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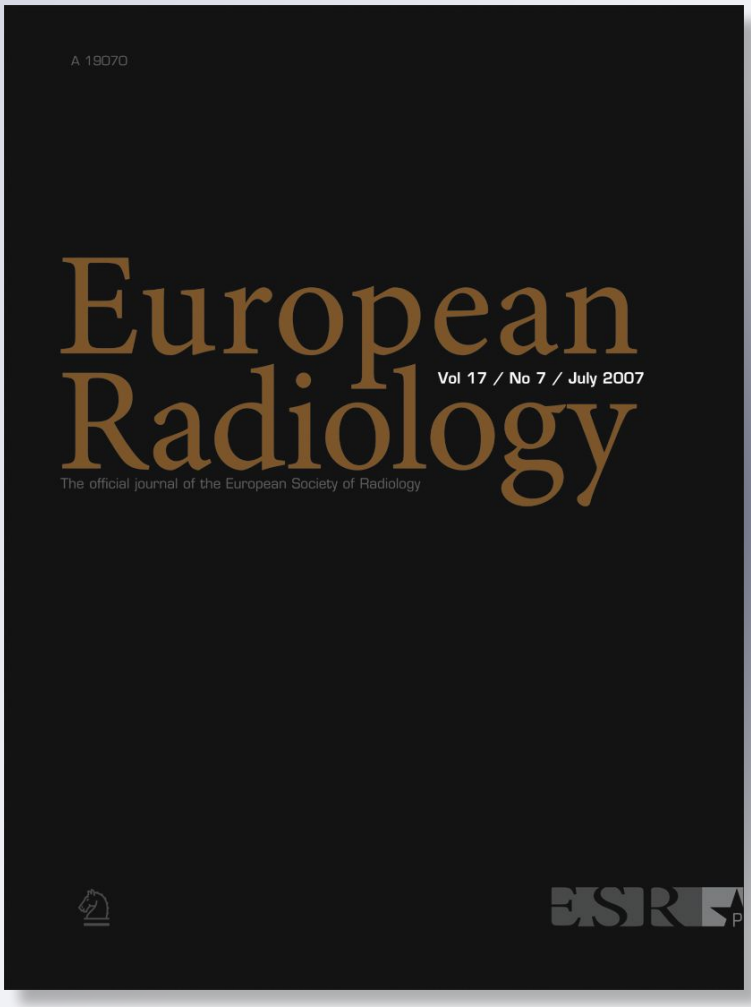

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VASCULAR-INTERVENTIONAL

Radio-opaque ethylcellulose-ethanol is a safe and efficient sclerosing agent for venous malformations

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Abstract
Objective To evaluate the efficacy and safety of gelified ethanol, a newly developed sclerosing agent for slow-flow vascular malformations.
Methods Seventy-nine sclerotherapy procedures were performed on 44 patients with 37 venous malformations, 2 glomuvenous malformations, 2 lymphatic malformations, 2 lymphatico-venous malformations, and 1 Klippel-Trenaunay syndrome. The median injected volume was 1.00 mL/site of injection. Effects of sclerotherapy on pain, functional and cosmetic disturbance were statistically evaluated with a final result score. Local and systemic complications were recorded.
Results The mean Visual Analogue Scores were 5.20±2.81 before and 1.52±1.25 after treatment ($p<0.001$). Functional and aesthetic improvement was achieved in 31/35 patients (89%) and in 33/41 (80%), respectively. Minor local side effects included necrosis with or without issue of ethylcellulose, palpable residue, and hematoma. No systemic side-effects occurred.
Conclusion Per mL used, radio-opaque gelified ethanol is at least as effective as absolute ethanol. No systemic complica-

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tion was observed, as only a low dose of ethanol was injected. Indications for sclerotherapy can be widened to areas with higher risk for local side effects (hands and periocular region), as ethanol is trapped in the lesion. Careful injection procedure is though necessary, because only a limited amount of ethylcellulose can be used per puncture.

