ORIGINAL ARTICLES

UDC: 616.14:616.5-002
DOI: https://doi.org/10.2298/VSP190821023V

Contact sensitization in patients with chronic venous insufficiency and the impact of the disease duration on the risk of occurence of contact sensitization

Kontaktna senzibilizacija kod bolesnika sa hroničnom venskom insuficijencijom i uticaj dužine trajanja bolesti na rizik od nastanka kontaktne senzibilizacije

Ljuba Vujanović*†, Marina Jovanović *†, Milan Matić*†, Sanja Jakovljević†, Zoran Golušin*†

***Clinical Center of Vojvodina, Clinic for Dermatovenereology, Novi Sad, Serbia;**
†University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

Abstract

Background/Aim. Development of allergic contact dermatitis as a complication of treatment of chronic venous insufficiency (CVI) is well known. The aim of this study was to determine the incidence and risk of eczematous contact sensitization in patients with CVI, as well as the correlation between disease duration and contact sensitization. **Methods.** The study involved 266 subjects examined during three-year-period who were divided into two groups: the study group included patients with CVI referred for allergy testing due to suspected contact dermatitis, and the control group included the ones without CVI patch tested for suspected contact dermatitis. The severity of CVI was assessed by Clinical Etiology-Anatomy-Pathophysiology (CEAP) classification. Thereafter, each patient underwent patch testing. **Results.** The incidence of contact sensitization among patients with CVI was 49.3%. In these patients, the incidence of contact sensitization to the European standard battery of allergens was 31.55%; to the battery specific for CVI it was 28.45%. Patients with CVI had a 2.45-fold higher risk for developing contact sensitization to two or more allergens, and a 3.69-fold higher risk for developing contact sensitization to five or more allergens compared to those without CVI. The prevalence of contact sensitization in patients with CVI was not significantly different from those without CVI. There was a positive correlation between the incidence of contact sensitization and the duration of the disease. **Conclusion.** Patients with CVI had no statistically significantly distinct contact sensitization prevalence and had 2.45 and 3.69 times higher risk to manifest contact sensitization to two and more allergens and five and more allergens, respectively, than patients with no CVI. The positive correlation between frequency of contact sensitization and disease duration was found.

Key words:
dermatitis, contact; incidence; risk assessment; venous insufficiency.

Apstrakt

Uvod/Cilj. Poznato je da se tokom lečenja hronične venske insuficijencije (HVI) može razviti, kao komplikacija, alergijski kontaktni dermatitis. Cilj rada je bio da se utvrde rizik i učestalost kontaktne senzibilizacije ekcemskog tipa kod obolelih od HVI, kao i postojanje korelacije između dužine trajanja bolesti i kontaktne senzibilizacije. **Metode.** Istraživanjem su obuhvaćena 266 ispitanika. Formirane su dve grupe: eksperimentalna grupa (bolesnici sa HVI, upućeni na alergološko testiranje pod sumnjom na postojanje kontaktnog dermatitis) i kontrolna grupa (ispitanici bez HVI, epikutano testirani pod sumnjom na postojanje kontaktnog dermatitisa). Težina HVI procenjivana je na osnovu *Clinical Etiology-Anatomy-Pathophysiology* (CEAP) klacifikacije. Svaki ispitanik je bio podvrgnut alergološkom epikutanom testiranju *patch* testom. **Rezultati.** Učestalost kontaktne senzibilizacije među obolelima od HVI iznosila je 49,3%. Učestalost kontaktne senzibilizacije kod osoba sa HVI na alergene iz sastava Evropske standardne baterije iznosila je 31,55%, a na alergene iz baterije specifične za HVI 28,45%. Prevalencija kontaktne senzibilizacije kod osoba sa HVI nije se statistički značajno razlikovala od prevalencije kod osoba bez HVI. Bolesnici sa HVI su imali 2,45 puta viši rizik od nastanka kontaktne senzibilizacije na dva i više alergena, a 3,69 puta viši rizik od nastanka kontaktne senzibilizacije na pet i više alergena u odnosu na bolesnike bez HVI. Učestalost

Correspondence to: Ljuba Vujanović, Clinical Center of Vojvodina, Clinic for Dermatovenereology, Almaška 18, 21 000 Novi Sad, Serbia. E-mail: ljuba.vujanovic@mf.uns.ac.rs

kontaktne senzibilizacije je bila u pozitivnoj korelaciji sa dužinom trajanja bolesti. **Zaključak.** Bolesnici sa HVI nisu imali statistički značajno veću prevalenciju senzitizacije, a imali su 2,45 puta, odnosno 3,69 puta viši rizik od nastanka kontaktne senzibilizacije na dva i više alergena i na pet i više alergena, redom, u odnosu na bolesnike bez HVI. Nađena je pozitivna korelacija između učestalosti kontaktne senzibilizacije i dužine trajanja bolesti.

