

The role of cryosurgery in the treatment of varicosity

PhD Thesis

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Abbreviations

| | |
|-------|--|
| AASV | anterior accessory saphenous vein |
| ANOVA | analysis of variances |
| BMI | body mass index |
| CEAP | clinical etiologic anatomic pathologic |
| CFV | common femoral vein |
| CVI | chronic venous insufficiency |
| DUS | duplex ultrasound |
| DVT | deep vein thrombosis |
| EHIT | endovenous heat induced thrombosis |
| EVTA | endovenous thermal ablation |
| EVLA | endovenous laser ablation |
| GSV | great saphenous vein |
| LMWH | low molecular weight heparin |
| MOCA | mechanochemical ablation |
| PE | pulmonary embolism |
| RFA | radiofrequency ablation |
| SFJ | saphenofemoral junction |
| ST | superficial thrombophlebitis |
| SPJ | saphenopopliteal junction |
| SSV | short saphenous vein |
| SVT | superficial vein thrombosis |
| TE | tromboembolism |
| UGFS | ultrasound guided foam-sclerotherapy |
| VAS | visual analog scale |
| VCSS | venous clinical severity score |

Introduction

Symptomatic CVI and the different manifestations of varicosity are presented among the 2 to 40% of the adult population. According to the results of the Bonn Vein Study, the symptoms of CVI occur twice more among women and the extremes of body weight are risk factors for the disease. The Edinburgh Vein Study investigated the incidence and distribution of vein reflux. According to their results, the authors conclusion was that the presence of reflux was in an unambiguous relation with varicosity. In the Vein Consult Program, the prevalence of CVI was 64% in the studied wide population, the less serious manifestations were more frequent among woman but the ratio was balanced between the genders by the aggravation of clinical signs.

In the treatment of CVI, cosmetic considerations have gained more role in the last years. Similarly to other diseases, varicosity would be treated efficiently, if the reasons were abolished. Endovenous ablation methods have spread for treating truncal vein incompetences in the last decade. Recent international guidelines suggest EVTA as primary choosen procedure. The widely known among them are RFA and EVLA.

Cryosurgery is capable to treat the incompetence of the GSV. Cryosclerosis is a type of EVTA, cryostripping is an alternate to classical stripping.

Objectives

The aim of this thesis was to determine the place of cryosurgery dated back to centuries according to our knowledge in phlebology.

The frame of this thesis is as follows:

1. In the first chapter, a systematic review of the available literature is presented, then the raw pile of information is analysed by meta-analytic methods to determine the role of cryosurgery in the treatment of GSV incompetence according to the present scientific knowledge.
2. A retrospectiv analysis of the experiences with cryostripping routinely applied for some cases of superficial thrombophlebitis at the Department of Surgery in the Kanizsai Dorottya Hospital is presented in the next chapter of this work.
3. The analysis of cryosclerosis which is a forgotten endovenous GSV ablation method is demonstrated by the short and medium term results of a prospectiv non-randomized study.

The role of cryosurgery in the treatment of the incompetent GSV

Introduction

In the treatment of incompetence of the GSV, two cryosurgical methods were described in the fourth quarter of the last decade. Cryosclerosis was introduced by Milleret and LePivert in the 1980s. Cryostripping, an alternate to classical stripping, was described later, dated to the early 1990s.

Patients and methods

A systematic review was planned to evaluate *primary* the short- and long-term efficacy (the rate of residual incompetent GSV) of the known cryosurgical methods applied in the treatment of the incompetence of the GSV. *Secondary* aims of this study were to analyze the available data about the frequent postoperative complications related to GSV stripping (saphenous nerve injury, bruising) and quality of life (QOL) measurements.

Literature search. The PubMed database was searched with the keywords 'cryosclerosis', 'cryoablation', 'great saphenous vein', 'cryostripping', 'cryo-stripping', 'cryosurgery varicose veins' and 'cryosurgery great saphenous vein' by all of the authors in September 2014.

Data extraction. The number of patients, the rate of residual incompetent GSV at follow-up (at least at 6 months), the data of frequent postoperative complications (bruising and neural damage), the records of the QOL measurements were collected for meta-analysis.