Key Points

- *Development of a new sclerosing agent for venous malformations.*
- *Interesting novel way to deliver alcohol to slow-flow vascular malformations.*
- *Alcohol-based with less local and systemic side-effects.*

Keywords Sclerotherapy · Interventional radiology · Vascular malformation · Alcohol · Slow-flow

Abbreviations

VM	Venous malformation
LM	Lymphatic malformation
LVM	Lymphatico-venous malformation
GVM	Glomuvenous malformation
KT	Klippel-Trenaunay syndrome
VAS	Visual Analogue pain Score

Introduction

Slow-flow vascular malformations, especially those with a venous component, account for the majority of consultations in interdisciplinary centers for vascular anomalies [1, 2]. These lesions are present at birth, slowly worsen with age, and can infiltrate superficial and deep tissues. Depending on the size and location, they can cause pain, swelling, functional impairment and cosmetic prejudice. They can involve entire anatomical areas and, therefore, cure is often impossible, and management aims to relieve functional or cosmetic disabilities. Aetiopathological genetic defects have been elucidated for some of them, but this has not yet led to development of specific treatments [3–6].

Management of venous malformations includes compression, surgical resection and obliteration of the channel lumens by percutaneous sclerotherapy [7]. Sclerosing agents through direct vessel wall contact, cause endothelial damage, inflammation and fibrosis that obliterate the vascular channels. Ideally, the sclerosant should cause vascular injury and remain in place for sufficient time to permanently injure the endothelium [8]. Among the sclerosing agents, absolute ethanol is the most effective one with the lowest recurrence rate [9–12]. It causes instant precipitation of endothelial cell proteins through denaturization and cellular dehydration. However, it is an aggressive agent that can cause transmural vessel necrosis and sometimes ethanol leakage which is associated with serious local and systemic side effects including death [13–20].

Toxicity of absolute ethanol is mainly due to the diffusiveness of alcohol and high therapeutic doses that are needed during procedures. Some trials have been made to limit the diffusion. Absolute ethanol mixed with zein and oleum papavaris (Ethibloc®, Ethicon, Hamburg, Germany), which was frequently used in Europe, but not approved by the Food and Drug Administration (FDA, USA), is no longer commercially available due to post-sclerotherapy corrections needed to remove residual zein [21, 22]. Detergent sclerosants, with or without microfoam, are less aggressive than ethanol, but there is a greater tendency for recanalization of the vascular channels [23–25]. Hence, there is a great need for a better sclerosing agent, which would be as efficient as absolute ethanol, but less dangerous.

Ten years ago, we generated a modified ethanol sclerosing agent on the basis of a gel composed of ethylcellulose, a natural ligand commonly used to coat pills [26, 27]. This product is under revision for CE marked. The rapid formation of ethylcellulose framework traps ethanol within the malformation, increasing the contact time between the sclerosant and the endothelium and hence the power of sclerosis. This allows injection of smaller quantities of ethanol increasing safety. In this five-year prospective study, we evaluate the efficacy and safety of this agent.

Materials and methods

We conducted a prospective study from January 2004 to December 2008 in 2 interdisciplinary centres for vascular anomalies composed mainly of plastic surgeons, dermatologists, hematologists, radiologists and interventional radiologists (Table 1). This study was approved by the ethics committee and all patients signed an informed consent.

Patients

We included 44 patients with mucosal, cutaneous, subcutaneous and/or muscular slow-flow malformations diagnosed by either interdisciplinary team. Patients complained of pain, functional and/or cosmetic impairment. The diagnosis was made by clinical evaluation and confirmed by Doppler ultrasound. Magnetic resonance imaging with T1, T2-weighted and Fat-saturated sequences was done to evaluate the extensiveness within the surrounding tissues and organs. Both centres used the biological classification proposed by Mulliken and Glowacki, and adopted by ISSVA (International Society for the Study of Vascular Anomalies) [1]. The enrolled vascular malformations were all slow-flow and subclassified as venous malformations (VM, n=37), glomuvenous malformations (GVM, n=2)