Ključne reči:
dermatitis, kontaktni; incidenca; rizik, procena; venska insuficijencija.

Introduction

Chronic venous insufficiency (CVI) is a consequent condition to incompetence of the lower extremity veins [1].

According to statistics of the World Health Organization (WHO), around 15% of the general population suffer from chronic venous insufficiency, with increased prevalence in older age [2, 3]. In 70–80% of cases, CVI is the crucial etiological factor in the occurrence of venous ulcerations [4].

CVI is a disease characterized by chronic recurrent course demanding long-term therapy and monitoring. Adverse reactions and complications may develop during the treatment of CVI. The most common complication due to the local therapy is contact allergic dermatitis manifested either on the site of the drug application or on the other parts of body in the form of disseminated lesions. Allergic contact dermatitis emerges during the treatment in 60% to 80% in patients with CVI, including patients with venous ulcerations [5–7].

The aim of this research was to determine the frequency of contact sensitization, prevalence of contact sensitization to studied allergens, polyvalent sensitization and possible risk for development of contact sensitization with respect to the length of duration of CVI. The study included patients with symptoms of contact dermatitis.

Methods

Patients

This study was cross-sectional and included 266 patients suspected to have contact derimatitis (CD), treated at the Clinical Centre of Vojvodina in Novi Sad (Serbia) in a three-year-period, from 2010 to 2013. The patients were divided into two groups: the experimental group which encompassed patients suffering from CVI suspected to have CD (CVI group) and the control group involving subjects suspected to have CD without presence of CVI (CD group). The CVI group counted 150 cohorts (96 women and 54 men, of average age 64.24 ± 12.01 years), while the control group involved 116 subjects (89 women and 27 men, of average age 45.55 ± 17.00 years). Patients with CVI were older than those from the control group ($p < 0.001$), with small but statistically significant difference. There was statistically significant difference in gender structure between examined groups ($p < 0.001$) due to higher percent of females in the control group than in the experimental group.

All the patients were thoroughly examined; the venous duplex ultrasound of lower extremities was performed, Ankle Brachial Pressure Index (ABPI) was done as well as the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification in patients with CVI.

Informed consent was obtained from all patients in accordance with the Institutional Review Board Policy, and the research protocol followed the ethical guidelines of the 1975 Declaration of Helsinki.

Each of the subjects fulfilled appropriate questionnaire as well as written consent for the further investigation. Questionnaires were adapted to the research and included personal data, family and professional details, anamnesis, disease course, duration of disease, potential deteriorating factors, signs and symptoms indicative to allergic contact dermatitis. Excluding criteria were: data about atopic diathesis such as presence of allergic conjunctivitis, rhinitis, asthma and atopic dermatitis; patients suffering from any systemic disease; patients on the immunosuppressive therapy in the previous six months; patients exposed to intensive sunlight during last four weeks before testing; systemic and local application of corticosteroids during last four weeks before the testing; active dermatitis at the time of testing; pregnancy and breastfeeding.

Patch test

Allergy test was conducted in all subjects with allergens from the European Standard Series of Allergens (28 allergens) (Table 1) and locally modified standard series for leg ulcer (23 allergens) (Table 2) which are of production from Chemotechnique Diagnostics® (Vellinge, Sweden). The test site was intact upper back skin. Allergens were applied on skin, while their occlusion was aided by specific chambers and hypoallergenic adhesive test tape: Curatest® from Lohmann & Rauscher, Neuwied, Germany. They were removed and read at D2, D3, D4 and D7. According to International Contact Dermatitis Research Group (ICDRG) reactions of intensity + and above were regarded as positive.

Statistical analysis

In the statistical data processing the calculation of the percentage structure, arithmetic mean, and standard deviation were used. During the further analysis, the χ^2 test was done to compare means proportion; *t*-test for independent samples to differ contact sensitization between studied groups; Population Adjusted Frequency of Sensitization (PAFS) standardization, in order to overcome differences in frequency of contact sensitization relative to gender and age of subjects; the Pearson`s r and Spearman's ρ correlation coefficient for assessment of the association between disease duration and contact sensitization (IBM SPSS Statistics 20.0).