Meta-analysis. The MetaXL software (version 2.2, additional software for Microsoft Excel, Epigear International) was applied. The IVhet-model was chosen for meta-analysis which is an inverse variance method developed by Doi et al. The significance threshold was set at $p < 0.05$.

Results

Literature search on cryostripping. PubMed search identified 42 unique publications, 5 of them (3 trials) satisfied the inclusion and exclusion criterias. These papers included information about cryostripping compared to classical stripping (2 articles / 2 trials) and cryostripping compared to EVLA (3 article / 1 trial) with total of 659 operated limbs. Meta-analysis could be performed only on the short-term clinical effectiveness and postoperative neural damage. The records of bruising and the data of QOL measurements were not uniform and comparable, the necessary statistical elements were not available, so meta-analysis could not be performed. Only one publication included data about the long term comparison of cryostripping and EVLA.

Meta-analysis on cryostripping. Regarding the short term clinical effectiveness there was no significant difference between cryostripping and stripping (*Figure 1*). Saphenous nerve injury was present with similar incidence rates in each group (*Figure 2*).

Figure 1. Forest plot on clinical effectiveness.

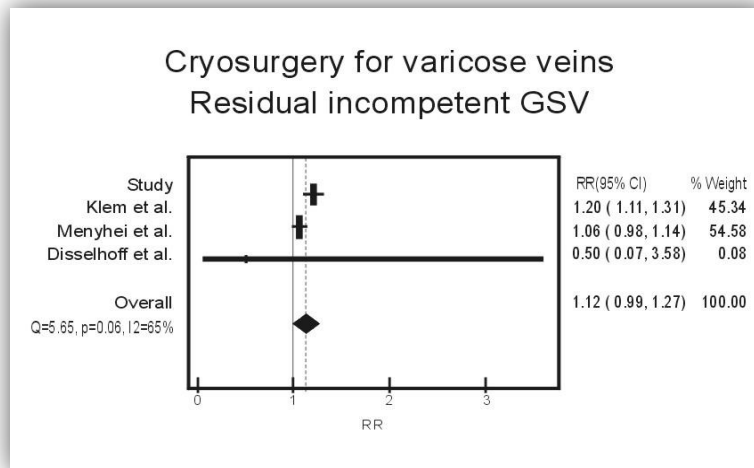
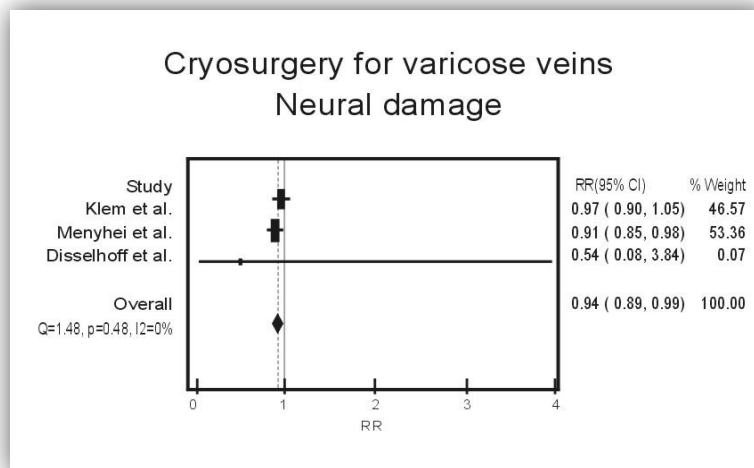


Figure 2. Forest plot on sensory abnormalities.



Literature search on cryosclerosis. Only 2 comparative consecutive trials were available in the PubMed database. One of them was a long conducted study on 800 patients, but there were no exact information in the article whether randomization or statistical analysis were performed or not, there were too few details about the characteristics of patients and the investigated methods to carry out a meta-analysis. The other publication is about our study of cryosclerosis that contains only short term results. The publications were not suitable to perform a meta-analysis.

