total	
		Compression	Crossectomy	Laser	Muller	No treatment	SCT	Strip		VNUS
Centrum		0	0	0	0	1	0	0	0	1
	ZMC	0	3	0	104	2	62	1	110	282
	BC	0	0	33	0	0	11	0	0	44
	FCG	0	0	0	1	0	2	0	5	8
	FCO	6	0	1	0	7	5	0	35	54
	WFG	0	1	38	3	1	2	0	0	45
Total		6	4	72	108	11	82	1	150	434

Group 1 (C1–C3 with SCT)

The mean baseline (T-0) HADS DEPRESSION (0-3) scale scores is 2.52 (s.d. 0.54, n = 83).

The mean one-year difference between T-12 HADS depression (0-3) scale scores and baseline T-0 scores is -0.04, so there is no improvement at one year.

The mean baseline (T-0) HADS ANXIETY (0-3) scale scores is 2.11 (s.d. 0.54, n = 83).

The mean one-year difference between T-12 HADS anxiety (0-3) scale scores and baseline T-0 scores is -0.03, so there is no improvement at one year.

Group 2 (C1–C6 with an invasive treatment)

The mean baseline (T-0) HADS DEPRESSION (0-3) scale scores is 2.54 (s.d. 0.51, n = 329).

The mean one-year difference between T-12 HADS depression (0-3) scale scores and baseline T-0 scores is +0.09 (3% difference), so there is a statistically significant, one-year positive change (one-sample t-test $P < 0.05$).

The mean baseline (T-0) HADS ANXIETY (0-3) scale scores is 2.21 (s.d. 0.49, n = 330).

The mean one-year difference between T-12 HADS anxiety (0-3) scale scores and baseline T-0 scores is +0.09 (3% difference), so there is a statistically significant, one-year positive change (one-sample t-test $P < 0.05$).

Means are also shown in Table 3.

Regression analysis

In a linear trend regression analysis, controlled for baseline scores, gender and age, patients in group 2 show significantly higher one-year improvement in the QoL of their psychological state of mind than patients in group 1 (beta 0.158 $p = 0.002$).

Also the HADS depression and anxiety scores are affected by treatment modalities. Patients in group 1 show one-year QoL improvement, specifically in the CIVIQ psychological scale, which in turn will have eventually lowering effects on their feelings of depression and anxiety in the HADS score.

In conclusion the HADS anxiety and depression scores are indirectly but significantly determined by the Psychological Scale scores of the CIVIQ questionnaire. A higher (better) CIVIQ score leads to lower (better) HADS scores. The CIVIQ scales are

Table 3. CIVIQ domains vs binary treatment group

Disease specific Quality-of-Life (CIVIQ) social domain cross-tabulated with binary treatment group for T0-12 LOCF.

Treatment groups		CIVIQ-social scale-T0	CIVIQ-social scale-T6	CIVIQ/LOCF-social scale-T12
CI-C3 & SCT	Mean	80,32	82,90	80,23
	Std. Deviation	20,90	18,82	20,46
	Minimum	8,33	33,33	16,67
	Maximum	10,000	10,000	10,000
	N	83	58	59
Other-treatment	Mean	73,46	81,26	80,56
	Std. Deviation	23,40	21,95	22,51
	Minimum	0,00	0,00	0,00
	Maximum	10,000	100,00	100,00
	N	319	215	221
Total	Mean	74,87	81,61	80,49
	Std. Deviation	23,05	21,30	22,06
	Minimum	0,00	0,00	0,00
	Maximum	10,000	100,00	100,00
	N	402	273	280

Disease specific Quality-of-Life (CIVIQ) psychological problems domain cross-tabulated with binary treatment group for T0-12 LOCF

Treatment groups		CIVIQ- psychological scale-T0	CIVIQ- psychological scale-T6	CIVIQ/LOCF- psychological scale-T12
CI-C3 & SCT	Mean	78,93	81,37	80,79
	Std. Deviation	17,42	15,36	15,62
	Minimum	14,71	45,45	36,11
	Maximum	10,000	100,00	100,00
	N	83	58	59
Other-treatment	Mean	78,20	84,30	86,77
	Std. Deviation	18,20	17,66	14,50
	Minimum	0,00	0,00	0,00
	Maximum	10,000	100,00	100,00
	N	328	222	224
Total	Mean	78,34	83,69	85,52
	Std. Deviation	18,02	17,23	14,91
	Minimum	0,00	0,00	0,00
	Maximum	10,000	100,00	100,00
	N	411	280	283