Table 1

Standard European battery of contact allergens (Chemotechnique Diagnostics® Vellinge, Sweden, 2013)

1.	Potassium dichromate petrolatum 0.5%
2.	Neomycin Sulphate petrolatum 20.0%
3.	Thiuram Mix petrolatum 1.0%
4.	Fragrance Mix II petrolatum 14.0%
5.	Cobalt chloride petrolatum 1.0%
6.	Paraphenylenediamine free base petrolatum 1.0%
7.	Benzocaine petrolatum 5.0%
8.	Formaldehyde aqua 1.0%
9.	Colophony petrolatum 20.0%
10.	Clioquinol petrolatum 5.0%
11.	Balsam of Peru petrolatum 25.0%
12.	N-Isopropil-N-phenyl paraphenylenediamine petrolatum 0.1%
13.	Wool alcohols petrolatum 30.0%
14.	Epoxy resin petrolatum 0.1%
15.	Mercapto Mix petrolatum 1.0%
16.	Budesonid petrolatum 0.1%
17.	Paraben Mix petrolatum 16.0%
18.	Paratertiarybutyl phenol formaldehyde resin petrolatum 1.0%
19.	Fragrance Mix petrolatum 8.0%
20.	Quaternium-15 petrolatum 1.0%
21.	Nickel Sulphate, $6H_2O$ petrolatum 5.0%
22.	5-Chloro-2-methyl-4-isothiazolin-3-one + 2-Methyl-4-isothiazolin-3-one (3 : 1 in Water) aqua 0.01%
23.	Mercaptobenzothiazole petrolatum 2.0%
24.	Sesquiterpene lactone Mix petrolatum 0.1%
25.	Tixocortol pivalate petrolatum 1.0%
26.	Dibromodicyanobutane petrolatum 0.3%
27.	Hydroxy-methyl-pentylcyclohexene- carboxaldehyde (HMPCC or HICC) (Lyral®) petrolatum 5.0%
28.	Primin petrolatum 0.01%

Table 2

Specific battery of contact allergens for chronic venous insufficiency

1.	Amerchol petrolatum 50.0%
2.	Fusidic acid sodium salt petrolatum 2.0%
3.	Chlorhexidine digluconate aqua 0.5%
4.	Benzalkonium chloride petrolatum 0.1%
5.	Bacitracin petrolatum 20.0%
6.	Cetyl/stearil alcohol petrolatum 20.0%
7.	Butyl hydroxytoluene (BHT) petrolatum 2.0%
8.	Chloramphenicol petrolatum 5.0%
9.	Benzoyl peroxide petrolatum 1.0%
10.	Propyleneglycol petrolatum 5.0%
11.	Propolis petrolatum 10.0%
12.	Thiomersal petrolatum 0.1%
13.	Sorbic acid petrolatum 2.0%
14.	Chlorocresol (PCMC) petrolatum 1.0%
15.	Trolamine petrolatum 2.5%
16.	Sorbitan sesquioleate petrolatum 20.0%
17.	Tixocortol pivalate petrolatum 1.0%
18.	Phenylmercuric acetate petrolatum 0.01%
19.	Chloracetamide petrolatum 0.2%
20.	Diazolidinyl urea petrolatum 2.0%
21.	Imidazolidinyl urea petrolatum 2.0%
22.	Gentamycin sulphate petrolatum 20.0%
23.	Sulphanilamide petrolatum 5.0%

Results

Positive reactions during the patch test were revealed in 60.7% of patients with CVI and in 50% of patients belonging to the control group. There was no statistically significant difference between rates ($\chi^2 = 0.063$; df = 1; $p = 0.731$). PAFS standardization was done in order to overcome significant difference between groups with regard to gender and age of the subjects. Sensitivity rate to at least one allergen in the examined series in the experimental group was 49.3%, while it was 40.5% in the control group. The difference between the groups did not reach significant level ($z = 0.6870 < 1.96$; $p > 0.05$). The prevalence of sensitization to allergens from the European Standard Series of Allergens

was estimated and amounted 31.55% in the experimental group and 32.07% in the control group with no statistically significant difference ($z = 0.9280 < 1.96$; $p > 0.05$). The frequency of sensitization to allergens of locally modified standard series for leg ulcers was 28.45% in the experimental group, while it counted 21.62% in the control group with no statistically significant difference ($z = -0.82 < 1.96$; $p > 0.05$) as well as with regard to gender.

The most common contact sensitizers of the European Standard Series of Allergens in the CVI group and control group are presented in Table 3, while those from locally modifed standard series for leg ulcers are shown in Table 4.