Conclusions

The meta-analysis suggests that cryostripping is a feasible method in experienced hands similarly to classical stripping besides its known better cosmetic results and saphenous nerve injury is not related more frequently to the studied procedure. Lack of long conducted comparative trials the long term clinical effect of the method is undescribed.

Cryosclerosis is a possible alternative to the known and widely spread endovenous ablation techniques, but its real place has remained undetermined in phlebology due to the lack of strong evidences, especially on long term outcome, to date.

The relevancy of cryostripping in the treatment of superficial thrombophlebitis

Introduction

ST and SVT are synonyms. The disease was underestimated until recently. SVT is a common complication of varicosity and varies in appearance. TE could be associated to ST frequently, ipsi- or contralateral DVT with a high rate but PE with a low risk.

The treatment of SVT is routinely non-surgical. LMWH treatment should be administered in prophylactic doses regarding the recent evidences in every types of SVT to decrease the risk of thromboembolic complications at least 4-6 weeks long.

Patients and methods

A retrospective analysis of our cases was carried out from the available records between the October 2001 and the October 2014. Patients treated due to SVT were searched. The records of patients characteristics (age, gender, limb ratio, etiology, history, the records of DUS, DVT/PE in history), thromboembolic events related to SVT, the presence of residual varices and the recovery period (days to regain full physical activity or to disappear the inflammatory signs) were recorded by collecting the data from the available medical files.

Methodology. The non-surgical approach (*Conservative Treatment Group* - patients who were not selected for surgery because of less serious disease, symptoms occurred mid-thigh and/or below the knee, denial of surgery) consisted of wearing compression stockings, early mobilisation, venoactive drugs, NSAID, ointment containing heparin or derivatives. LMWH was not administered routinely because most of the patients were treated before the CALISTO-study and the guidelines based on its findings. The *Cryostripping Group* consisted of patients with ascending thrombophlebitis of the GSV. Almost each patient, except for two of them, had symptoms above the knee and the erythema near to the groin. DUS was performed just for 100 patients of the groups because it was not performed routinely to investigate ST at our institute until recently. If the ultrasound had confirmed thrombus closer than 10cm to the SFJ, surgical approach would have been also chosen even if the clinical signs did not refer to the affection of the femoral part of the GSV (the two above mentioned cases). The operation for the ascending thrombophlebitis of the GSV was nearly the same as for cases with primary varicose veins. High ligation of the GSV, proximal femoral cryostripping and local thrombectomy through microincisions were performed. We used the Erbokryo CA 300 (Erbe Elektromedizin GmbH, Germany) device for cryostripping. We used perioperative (during hospital stay) prophylactic LMWH shots (40 mg enoxaparine/Clexane

subcutaneous injection daily). The patients were advised to wear compression stockings for 8 weeks after surgery. All surgical interventions were performed under spinal anesthesia on an inpatient basis.

Statistical analysis. Chi square tests were carried out to analyse the categorical variables (sex and limb ratios, DVT/PE in history, the records of DUS) and ANOVA was performed to compare variances between age, etiology, the occurrence of TE, residual varices and time for recovery. The significance threshold was set at $p < 0,05$. The SPSS (version 20., IBM Corporation, USA) software was applied to perform statistical analyses.

Results

Patients. 246 cases were eligible for the study. 152 patients were treated conservatively. 94 patients underwent surgery because of the ascending thrombophlebitis of the GSV. 73% of the patients were women in each group. In the conservatively treated group, the inflammatory signs were present below the knee in the 67% of the cases and 93% of the patients had primary varicosity alone. 98% of the patients had inflammatory signs on the thigh in the cryostripping group. 95% of the surgically treated cases with SVT was in correlation with primary varicosity alone. Thromboembolic event in history was present in 6% of the patients in each group.