Table 1 Patients and results

Pts #	Age at sclerosis	Localization	Size cm2	D	Symptoms	# of proc	vol EE cc	Anest	Pt's app	Improvement after sclerosis	VAS before sclerosis /10	VAS after sclerosis /10	Invest's app	Local s-eff	S s-eff	Result-score /10
1	12	Right side nose	<10	VM	Esthet, Funct	1,0	2,00	General	QG	Esthet & Funct	6,00	0,00	QG	Hematoma	None	8,00
2*	16-19	Left hand transfixant	>10	VM	Esthet, Funct	9,0	0.6:0.8:3;3:0.8; 4.5:1:0.9	General	QG	Esthet & Funct	8,00	1,00	QG	None	None	7,00
3	9	Palate exophytic	<10	VM	Funct, Bleeding	1,0	0.7	General	QG	Funct, no Bleeding	4,00	1,00	QG	None	None	6.25
4*	34	Left buttock	>10	VM	Esthet, Funct	4,0	1;3;1;1	General	QG	Esthet & Funct	8,00	3,00	QG	Necrosis with issue EC #2	None	7,00
5	9	Upper lip: vermillion	<10	VM	Esthet	2,0	0:4:0.5	General	QG	Esthet	0,00	0,00	QG	None	None	6.6
6	1	Left part of neck	<10	LM	Esthet	1,0	1,00	General	B	None	0,00	0,00	B	None	None	0,00
7	12	Lip, oral cavity, cheek	<10	VM	Esthet, Funct	2,0	0.8:0.8	General	QG	Esthet & Funct	3,00	1,00	QG	None	None	7,00
8	12	Nose	<10	VM	Esthet	2,0	0.3:0.1	General	G	Esthet	0,00	0,00	G	None	None	8.33
9*	7	Lower lip, oral cavity	<10	VM	Esthet	4,0	0.5:0.3:0.4:0.6	General	QG	Esthet	0,00	0,00	QG	None	None	6.6
10*	7	Lower lip, oral cavity	<10	VM	Esthet, Funct	3,0	1,8;1.8;0.8	General	QG	Esthet & Funct	5,00	1,00	QG	Necrosis #1,2,3	None	7,00
11	6	Back, right hand, left foot	>10	GVM	Esthet, Funct	1,0	1.6	General	B	None	3,00	1,00	B	Necrosis with issue EC	None	1.00
12	20	Left foot, toes	>10	VM	Esthet, Funct	1,0	0.8	General	QG	Funct	9,00	3,00	QG	Necrosis	None	5.00
13	34	Right ankle, foot	<10	VM	Funct	2,0	0.8;1	General	VG	Funct	8,00	0,00	VG	Necrosis with issue EC #2	None	10,00
14	28	Vulva	<10	LVM	Esthet, Funct	2,0	0.4:0.4	General	QG	Esthet & Funct	8,00	2,00	QG	None	None	7.00
15	14	Leg, ankle, foot	>10	VM	Esthet, Funct	1,0	1.00	General	QG	Esthet & Funct	9,00	3,00	G	Necrosis	None	8.00
16*	16	Left intraoral cheek	<10	VM	Esthet, Funct	1,0	2.5	General	VG	Esthet & Funct	6,00	1,00	VG	None	None	9.00
17	38	Face: periocular	<10	VM	Esthet, Funct	2,0	0.3:0.3	General	G	Esthet & Funct	4,00	0,00	G	Necrosis #1,2	None	9.00
18	35	Upper lip: cut & muc	<10	VM	Esthet	2,0	0.4:0.4	General	QG	Esthet	4,00	1,00	QG	None	None	6.25
19	28	Vulva	>10	VM	Esthet, Funct	1,0	1.00	General	G	Funct	6,00	1,00	VG	None	None	7,00
20	17	Left arm	>10	LVM	Esthet, Funct	1,0	1.5	General	QG	Funct	7,00	3,00	QG	None	None	6.00
21*	17	Upper lip: cut & muc	<10	VM	Esthet, Funct	1,0	0.8	General	G	Esthet & Funct	5,00	2,00	G	None	None	9.00
22	39	Left forearm	>10	VM	Esthet, Funct	1,0	3.00	General	VG	Esthet & Funct	5,00	0,00	VG	None	None	10,00