Disease specific Quality-of-Life (CIVIQ) physical functioning domain cross-tabulated with binary treatment group for T0-12 LOCF

Treatment groups		CIVIQ- physical scale-T0	CIVIQ- physical scale-T6	CIVIQ/LOCF- physical scale-T12
CI-C3 & SCT	Mean	76,96	83,44	81,14
	Std. Deviation	23,19	17,94	18,45
	Minimum	0,00	41,67	43,75
	Maximum	10,000	100,00	100,00
	N	83	58	59
Other-treatment	Mean	69,13	80,97	81,36
	Std. Deviation	25,03	21,31	20,76
	Minimum	0,00	0,00	0,00
	Maximum	10,000	100,00	100,00

(continued)

Table 3. Continued.

Total	N	325	220	222
	Mean	70,72	81,48	81,32
	Std. Deviation	24,84	20,65	20,27
	Minimum	0,00	0,00	0,00
	Maximum	10,000	100,00	100,00
	N	408	278	281

Disease specific Quality-of-Life (CIVIQ) pain domain cross-tabulated with binary treatment group for T0-12 LOCF

Treatment groups		CIVIQ-pain scale-T0	CIVIQ-pain scale-T6	CIVIQ/LOCF-pain scale-T12
CI-C3 & SCT	Mean	69,88	73,56	74,99
	Std. Deviation	21,92	22,59	21,75
	Minimum	6,67	15,38	18,75
	Maximum	10,000	100,00	100,00
	N	83	58	59
Other-treatment	Mean	61,99	72,46	76,37
	Std. Deviation	21,82	23,34	20,81
	Minimum	0,00	0,00	6,25
	Maximum	10,000	100,00	100,00
	N	329	224	224
Total	Mean	63,58	72,69	76,08
	Std. Deviation	22,04	23,15	20,98
	Minimum	0,00	0,00	6,25
	Maximum	10,000	100,00	100,00
	N	412	282	283

Hospital anxiety depression scale (HADS), depression and anxiety scores cross-tabulated with binary treatment group for T0-12 LOCF

Treatment groups		HADS- depression score-T0	HADS- depression score-T6	LOCF/HADS- depression score-T12	HADS- anxiety score-T0	HADS- anxiety score-T6	LOCF/HADS- anxiety score- T12
CI-C3 & SCT	Mean	2,52	2,52	2,48	2,11	2,10	2,08
	Std. Deviation	0,54	0,48	0,52	0,54	0,53	0,57
	Minimum	0,86	1,14	0,71	0,43	0,29	0,29
	Maximum	3,00	3,00	3,00	3,00	3,00	3,00
	N	83	57	59	83	58	59
Other-treatment	Mean	2,54	2,60	2,63	2,21	2,27	2,30
	Std. Deviation	0,51	0,47	0,45	0,49	0,46	0,45
	Minimum	0,67	0,43	0,43	0,57	0,71	0,86
	Maximum	3,00	3,00	3,00	3,00	3,00	3,00
	N	329	222	224	330	225	225
Total	Mean	2,54	2,59	2,60	2,19	2,24	2,26
	Std. Deviation	0,51	0,47	0,47	0,50	0,48	0,48
	Minimum	0,67	0,43	0,43	0,43	0,29	0,29
	Maximum	3,00	3,00	3,00	3,00	3,00	3,00
	N	412	279	283	413	283	284

determined by the treatment group, group 2 shows significant improvement compared to group 1.

Discussion

CEAP is based on clinical opinion of physician, scoring the observed clinical symptoms of venous

disease.⁷ The disease specific QoL assesses the perceived effects of the varicose veins, which are determined by more than just the clinical symptoms (redness, varicose veins, skin changes).⁸ The HADS questionnaire (consists of a seven-item depression scale and a seven-item anxiety scale) detecting depression and anxiety in patients with physical problems,

without considering the somatic symptoms and physical condition of the patient.