Thromboembolic events. DUS findings were available for the 34% and 51% of the cases in the conservative treatment and cryostripping groups, respectively. The ultrasound confirmed 4 ipsilateral DVTs (6% of the cases; 3 of them was reported without the involvement of the GSV, one of these patients underwent surgery due to contralateral SVT previously and had DVT in history) in the conservatively treated group. Two patients suffered from PE in this group, neither ipsi- nor contralateral DVT were identified, one of them underwent surgery due to SVT several months earlier. Two contralateral DVTs (2% of the cases; each was present with the involvement of the GSV, one patient had previous DVT) were reported in the cryostripping group. Two surgically treated patients suffered from PE, neither ipsi- nor contralateral DVT was identified, none of them had previous TE, one of them had a cancer in history. PE was assessed by chest CT performed according to the complaints, symptoms and clinical signs. During surgery, thrombus was found in the SFJ in 69% of the patients suffering from ascending GSV thrombophlebitis. 33 of them underwent DUS preoperatively, which confirmed 29 clots in the SFJ correctly (88% accuracy).

Residual varices, recovery and complications. 69% of the conservatively treated patients and 15% in the cryostripping group had residual varices at follow up (at least 4 weeks after confirmation of the diagnosis). The mean time for recovery was 26 and 15 days in the

conservative treatment and cryostripping groups, respectively. There was no major bleeding observed after surgery. Severe wound healing disorder due to lymphorrhea occurred in two cases that needed additional wound care. Erythema after groin dissection and bruising were frequent.

Statistical analysis. Regarding the sex and limb ratios, etiology and the records of DUS, the groups were similar. The distribution of age and thromboembolic events in history were present with significant differences. TE related to SVT occurred with similar incidence in the groups. Residual varices were present with a lower rate in the cryostripping group. The time for recovery was significantly shorter after the operations than in the conservatively treated group.

Conclusions

It should be stressed that there is a tight connection between ST, DVT and TE. Primary surgery for GSV thrombophlebitis does not seem to provide a lower risk for further TE. It is hard to define when to decide to perform high ligation with or without cryostripping. The challenge is to specify the risk factors that can increase the chance for TE. Performing cryostripping due to the ascending thrombophlebitis of the GSV seems to result in a favourably low recurrence rate and shorter recovery.

The role of endovenous cryoablation in the treatment of the incompetent GSV

Introduction

However varicosity is a benign disease, it can be a challenge worldwide. Its prevalence is high and it has a serious role in the evolvement of crural ulcers. If the reason of CVI had been the incompetence of the SFJ, high ligation with GSV stripping would have been the chosen method until the end of the last century. In the last decade, endovenous ablation procedures have been gaining more and more popularity in the treatment of the incompetence of the GSV.

Patients and methods

Patients. 96 cases have been involved in our study. After giving detailed information, the patient and the surgeon decided together about the chosen method. Unilateral operations were performed. Cryoclerosis was carried out on 48 limbs, the others received classical stripping. The patients underwent a follow up examination on the 1st and 7th day, then on 6th week after surgery to assess the short term results. 2 years after the procedures, the patients were remanded for follow up visits by mail or phone.

As primary end-point of the study, the occlusion of the treated GSV segments were investigated on the *short term* (at 6 weeks) and on the *mid term* (at 2 years). The newly developed SFJ incompetence, segmental or total recanalization of the treated GSV were regarded as technical or anatomical unsuccess. The DUS of the lower limbs were performed by an independent radiologist (at 6 weeks and 2 years). GE LOGIQ 5 (General Electric Company, USA) ultrasound device was applied. *Secondarily,* we investigated the characteristics of patients, duration of the operations, days of hospital stay, frequent postoperativ complications (bruising, wound healing disorder, lymphorrhea, sensory abnormalities, limb swelling after surgery), postoperativ pain (Likert-scale – VAS), interval (in days) for regaining full physical activity by questionnaires on the *short term*. Also the characteristics of patients, even the BMI, the follow up interval, the changes of clinical stage (appearance of recurrent varicosity), the CEAP classification and changes in the VCSS were analyzed on the *mid term*. Follow up visits were performed on an outpatient basis. Postoperativ complications were rated by surgical physical examination. Pain was monitored by VAS according to the integrated opinion of the patients. The time for full recovery was determined similarly. BMI was corrected for age and gender. The CEAP classification and VCSS were assessed by the physician. Every newly developed varicose vein due to