23	28	Multifocal	<10	VM	Esthet, Funct	2,0	0.8:0.8	Local	G	Esthet & Funct	6,00	2,00	QG	None	None	7.5
24	18	Trunk, upper left limb	>10	KT	Esthet, Funct	2,0	5:9	General	B	None	7,00	4,00	B	None	None	1.00
25*	17	Trunk, upper left limb	>10	VM	Esthet, Funct	2,0	1;1	General	QG	Esthet & Funct	7,00	2,00	QG	None	None	7.00
26	29	Left side nose	<10	VM	Esthet, Funct	1,0	0.3	Local	B	None	7,00	3,00	QG	None	None	2.00
27	26	Left arm, elbow	>10	LM	Esthet, Funct	1,0	0.8	General	VG	Funct	8,00	2,00	VG	None	None	8.00
28	39	Left upper eyelid	>10	VM	Esthet, Funct	2,0	0.8;1	General	VG	Esthet & Funct	8,00	3,00	QG	None	None	9.00
29	6	Upper lip: cut & muc	<10	VM	Esthet	1,0	0.4	General	QG	Esthet	0,00	0,00	QG	None	None	6.6
30	16	Lower lip: cut & muc, chin, cheek	>10	VM	Esthet	2,0	0.8:0.8	General	QG	Esthet	6,00	0,00	QG	None	None	7.5
31	66	Right face: eylids, orbit	>10	VM	Esthet, Funct	2,0	2:2:2.5	General	QG	Esthet & Funct	7,00	3,00	QG	Necrosis #1, with issue EC #2	None	8,00
32	49	Oral cavity, tongue to pharynx	>10	VM	Esthet, Funct	1,0	2.5	General	B	Esthet	4,00	4,00	B	None	None	3,00
33	36	Right lower lip	<10	VM	Esthet	1,0	1.00	General	G	Esthet	6,00	2,00	VG	Palpable Residue	None	9.3
34	16	Right face: cheek, lip, oral cavity	>10	VM	Esthet, Funct	2,0	2.5;2	General	QG	Esthet & Funct	6,00	2,00	VG	None	None	8.00
35	13	Oral cavity, tongue, right face	>10	VM	Esthet, Funct	1,0	3.5	General	QG	Esthet & Funct	6,00	3,00	QG	None	None	7,00
36	18	Neck, scalp	>10	VM	Esthet, Funct	1,0	4.00	General	QG	Esthet & Funct	7,00	3,00	QG	None	None	7.00
37	3	Pelvis, perirectal, uterus, buttock	>10	VM	Esthet, Funct	2,0	1.5;3	General	QG	Esthet & Funct	6,00	2,00	QG	None	None	7.00
38	2	Left upper lip and cheek cut	>10	VM	Esthet, Funct	1,0	1.5	General	QG	Esthet & Funct	0,00	0,00	G	Necrosis	None	8.5
39	8	Cheek, lip: cut & muc	<10	VM	Esthet, Funct	1,0	1.00	General	G	Esthet & Funct	6,00	2,00	G	None	None	9.00
40	32	Right neck, face, palate	>10	GVM	Esthet, Funct	1,0	1.00	General	G	Esthet & Funct	8,00	2,00	VG	None	None	9.00
41	12	Face: preauricular	<10	VM	Esthet, Funct	1,0	1.00	General	G	Esthet & Funct	9,00	2,00	G	None	None	9.00
42	52	Intraoral, gum	<10	VM	Funct	1,0	0.8	Local	VG	Funct	2,00	0,00	G	None	None	6.8
43	57	Right upper lip	<10	VM	Esthet	3,0	0.8:0.8:0.8	Local	QG	Esthet	0,00	0,00	G	None	None	7.5
44	14	Right upper lip, cheek: cut & muc	>10	VM	Esthet, Funct	3,0	1;2.5;1	General	QG	Esthet & Funct	5,00	2,00	QG	None	None	7,00

Female
Male

* = additional sclerotherapy procedures after those reported in Sannier et al., Interven Radiol; 2004 (ref 27).