The appearance of different clinical symptoms of SVD may cause emotional disappointment and related psychological distress.⁴ There are no validated score systems, measuring PD in SVD. We assumed, that using of the validated HADS questionnaire in combination with the CIVIQ gives an insight in the complexity of psychological distress of patients having SVD. The HADS has been validated and tested with a variety of different somatic pathologies.^{9,10}

Our findings show that patients in group 2 (>C3) have significant, although indirect, higher (worse) HADS scores, in other words, patients in a higher C class suffer from more depression and anxiety.

As shown by these results the burden perceived by the patient is caused by more than just the clinical symptoms - QoL and psychological effects play a large role.

The significant improvement in both psychological (as measured with the HADS) and QoL (as measured with the CIVIQ-20) that we observe after successful invasive treatment could indicate that reimbursement of an invasive treatment is justified. The fact that only SCT for C1-C3 does not improve the psychological, QoL and clinical scores indicates that reimbursement might be questionable (in the line with the reimbursement policy of the Dutch Health Insurances) and could rightfully be classified as a cosmetic treatment.

Perhaps the choice for a specific treatment should not be made based only on a clinical observation, but also be based on the QoL and psychological burden of the disease. For example: a C3 patient with hardly any psychological and QoL impairment will probably only need SCT treatment but a C3 patient with an impaired QoL and psychological burden might benefit of an invasive treatment.

Current guidelines focus mainly on physical observations (C class, duplex ultrasound) and largely disregard QoL and psychosocial impairment.¹¹ This means that potentially a large number of patients is left untreated because their physical and “visible” disease is considered minor, while their QoL and psychological impairment might be very relevant and significant. A more QoL and psychological centered approach could improve this and would make patient treatment selection more efficient.

Conclusion

Significant psychological, QoL and clinical scores are observed after invasive treatment. SCT alone for C1-C3 does not improve the psychological, QoL and clinical scores. This makes reimbursement questionable for this group and the medical purpose of SCT as a single treatment.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

This study was approved by the local institutional review board, following the principles outlines in the Declaration to Helsinki. This trial was registered in the ISRCTN registry with study ID ISRCTN12085308

Guarantor

CHA Wittens.

Contributorship

Conception and design AG, FS, CHA. Analysis and interpretation AG, FS, CHA. Protocol development, gaining ethical approval IAJ, CHA, AG, FS. All authors collected data, reviewed and edited the manuscript and approved the final version of the manuscript.

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Appendix

Table A1. Disease specific Quality-of-Life (CIVIQ) pain domain cross-tabulated with CEAP C class for T0-I2 and T12-LOCF.

		CIVIQ-pain scale-T0	CIVIQ-pain scale-T6	CIVIQ-pain scale-T12	LOCF/CIVIQ-pain scale-T12
C1	Mean	73,10	80,38	80,83	81,78
	Std. Deviation	18,56	19,25	21,32	20,92
	Minimum	33,33	38,46	31,25	31,25
	Maximum	100,00	100,00	100,00	100,00
	N	29	20	15	20
C2	Mean	66,20	71,06	74,00	72,39
	Std. Deviation	22,46	24,60	23,85	24,93
	Minimum	6,67	23,08	18,75	18,75
	Maximum	100,00	100,00	100,00	100,00
	N	43	28	25	28
C3	Mean	63,63	72,94	77,01	76,28
	Std. Deviation	21,47	22,79	19,46	20,45
	Minimum	0,00	7,69	12,50	12,50
	Maximum	100,00	100,00	100,00	100,00
	N	292	203	144	204
C4	Mean	58,64	69,66	77,08	74,69
	Std. Deviation	22,78	25,28	20,51	21,00
	Minimum	0,00	0,00	6,25	6,25
	Maximum	100,00	100,00	100,00	100,00
	N	54	36	27	36
C5&C6	Mean	46,14	57,69	68,75	68,75
	Std. Deviation	24,74	5,44	0,00	0,00
	Minimum	6,67	53,85	68,75	68,75
	Maximum	91,11	61,54	68,75	68,75
	N	17	2	2	2
Total	Mean	63,21	72,76	76,86	76,04
	Std. Deviation	22,08	23,03	20,10	20,93
	Minimum	0,00	0,00	6,25	6,25
	Maximum	100,00	100,00	100,00	100,00
	N	435	289	213	290

Table A2. Disease specific Quality-of-Life (CIVIQ) psychological problems domain cross-tabulated with CEAP C class for T0-I2 and T12-LOCF.