neovascuogenesis, SFJ neoreflux, incompetence of the GSV or perforating vein in the same territory were regarded as clinical success. Evening ankle swelling was not considered as recurrent clinical sign because it could be the effect of many factors (long lasting orthostatic position during work, other reasons of CVI, heart disease, renal and hepatic failure). Additionally, vein pieces were harvested in 3 cases for further scientific investigations. Twice after the operations, the vein segments were assessed by the usual photomicroscopic examination (hematoxylin-eosin stain). Once, more vein pieces were harvested, then one in native condition and three after 5, 10, 15 seconds lasting freezing were transferred to the appropriate glutaraldehyde medium, then they were sent to the Institute of Anatomy, Cell and Developmental Biology at Eötvös Loránd University for embedding and taking pictures which were evaluated at the Central Electron Microscope Laboratory at the University of Pécs. At 2 years follow up, we had to perform high ligation again and additional cryostripping due to the incompetence of the GSV in one case. During surgery, a vein piece was harvested from the crusted, segmentally strictured but recanalized GSV for photomicroscopic examination. Hematoxylin-eosin, Picrosirius red and *in situ* immunohistochemical stains (CD68, CD34, S-100) were performed by our local colleagues.

Procedures. Cryosclerosis was carried out after groin dissection and modified high ligation (the transection of the branches was avoided, only ligation was done). Through venotomy, a reusable cryoprobe was introduced into the GSV from the groin downward just below the knee, then segmental freezing sections were performed at -81 degrees of Celsius till 15 seconds. The probe was pulled back discontinuously repeating the freezing sections over 5 centimeters long segments and during melting it was drawn a little in order to rupture the endothelium. At the end of the cryoablation, the venotomy was closed and the SFJ was ligated. The Erbokryo CA (Erbe Elektromedizin GmbH, Germany) cryosurgical system (cryogenic agent: N₂O) was used for cryosclerosis. Below 8 mm of saphenous trunk diameter the flexible probe, for the other surgeries the rigid device was introduced into the vessel lumen. After groin dissection and high ligation, classical stripping with a disposable veinstripper (Vastrip Special, Astra Tech AB, Sweden) was carried out from below the knee upward to the groin in the other group. Phlebectomy of varices with Varadi-hooks and Smetana-knives were performed in both of the groups finally. All unilateral procedures were carried out under spinal anesthesia on an inpatient basis. Elastic bandage was applied on the legs at the end of the operation. One day after treatment, it was changed to class II full length graduated compression stockings. LMWH-shots (40mg enoxaparine/Clexane subcutaneous

injection daily) were administered perioperatively (one day before and after surgery). The patients were advised to load themselves increasingly.

Statistical analysis. Chi square tests were performed for the categorical variables like gender and limb ratios. One-way ANOVA was performed to compare the variances of the ordinal and continuous variables (age, duration of operation, days of hospital stay, postoperative complications, pain after surgery, recovery time, BMI, follow up, CEAP-classification, VCSS). The anatomical and clinical success rates were evaluated by Kaplan-Meier life table analysis. Recurrence rates were compared by log rank test. The significance threshold was set at $p < 0,05$. The SPSS (version 20., IBM Corporation, USA) software was applied to perform statistical analyses.

Results

Patients. DUS was planned on those lower limbs which received cryosclerosis but it was performed only in 30 cases due to poor patient compliance even at 6 weeks after surgeries. All of the questionnaires were sent back (96 cases). Interestingly, 22 limbs were lost to follow-up in each group leaving 52 cases for mid term (at 2 years) evaluation.

Short term. The patients were similar demographically except for age. There was no difference between the groups regarding the durations of operations and hospital stay. We did not experience severe bleeding or wound healing disorder, other comorbidity or death in any of the groups. TE occurred in one patient received stripping (low risk PE, the DUS did not reveal neither ipsi- nor contralateral DVT). Early recanalization was observed in two cases (6,7%) 6 weeks after surgery, the treated segment of the GSV was thrombosed in the other 28 limbs.