The monosensitization rate to one of the examined allergens was 49.3% in the CVI group and 40.5% in the control group. Sensitivity to more than two allergens was determined in 25.3% subjects in the CVI group and in 10.3% of patients with contact dermatitis (the control group). Sensitivity to more than five allergens accounted 9.6% in the CVI group and 2.6% in the control group (Table 5).

The difference in sensitivity rates to at least one allergen was not statistically significant ($\chi^2 = 1.71$; $p > 0.05$); for two and more allergens (≥ 2) it reached statistical significance ($\chi^2 = 8.671$; $p < 0.05$), as well the difference between positive sensitivity rates to five and more allergens (≥ 5) p ($\chi^2 = 3.914$; $p < 0.05$).

Besides the *t*-test for independent samples related to distribution of reactivity in examined groups as well as single values of χ^2 test used to present statistically significant difference, the relative risk (RR) [odds ratio (OR), 95% confidence interval (CI)] for developing contact dermatitis in patients in the CVI group versus patients in the control group was determined. It was not estimated higher risk for contact sensitization to at least one allergen (RR 1.217; 95% CI 0.921-1.609; $p > 0.05$). However, subjects in the CVI group had 2.5 times higher risk for manifesting contact sensitization to at least two allergens (RR 2.456, 95% CI 1.664-3.627; $p < 0.05$); and 3.5 times higher risk for polysensitization (RR 3.692, 95% CI 1.961- 6.951; $p < 0.05$).

Average disease duration was 18.72 years, ranging from three months to 60 years. The correlation between disease duration and contact sensitization is shown in Table 6. The weak, positive correlation between CVI duration and contact sensitization was estimated ($\rho = 0.165$), but accomplished statistical significance ($p = 0.044$).

Table 3

Standardized sensitivity rates to allergens from standard battery in the experimental (CVI) group

	Allergen	USR	SRA	SRF	SRM	SR
1	Potassium dichromate	0.67	0.35	0.51	0.00	0.30
2	Neomycin sulphat	5.33	3.91	3.36	4.37	3.76
3	Thiuram mix	3.33	1.44	1.31	1.59	1.43
4	Fragrance mix II	4.00	2.38	2.00	1.87	1.95
5	Cobalt chloride	1.33	1.25	1.87	0.00	1.12
6	Paraphenylenediamine free base	1.33	0.59	0.00	1.59	0.64
7	Benzocaine	0.00	0.00	0.00	0.00	0.00
8	Formaldehyde	3.33	1.44	1.80	1.11	1.52
9	Colophony	7.33	3.64	4.70	2.56	3.84
10	Clioquinol	2.00	0.83	0.00	2.08	0.83
11	Balsam of Peru	9.33	4.29	2.45	6.90	4.23
12	N-isopropyl-N-phenyl paraphenylenediamine	1.33	5.81	5.88	0.00	3.53
13	Wool alcohols (lanolin)	11.33	11.08	13.25	3.92	9.51
14	Epoxy resin	0.67	0.35	0.00	1.11	0.44
15	Mercapto mix	0.67	0.26	0.33	0.00	0.20
16	Budesonid	6,67	3.89	3.54	5.18	4.20
17	Paraben mix	3.33	1.94	0.83	2.36	1.44
18	Paratertiarybutyl phenol formaldehyde resin	0.67	0.35	0.00	1.11	0.44
19	Fragrance mix	12.67	12.05	11.47	7.86	10.02
20	Quaternium-15	0.00	0.00	0.00	0.00	0.00
21	Nickel sulphate, $6H_2O$	6.00	4.72	6.31	0.48	3.98
22	5-chloro-2-methyl-4-isothiazolin-3-one+2-methyl-4-isothiazolin-3-one (3:1 in water)	4.67	7.93	6.71	5.42	6.20
23	Mercaptobenzothiazole	0.67	0.24	0.00	0.48	0.19
24	Sesquiterpene lactone mix	2.67	1.77	0.65	4.19	2.07
25	Tixocortol pivalate	2.00	0.95	0.83	1.11	0.94
26	Dibromodicyanobutane	4.67	7.07	6.21	3.44	5.10
27	Hydroxymethylpentylcyclohexenecarboxaldehyde (Lyral)	2.00	1.51	0.33	4.19	1.87
28	Primin	2.67	6.91	5.88	1.87	4.28

CVI – chronic venous insufficiency; USR– unstandardized rates; SR – standardized rate; SRA – SR to age; SRF – SR for females; SRM – SR for males.