		CIVIQ-psychological scale-T0	CIVIQ-psychological scale-T6	CIVIQ-psychological scale-T12	LOCF/CIVIQ-psychological scale-T12
C1	Mean	80,53	85,25	82,78	83,52
	Std. Deviation	17,43	13,21	15,54	14,06
	Minimum	29,41	54,55	47,22	47,22

(continued)

Table A2. Continued.

		CIVIQ-psychological scale-T0	CIVIQ-psychological scale-T6	CIVIQ-psychological scale-T12	LOCF/CIVIQ-psychological scale-T12
C2	Maximum	100,00	100,00	100,00	100,00
	N	29	20	15	20
	Mean	79,89	80,95	82,44	81,94
	Std. Deviation	16,67	19,22	18,39	18,46
	Minimum	20,59	18,18	36,11	36,11
C3	Maximum	100,00	100,00	100,00	100,00
	N	43	28	25	28
	Mean	78,79	84,52	86,62	86,34
	Std. Deviation	18,062	16,85	13,58	14,49
	Minimum	0,00	0,00	36,11	0,00
C4	Maximum	100,00	100,00	100,00	100,00
	N	292	201	144	204
	Mean	73,44	79,66	85,56	84,37
	Std. Deviation	19,00	18,94	13,29	14,53
	Minimum	26,47	12,12	50,00	50,00
C5&C6	Maximum	100,00	100,00	100,00	100,00
	N	53	36	27	36
	Mean	74,23	83,33	81,94	81,94
	Std. Deviation	13,19	6,43	9,82	9,82
	Minimum	41,18	78,79	75,00	75,00
Total	Maximum	91,18	87,88	88,89	88,89
	N	16	2	2	2
	Mean	78,19	83,61	85,68	85,45
	Std. Deviation	17,89	17,10	14,26	14,85
	Minimum	0,00	0,00	36,11	0,00
	Maximum	100,00	100,00	100,00	100,00
	N	433	287	213	290

Table A3. Hospital anxiety depression scale (HADS) anxiety score cross-tabulated with CEAP C class for T0-T12 and T12-LOCF.

		HADS-anxiety score-T0	HADS-anxiety score-T6	HADS-anxiety score-T12	LOCF/HADS-anxiety score-T12
C1	Mean	2,17	2,12	2,13	2,16
	Std. Deviation	0,51	0,40	0,61	0,53
	Minimum	0,71	1,14	0,86	0,86
	Maximum	3,00	3,00	3,00	3,00
	N	29	20	15	20
C2	Mean	2,15	2,11	2,08	2,10
	Std. Deviation	0,52	0,54	0,51	0,50
	Minimum	0,57	0,86	0,86	0,86
	Maximum	3,00	2,86	2,86	2,86
	N	43	28	25	28
C3	Mean	2,20	2,26	2,30	2,28
	Std. Deviation	0,51	0,49	0,48	0,48
	Minimum	0,43	0,29	0,86	0,29
	Maximum	3,00	3,00	3,00	3,00
	N	293	204	146	205
C4	Mean	2,14	2,30	2,30	2,30
	Std. Deviation	0,48	0,39	0,40	0,41
	Minimum	0,57	1,43	1,14	1,14
	Maximum	3,00	3,00	2,86	3,00
	N	54	36	27	36

(continued)

Table A3. Continued.

		HADS-anxiety score-T0	HADS-anxiety score-T6	HADS-anxiety score-T12	LOCF/HADS-anxiety score-T12
C5&C6	Mean	2,33	2,36	2,43	2,43
	Std. Deviation	0,27	0,10	0,20	0,20
	Minimum	1,86	2,29	2,29	2,29
	Maximum	2,86	2,43	2,57	2,57
	N	17	2	2	2
Total	Mean	2,19	2,24	2,27	2,26
	Std. Deviation	0,50	0,48	0,49	0,48
	Minimum	0,43	0,29	0,86	0,29
	Maximum	3,00	3,00	3,00	3,00
	N	436	290	215	291

Table A4. Hospital anxiety depression scale (HADS) depression score cross-tabulated with CEAP C class for T0-T12 and T12-LOCF.