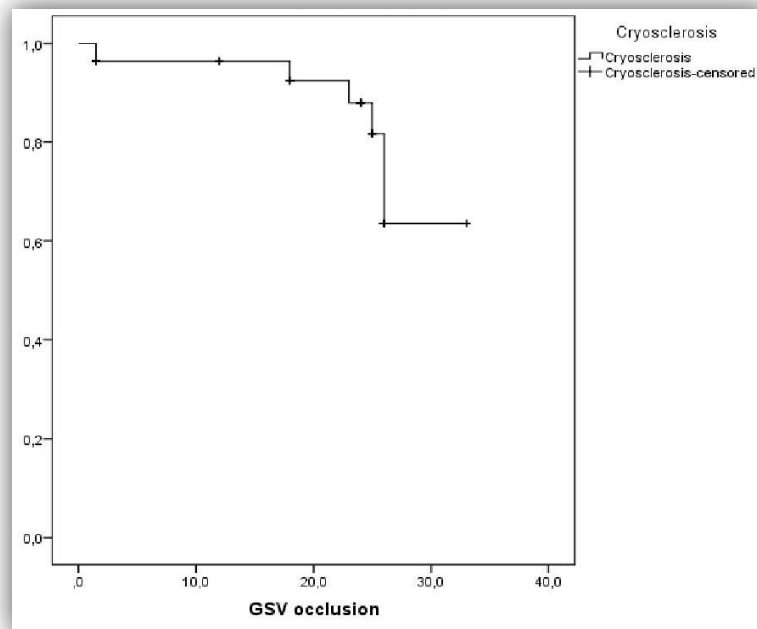
The complications (mild wound healing disorder, lymphorrhea, limb swelling) related to surgery showed same incidence. Temporary sensory abnormalities were frequent in both of the groups but permanent saphenous nerve injury occurred significantly in a higher rate between the patients received stripping. According to the analysis of the records of pain related to surgery and bruising, cryosclerosis is less invasive than conventional stripping. Recovery was significantly shorter after endovenous cryoablation.

The photomicroscopic evaluation of the vein pieces did not show any changes in the wall but the electronmicroscopic comparison of the vein pieces (the intact sample and especially the piece received 15 seconds long lasting freezing) proved supravital damages. Endothelial injuries were revealed (tapering of tissue, shrinkage, core fragmentation - necrotical appearance of the cells) and the thickening of the muscle in the subendothelial layer and tunica media were shown.

Mid term. The patients were matched demographically except for age similarly to the results on the short term. The mean follow-up was 23,5 and 23,9 months in the cryosclerosis and stripping groups, respectively.

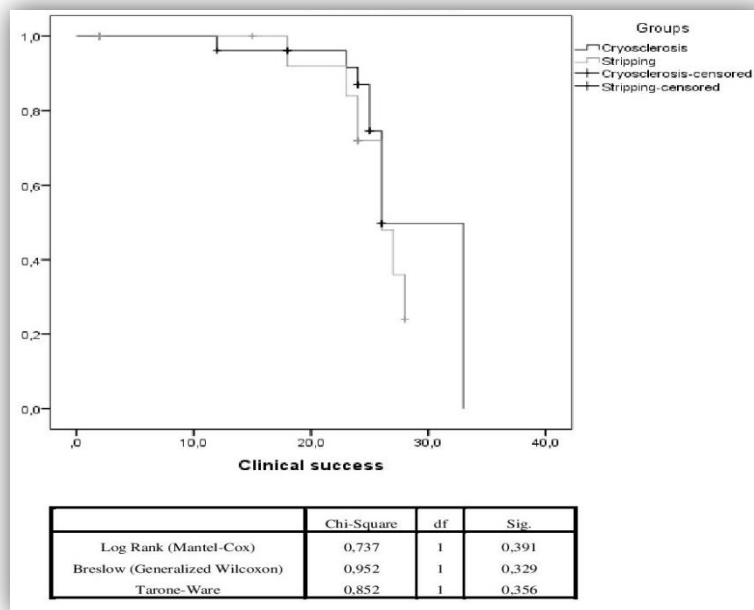
The anatomical success rate of cryosclerosis was 80,8% on the mid-term. 13 of the assessed GSV on the available limbs were present as a fibrotic cord and 8 of them were absent. One incompetent trunk causing recurrent varicosity was detected. 4 reopened GSV with slow laminar flow without any clinical relevancy were also found. A Kaplan-Meier life table analysis presents the evolvement of recanalization over time (*Figure 3.*).