Table 4

Standardized sensitivity rates to allergens from specific battery for chronic venous insufficiency (CVI) in the experimental (CVI) group

	Allergen	USR	SRA	SRF	SRM	SR
1	Amerchol®	13.33	9.34	11.37	7.11	9.66
2	Fusidic acis sodium salt	9.33	4.50	4.64	3.94	4.36
3	Chlorhexidine digluconate	1.33	5.80	5.56	048	3.53
4	Benzalkonium chloride	0.00	0.00	0.00	0.00	0.00
5	Bacitracin	4.00	7.50	8.59	1.59	5.79
6	Cetyl/stearil alcohol	5.33	2.39	1.66	3.19	2.27
7	Butyl hydroxytoluene (BHT)	3.33	2.10	0.83	4.67	2.37
8	Chloramphenicol	2.00	0.76	0.00	2.95	1.18
9	Benzoyl peroxide	2.00	6.14	6.04	1.11	4.07
10	Propyleneglycol	0.67	0.24	0.00	0.48	0.19
11	Propolis	14.00	11.89	9.17	11.80	10.22
12	Thiomersal	1.33	0.59	0.00	1.59	0.64
13	Sorbic acid	3.33	2.12	1.14	4.81	2.61
14	Chlorocresol (PCMC)	0.00	0.00	0.00	0.00	0.00
15	Trolamine	4.00	2.27	1.98	1.87	1.93
16	Sorbitan sesquioleate	7.33	6.49	7.20	4.91	6.28
17	Tixocortol pivalate	0.00	0.00	0.00	0.00	0.00
18	Phenylmercuric acetate	0.00	0.00	0.00	0.00	0.00
19	Chloracetamide	0.00	0.00	0.00	0.00	0.00
20	Diazolidinyl urea	1.33	0.50	0.33	0.48	0.39
21	Imidazolidinyl urea	2.00	0.95	0.83	1.11	0.94
22	Gentamycin sulphate	3.33	2.15	3.05	2.22	2.72
23	Sulphanilamide	1.33	0.69	0.00	2.22	9.66

USR – unstandardized rates; SR – standardized rate; SRA – SR to age; SRF – SR for females; SRM - SR for males.

Table 5

Distribution of standardized sensitization rates to one, two and more allergens among studied groups

Studied groups	One positive reaction (%)		Two and more positive reactions (%)		More than five positive reactions (%)	
	yes	no	yes	no	yes	no
CVI (n = 150)	49.30	50.70	25.30	74.70	9.60	90.40
CD (n =116)	40.50	59.50	10.30	89.70	2.60	97.40

CVI group – patients with chronic venous insufficiency (CVI) suspected to have contact dermatitis (CD); CD group – subjects without CVI suspected to have CD.

Table 6

Correlation between disease duration and contact sensitization (Spearman's coefficient of correlation - ρ)

Parameters	ρ (p-value)
Contact sensitization (n = 150)	0.165 (0.044)
Contact sensitization (normalized) (n = 150)	0.165 (0.044)

Discussion

Considering age of all subjects (from 17 years to 86 year), the average age was more than 50 years, precisely 54.89 years [standard deviation (SD) 14.53], which is in accordance with data from previous population and clinical research [8, 9]. The average age of patients suffering from chronic venous disease was 64.25 years (SD 12.06) as it has been reported in other studies (63.1 to 74.2 years) [5, 6, 10–16]. In literature data review, average age of patients with contact dermatitis is between 40.3 and 51 years as it was in our control group with age of 45.55 years in mean [16].

The prevalence of contact sensitization was assessed at 60.67% before PAFS standardization. According to the literature, frequency of contact sensitization among patients with CVI is from 46% to 80%, although most authors studied only patients suffering from venous ulcers as severe form of the disease. The lowest prevalence of contact sensitization of 46% has been reported in Canadian study among patients with venous ulcers [17] due to misreading of allergy test, while Jindal et al. [18] estimated it at 50%. Having done PAFS standardization, the prevalence of contact sensitivity in our research was 49.3% in the CVI group and 40.5% in CD group. We could not find data in available literature about standardized contact sensitization prevalence within patients suffering from CVI. German authors reported prevalence rate of 53.8% [19]. In the CVI group, most of subjects who manifested positive reaction were 70–79 years old, with

contact sensitivity rate of 50% which is in compliance with results reported in England, America, Poland and Croatia − 51%, 52%, 56% and 48%, respectively [5, 7, 11, 15].