		HADS-depression score-T0	HADS-depression score-T6	HADS-depression score-T12	LOCF/HADS-depression score-T12
C1	Mean	2,52	2,57	2,40	2,46
	Std. Deviation	0,53	0,39	0,67	0,61
	Minimum	1,00	1,57	0,71	0,71
	Maximum	3,00	3,00	3,00	3,00
	N	29	19	15	20
C2	Mean	2,60	2,56	2,62	2,60
	Std. Deviation	0,48	0,55	0,45	0,46
	Minimum	1,00	1,14	1,71	1,71
	Maximum	3,00	3,00	3,00	3,00
	N	43	28	25	28
C3	Mean	2,56	2,62	2,62	2,63
	Std. Deviation	0,51	0,47	0,48	0,45
	Minimum	0,67	0,43	0,43	0,43
	Maximum	3,00	3,00	3,00	3,00
	N	292	202	146	204
C4	Mean	2,39	2,50	2,51	2,54
	Std. Deviation	0,54	0,43	0,44	0,43
	Minimum	0,71	1,57	1,43	1,43
	Maximum	3,00	3,00	3,00	3,00
	N	54	35	27	36
C5&C6	Mean	2,64	2,64	2,29	2,29
	Std. Deviation	0,30	0,10	0,00	0,00
	Minimum	2,00	2,57	2,29	2,29
	Maximum	3,00	2,71	2,29	2,29
	N	17	2	2	2
Total	Mean	2,54	2,59	2,59	2,60
	Std. Deviation	0,50	0,47	0,49	0,46
	Minimum	0,67	0,43	0,43	0,43
	Maximum	3,00	3,00	3,00	3,00
	N	435	286	215	290

Table A5. Disease specific Quality-of-Life (CIVIQ) pain domain cross-tabulated with treatment type for T0-T12 and T12-LOCF.

		CIVIQ-pain scale-T0	CIVIQ-pain scale-T6	CIVIQ-pain scale-T12	LOCF/CIVIQ-pain scale-T12
VNUS	Mean	62,62	72,60	78,07	77,28
	Std. Deviation	21,07	23,94	19,26	20,24
	Minimum	0,00	0,00	6,25	6,25
	Maximum	100,00	100,00	100,00	100,00

(continued)

Table A5. Continued.

		CIVIQ-pain scale-T0	CIVIQ-pain scale-T6	CIVIQ-pain scale-T12	LOCF/CIVIQ-pain scale-T12
Laser	N	152	114	82	114
	Mean	64,07	80,34	81,53	83,26
	Std. Deviation	21,63	20,14	18,95	17,03
	Minimum	6,67	30,77	31,25	31,25
	Maximum	100,00	100,00	100,00	100,00
SCT	N	72	33	22	33
	Mean	69,92	73,10	74,39	74,51
	Std. Deviation	21,79	22,67	21,48	21,88
	Minimum	6,67	15,38	18,75	18,75
	Maximum	100,00	100,00	100,00	100,00
Muller	N	84	59	51	60
	Mean	60,51	69,46	74,78	72,26
	Std. Deviation	22,91	23,14	20,59	22,29
	Minimum	6,67	15,38	18,75	18,75
	Maximum	100,00	100,00	100,00	100,00
Total	N	110	80	57	80
	Mean	63,78	72,72	76,66	75,99
	Std. Deviation	21,98	23,14	20,13	21,01
	Minimum	0,00	0,00	6,25	6,25
	Maximum	100,00	100,00	100,00	100,00
	N	418	286	212	287

Table A6. Disease specific Quality-of-Life (CIVIQ) psychological problems domain cross-tabulated with treatment type for T0-T12 and T12-LOCF.