Figure 3. Kaplan-Meier life table analysis showing the freedom from recanalization over time (during a 2 year period).



The clinical success rates (presence of recurrent varicose veins) were not favourable, 65,4% and 57,7%, in the cryosclerosis and stripping groups respectively. The log rank test did not show significant differences between the groups. A Kaplan-Meier life table analysis presents the development of clinical recurrence over time (*Figure 4.*).

Figure 4. Kaplan-Meier life table analysis showing the freedom from recurrence over time (during a 2 year period).



Truncal and perforating vein incompetences were frequent after endovenous cryoablation. One patient treated by cryosclerosis presented besides an occluded GSV an incompetent AASV and SSV simultaneously causing the clinical unsuccess. Neovasculogenesis and perforating vein incompetence were the reasons of recurrence in the stripping group. Due to incomplete stripping, an incompetent residual GSV was assessed in a leg treated previously by the classical method (*Table 1.*)

Table 1. The causes of recurrence.

| | Cryosclerosis n=26 of 48 | Stripping n=26 of 48 |
|---|------------------------------------|--------------------------------|
| Clinical recurrence | 9 (34,6%) | 11 (42,3%) |
| Incompetent GSV | 1 | 1 |
| Incompetent AASV | 1 | 0 |
| Incompetent SSV | 1 | 0 |
| Incompetent perforating veins | 4 | 3 |
| Neovascuogenesis | 3 | 7 |
| <p>Note: One patient evolved incompetent AASV and SSV simultaneously in the cryosclerosis group. Incompetent GSV was due to incomplete stripping.</p> | | |

There was significant improvement in the CEAP classification in each group. There was no significant difference observed regarding the CEAP classification between the groups neither at baseline nor on the mid term. VCSS reduced significantly in each group without remarkable differences between the groups.

Further surgery was performed on that leg in which incompetent GSV was found causing recurrent varicosity. High ligation was carried out again, then the crusted GSV underwent partial remodelling was removed. A vein piece was harvested for photomicroscopic pathologic evaluation. Hematoxyllin-eosin, Picrosyrius red and immunohistochemical stains (CD68, CD34, S-100) were performed. The physiological anatomical structure of the vein wall was unrecognizable. The wall was collagenized that was padded by endothelium.

Conclusions

It could be stated, that cryosclerosis seems to be efficient in the remodeling of the GSV, is less invasive than classical stripping and the mid term results are similar between the groups.

Presentation of new results

1. Saphenous nerve injury is not related more frequently to cryostripping offering better cosmetic results than to classical stripping.
2. Primary surgical intervention in the treatment of the ascending thrombophlebitis of the GSV does not decrease the risk of further TE.
3. Performing cryostripping for treating ascending thrombophlebitis of the GSV, faster recovery could be expected compared to conservative treatment.
4. Our prospectiv comparative trial proved that cryosclerosis was efficient in the treatment of the incompetent GSV both on the short and on the mid term.
5. Postoperative complications related to traditional varicose vein surgery were not associated to cryosclerosis more frequently.
6. Perfoming cryosclerosis, the CEAP classification and VCSS of the patients improve significantly that is similar to classical stripping.
7. There was no difference between cryosclerosis and classical stripping regarding the development of recurrent varicose veins in our study.
8. The photomicroscopic examination showed the partial remodeling of the GSV segment harvested from a patient operated due to recurrent varicosity two years after cryosclerosis.

Scientific activity

IF of original articles: 1,915

IF of systematic review (including meta-analysis): 2,103

IF of citable abstracts: 2,612

Publications

Foreign language:

- Bálint Renáta, Farics Ákos, Parti Krisztina, Vizsy László, Bátorfi József, Menyhei Gábor, **Bálint István Bence**. *Which endovenous ablation method does offer a better long term technical success in the treatment of the incompetent great saphenous vein? Review*. VASCULAR 24:(6) pp. 649-657. (2016) **IF (2016): 0,733**
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