Having analyzed unstandardized and standardized sensitization rates (regarding to gender and age) in the CVI group, differences were established. Significantly higher standardized sensitization rates were determined for N'N'' isopropyl-phenyl paraphenylenediamine (IPPD), dibromodicyanobutane, while standardized rates for fragrance mix, wool alcohols, colophony, balsam of Peru, nickel sulphate were significantly lower. Sensitization rates for cobalt chloride and hydroxy-methyl-pentylcyclohexene-carboxaldehyde (HMPCC or HICC) (Lyral®) were evidently not affected by either gender or age as they remained stable after standardization.

Following standardization, among the most common sensitizers were still Fragrance mix and wool alcohols with incidence of 10.2% and 9.51%, respectively, then, dibromodicyanobutane, methyl-chloro-isothiazolin, dibromodicyanobutane and primin.

The results could not be compared with otherstudies as there was no standardized relative incidence to gender and age in available literature data.

Apart from differences in sensitization rates (unstandardized and standardized), distinctions among some standardized sensitization rates to gender were observed. Females compared to males mostly reacted to wool alcohols (13.25% *vs* 3.92%, respectively), Fragrance mix (11.47% *vs* 7.86%, respectively), nickel sulphate (6.31% *vs* 0.48%, respectively), methyl-chloro-isothiazolin (6.71% *vs* 5.42%, respectively) and dibromodicyanobutane (6.21% *vs* 3.44%, respectively). These allergens are usual constituents in skin care products as well as in cosmetics, while nickel sulphate is found in alloys for bijouterie making, decorative hairpins, buckles, and other metal products widespread in everyday use. Because of that, it was expected that women would show a higher frequency of sensitization to previously mentioned allergens. Men in our study presented most frequent reactions to Fragrance mix (7.76%), balsam of Peru (6.90%), methyl-chloro-isothiazolin (5.42%), budesonide (5.18%), neomycin sulphate (4.37%), which are compounds in skin care products as well as in some local terapeutics. An intriguing and surprising paradox is that female subjects, although at low incidence, responded to potassium dichromate and cobalt chloride. Standardized relative incidences of those allergens were 0%. It is well known that sensitivity to metals such as potassium dichromate, nickel sulphate and cobalt chloride is increasingly common day by day [18, 20]. Hypersensitivity to potassium dichromate and cobalt chloride is usually related to professional exposure of men in engineering and construction, but there is also non-professional exposure in everyday life. The sensitization rate for those allergens in our research patently indicates sparing exposure due to disease [19]. The results were not compared to data reported in other research because of no information about standardized relative incidence to gender among patients suffering from CVI.

Analyzing unstandardized and standardized sensitization rates to allergens specific for CVI in the experimental group (CVI), standardized rates for sulfanilamide (9.66%), bacitracin (5.79%), benzoyl peroxide (4.07%), chlorhexidine digluconate (3.53%) were significantly higher, while standardized sensitization rates for propolis (10.22%), Amerchol® (9.66%), sorbitan sesquioleate (6.28%), fusidic acid (4.36%) were lower than in the control group..

Despite the increase and decrease in contact sensitization frequency caused by standardization of relative incidence, order of the most common sensitizers remained unchanged including propolis (10.22%), Amerchol® (9.66%), sorbitan sesquioleate (6.28%), bacitracin (5.79%) and fusidic acid (4.36%).

Processing standardized sensitivity rates, it was noticed that women were more likely to have an eczematous reaction than men to Amerchol® l (11.37% vs 7.11%, respectively), bacitracin (8.59% vs. 1.59%, respectively), sorbitan sesquioleate (7.20% vs. 4.91%, respectively), benzoyl peroxide (6.04% vs. 1.11%, respectively). Contrasting, men reacted to propolis in more cases (11.8% vs. 9.17%). All the mentioned allergens are contained in various pharmaceuticals for skin care or in topical medicaments used in CVI treatment as emulators and emolliens, or as an active agent (antibiotics). Contact sensitization to these allergens indicates to therapeutic habits of treating CVI in our population. The results have not been collated with as there were no comparable reports in available literature data.

According to standardization, the most common sensitizers were: wool alcohols (9.92%), paraphenylendiamine (7.34%), colophony (6.90%), nickel sulphate (5.93%) and potassium dichromate (4.23%).

Having processed data, the dissimilarity in standardized sensitization frequency among individual allergens were detected. Female subjects far more reacted to paraphenylendiamine, nickel sulphate, potassium dichromate, balsam of Peru, while male subjects showed more prevalent reaction to colophony and wool alcohols [21, 22].