		CIVIQ-psychological scale-T0	CIVIQ-psychological scale-T6	CIVIQ-psychological scale-T12	LOCF/CIVIQ-psychological scale-T12
VNUS	Mean	78,00	83,16	86,42	86,37
	Std. Deviation	18,02	17,07	13,97	13,07
	Minimum	17,65	12,12	40,63	40,63
	Maximum	100,00	100,00	100,00	100,00
	N	153	114	82	114
Laser	Mean	81,94	92,36	90,48	92,06
	Std. Deviation	15,53	9,14	11,18	10,08
	Minimum	20,59	66,67	63,89	63,89
	Maximum	100,00	100,00	100,00	100,00
	N	72	34	22	34
SCT	Mean	78,58	81,02	81,43	80,45
	Std. Deviation	17,60	15,46	15,57	15,71
	Minimum	14,71	45,45	36,11	36,11
	Maximum	100,00	100,00	100,00	100,00
	N	84	59	51	60
Muller	Mean	76,28	82,77	86,43	85,11
	Std. Deviation	19,68	20,24	14,25	17,45
	Minimum	0,00	0,00	36,11	0,00
	Maximum	100,00	100,00	100,00	100,00
	N	108	77	57	79
Total	Mean	78,35	83,71	85,64	85,46
	Std. Deviation	18,02	17,20	14,35	14,96
	Minimum	0,00	0,00	36,11	0,00
	Maximum	100,00	100,00	100,00	100,00
	N	417	284	212	287

Table A7. Hospital anxiety depression scale (HADS) anxiety score cross-tabulated with treatment type for T0-T2 and T12-LOCF.

		HADS-anxiety score-T0	HADS-anxiety score-T6	HADS-anxiety score-T12	LOCF/HADS-anxiety score-T12
VNUS	Mean	2,19	2,23	2,27	2,24
	Std. Deviation	0,48	0,45	0,51	0,48
	Minimum	0,57	0,71	0,86	0,86
	Maximum	3,00	3,00	3,00	3,00
	N	153	114	84	114
Laser	Mean	2,27	2,35	2,43	2,42
	Std. Deviation	0,38	0,41	0,34	0,37
	Minimum	1,00	1,57	1,71	1,57
	Maximum	3,00	3,00	3,00	3,00
	N	72	34	22	34
SCT	Mean	2,11	2,11	2,11	2,09
	Std. Deviation	0,54	0,53	0,55	0,57
	Minimum	0,43	0,29	0,86	0,29
	Maximum	3,00	3,00	3,00	3,00
	N	84	59	51	60
Muller	Mean	2,22	2,30	2,34	2,34
	Std. Deviation	0,56	0,49	0,41	0,43
	Minimum	0,57	1,00	1,29	1,00
	Maximum	3,00	3,00	3,00	3,00
	N	110	80	57	80
Total	Mean	2,19	2,24	2,27	2,26
	Std. Deviation	0,50	0,48	0,49	0,48
	Minimum	0,43	0,29	0,86	0,29
	Maximum	3,00	3,00	3,00	3,00
	N	419	287	214	288

Table A8. Hospital anxiety depression scale (HADS) depression score cross-tabulated with treatment type for T0-T2 and T12-LOCF.

		HADS-depression score-T0	HADS-depression score-T6	HADS-depression score-T12	LOCF/HADS-depression score-T12
VNUS	Mean	2,53	2,57	2,58	2,59
	Std. Deviation	0,48	0,47	0,48	0,45
	Minimum	0,71	0,71	0,86	0,86
	Maximum	3,00	3,00	3,00	3,00
	N	153	113	84	114
Laser	Mean	2,64	2,79	2,71	2,75
	Std. Deviation	0,41	0,30	0,37	0,32
	Minimum	1,29	1,71	1,57	1,57
	Maximum	3,00	3,00	3,00	3,00
	N	72	34	22	34
SCT	Mean	2,52	2,53	2,49	2,48
	Std. Deviation	0,57	0,48	0,51	0,52
	Minimum	0,86	1,14	0,71	0,71
	Maximum	3,00	3,00	3,00	3,00
	N	84	58	51	60
Muller	Mean	2,50	2,59	2,64	2,64
	Std. Deviation	0,58	0,50	0,51	0,48
	Minimum	0,67	0,43	0,43	0,43
	Maximum	3,00	3,00	3,00	3,00
	N	109	78	57	79
Total	Mean	2,54	2,59	2,59	2,60
	Std. Deviation	0,51	0,47	0,49	0,47
	Minimum	0,67	0,43	0,43	0,43
	Maximum	3,00	3,00	3,00	3,00
	N	418	283	214	287