Following standardization in regard to gender and age, various results about frequency of contact sensitization can be found in literature. Top ten allergens in research of Israeli, Turkey, Czech, Chinese, European and USA authors [23–26] are equal with ours. Freireich-Astman et al. [27] established that women more often reacted to nickel sulphate, paraphenylendiamine, potassium dichromate, balsam of Peru than men, which match our report except that our rates were quite lower. The separation of men in terms of frequency of contact hypersensitivity to colophony, wool alcohols and Fragrance mix taking into account occupational exposure to other allergens. In their research, Israeli authors [27] registered higher frequency of contact hypersensitivity to these allergens in men, while a statistically significant difference was evident only for wool alcohols. In contrast, Brasch et al. [26] in their study in Germany, had completely opposite results. The men in that research reacted to these three allergens more rarely than women but with no statistically significant difference.

Distinctions between unstandardized and standardized rates of sensitization were determined. The lower standardized rates were for Amerchol®, benzoyl peroxide, thiomersal, trolamine, sorbitan sesquioleate, imidazolidinyl urea, while the higher rates related to propolis, sorbic acid, chloracetamide, diazolidinyl urea and sulphanilamid. The sensitization rates of fusidic acid, chlorhexidine digluconate, cetyl/stearil alcohol, butyl hydroxytoluene, chloramphenicol stayed consistent after standardization process due to not been affected by gender or age.

The most common sensitizers were propolis (7.96%), sulphanilamid (5.00%), benzoil peroxyde (4.18%), diazolidinyl uea (3.25%) and Amerchol® (2.70%).

Only female subjects had positive reaction to fusidic acid, cetyl/stearil alcoho, butyl hydroxytoluene, sorbic acid, sorbitan sesquioleate, chloracetamide and imidazolidinyl urea. Reactivity to chlorhexidine digluconate, trolamine and sulphanilamid were registered only in men. The most specific difference according to gender was assessed for propolis and sulphanilamid for the benefit of men.

The battery of allergens used in other research are quite distinguish [28]. The series of allergens used by Austrian authors [28] and the one used in our study have two mutual allergens, propolis and propyleneglycol. There was no difference, in regard to gender, within male cohorts in Austrian report, while our male subjects were much more sensitized to propolis than women, accompanied by no presence of sensitization to propyleneglycol among men [23].

Conclusion

Contact sensitization prevalence in patients with CVI was not statistically significantly distinct from rates in subjects that have not presented CVI. Patients suffering from CVI had 2.45 times higher risk to manifest contact sensitization to two and more allergens, and 3.69 times higher risk for contact sensitization to five and more allergens than patients with no CVI. Furthermore, we established the positive correlation between frequency of contact sensitization and disease duration.

R E F E R E N C E S

1. *Kandolf Sekulović L, Dunić I, Karadaglić Đ.* Skin changes in peripheral blood vessel diseases In: Karadaglić Đ, editor. Dermatology. Beograd: Vojnoizdavački zavod; 2016; p. 1782−818. (Serbian)
2. *Lee AJ, Robertson LA, Boghossian SM, Allan PL, Ruckley CV, Fowkes FG,* et al. Progression of varicose veins and chronic venous insufficiency in the general population in the Edinburgh Vein Study. J Vasc Surg Venous Lymphat Disord 2015; 3(1): 18−26.
3. *Bergan JJ.* The Vein Book. New York, USA: Elsevier Academic Press; 2007; p. 323−401.
4. *Lopez AP, Phillips TJ.* Venous Ulcers.Wounds 1998; 10(5): 149−57.
5. *Saap L, Fahim S, Arsenault E, Pratt M, Pierscianowski T, Falanga V*, et al. Contact sensitivity in patients with leg ulcerations: a North americam study. Arch Dermatol 2004; 140(10): 1241−46.
6. *Jankićević J, Vesić S, Vukićević J, Gajić M, Adamić M, Pavlović MD.* Contact sensitivityin patients with venous leg ulcers in Serbia: comparison with contact dermatitis patients and relationship to ulcer duration. Contact Dermatitis 2008; 58(1): 32−6.
7. *Tavadia S, Bianchi J, Dawe RS, McEvoy M, Wiggins E, Hamill E,* et al. Allergic contact dermatitis in venous leg ulcer patient. Contact Dermatitis 2003; 48(5): 261−5.
8. *Akyol A, Boyvat A, Peksari Y, Gurgey E.* Contact sensitivity to standard series allergens in 1,038 patients with contact dermatitis in Turkey. Contact Dermatitis; 2005; 52(6): 333−7.
9. *Schnuch A.* PAFS: population-adjusted frequency of sensitization. (I) Influence of sex and age. Contact Dermatitis 1996; 34(6): 377−82.
10. *Bérard A, Abenhaim L, Platt R, Kahn SR, Steinmetz O.* Risk factors for the first time development of venous ulcers of the lower limbs: The influence of heredity and physical activity. Angiology 2002; 53(6): 647–57.
11. *Zmudzinska M, Czarnecka-Operacz M, Silny W, Kramer* L. Contact allergy in patients withchronic venous leg ulcers-possible role of chronic venous insufficiency. Contact Dermatitis 2006; 54(2): 100−5.
12. *Schäfer T, Böhler E, Ruhdorfer S, Weigl L, Wessner D, Filipiak B,* et al. Epidemiology of contact allergy in adults. Allergy 2001; 56(12): 1192−6.
13. *Barbaud A, Collet E, Le Coz CJ, Meaume S, Gillois P.* Contact allergy in chronic leg ulcers:results of a multicentre study carried out in 424 patiens and proposal for updated series ofpatch tests. Contact Dermatitis 2009; 60(5): 279−87.
14. *Machet L, Couhé C, Perrinaud A, Hoarau C, Lorette G, Vaillant L.* A high prevalence of sensitization still persists in leg ulcer patients: a retrospective series of 106 patients tested between 2001 and 2002 and a meta-analysis of 1975-2003 data. Br J Dermatol 2004; 150(5): 929−35.
15. *Marasović D, Vukšić I.* Allergic contact dermatitis in patients with leg ulcers. Contact Dermatitis 1999; 41(2): 107−9.
16. *Gupta G, Dawn G, Forsyth A.* The trend of allergic contact dermatitis in the elderly population over a 15-year period. Contact Dermatitis 1999; 41(1): 48−50.
17. *Smart V, Alavi A, Coutts P, Fierheller M, Coelho S, Linn Holness D,* et al. Contact allergens in persons with leg ulcers: a Canadian study in contact sensitization. Int J Low Extrem Wounds 2008; 7(3): 120−5.
18. *Jindal R, Sharma NL, Mahajan VK, Tegta GR.* Contact sensitization in venous eczema: preliminary results of patch testing with Indian standard series and topical medicaments. Indian J Dermatol Venereol Leprol 2009; 75(2): 136−41.
19. *Jovanović M, Božа P, Karadaglić Đ, Brkić S, Petrović A, Mimica Dukić N,* et al. Contact sensitivity in patients with psoriasis in Vojvodina. Int Arch Allergy Immunol 2009; 148(4): 311−20.
20. *Erfurt-Berge C, Mahler V.* Contact Contact sensitization in patients with lower leg dermatitis, chronic venous insufficiency, and/or chronic leg ulcers: assessment of the clinical relevance of contact dermatitis. J Investig Allegol Clin Innunol 2017; 27(6): 378−96.
21. *Thyssen JP, Linneberg A, Menné T, Nielsen NH, Johansen JD.* The prevalence and morbidity of sensitization to fragrance mix I in the general population. Br J Dermatol 2009; 161(1): 95−101.
22. *Kuljanac I, Knežević E, Cvitanović H.* Epicutaneous patch test results in children and adults with allergic contact dermatitis in

Karlovac county: a retrospective survey. Acta Dermatovenerol Croat 2011; 19(2): 91−7.

23. *Lazarov A.* European Standard Series patch test results from a contact dermatitis clinic in Israel during the 7-year period from 1998 to 2004. Contact Dermatitis 2006; 55(2): 73−6.
24. *Modjtahedi BS, Modjtahedi SP, Maibach HI.* The sex of the individual as a factor in allergic contact dermatitis. Contact Dermatitis 2004; 50(2): 53−9.
25. *Akasya-Hillenbrand E, Ozkaya-Bayazit E.* Patch test results in 542 patients with suspected contact dermatitis in Turkey. Contact Dermatitis 2002; 46(1): 17−23.
26. *Brasch J, Schnuch A, Uter W.* Information Network of Departments of Dermatology (IVDK) in Germany; German Contact Dermatitis Group (DKG). The profile of patch test reactions to common contact allergens is related to sex. Contact Dermatitis 2008; 58(1): 37−41.
27. *Freireich-Astman M, David M, Trattner A.* Standard patch test results in patients with contact dermatitis in Israel: age and sex differences. Contact Dermatitis 2007; 56(2): 103−7.
28. *Wöhrl S, Hemmer W, Focke M, Götz M, Jarisch R.* Patch testing in children, adults, and the elderly: influence of age and sex on sensitization patterns. Pediatr Dermatol 2003; 20(2): 119−23.

Received on August 21, 2019
Accepted on February 28, 2020
Online First March, 2020