D: diagnosis
# of Proc: number of procedures
Vol EE: volume od ethylcellulose-ethanol
Anest: anesthesia
Pt's app: patient's apreciation

Invest's app: investigator's appreciation
Local s-eff: local side-effect
S s-eff: systemic side-effect
Grade: Result-score
Invest's app: Investigator's appreciation

VM: venous malformation
GVM: glomuvenous malformation
LM: lymphatic malformation
LVM: lymphatico-venous malformation
s-effect=side effect

VG: very good
G: good
QG: quite good
B: no change/bad

EC: Ethylcellulose
Cut:Cutaneous
Muc: Mucosal
VAS: Visual Analogic pain Score

VG: Very Good
G: Good
QG:Quite Good

[28], lymphatic malformations (LM, n=2), lymphatico-venous malformations (LVM, n=2) and Klippel-Trenaunay syndrome (KT, n=1). The following data were recorded (Table 1):

a) before interventional procedure: sex, age, clinical size of the malformation (≤10 cm^2, >10 cm^2) and localization, subdivided into areas of higher risk (face, lips, oral cavity, hands and feet) and lower risk (neck, limbs and trunk) for local complications. Moreover, pain (during daily activities, effort and hormonal variations) was graded (Visual Analogue Scale, VAS 0–10), and functional and esthetic prejudice were noted.
b) during interventional procedure: type of anesthesia (local, general), amount of radio-opaque ethylcellulose-ethanol injected, and pre and post-procedure treatment (analgesics, and Low Molecular Weight Heparin, if important or severe localized intravascular coagulopathy (LIC) was unraveled before interventional procedure) [2, 7, 27, 29].
c) at 6 months' follow-up after the last procedure: 1) change in pain (relief, residual or intermittent, no change), 2) functional impairment, 3) esthetic prejudice, as well as 4) global acceptance by the patient and 5) by the interdisciplinary team. These five items were graded from 0 to 2 each, and summed for a Result-score per patient (Table 2). If less than 5 items were relevant for a patient (but always a minimum of three), the summed score was extrapolated to the scale of 0–10. Quantitative analysis of pain was assessed by Visual Analogue Scale (VAS). Local side effects were looked for: edema, epidermolysis, haematoma, palpable residue, abcess, necrosis of the skin with or without discharge of ethylcellulose, paresthesia and nerve palsy. Systemic side effects, such as hemolysis, renal failure, myocarditis and collapse,

Table 2 Grading of sclerotherapy results

Evaluated items	Grades			
	2	1.5	1	0
Pain	Relief		Residual intermittent	No change
Functional impairment	Better			No change
Esthetic predjudice	Better			No change
Patient's appreciation	Very good	Good	Quite good	No change/Bad
Investigator's appreciation	Very good	Good	Quite good	No change/Bad

were also searched for. For certain patients, more than 1 sclerotherapy procedure was performed if clinical improvement was not sufficient, or if the lesion required large volumes of sclerosing agent.

Sclerosing agent

To trap ethanol better in the lesion, we wanted to enhance its viscosity. We employed ethylcellulose, a natural substance commonly used as a ligand, or to coat pills, granules and microcapsules [30]. Ethylcellulose is a hydrophilic substance with a fast and high thickening potential in aqueous media (Fig. 1a–c). It is also very stable and soluble in ethanol. It does not induce allergy or irritation. The ethylcellulose-ethanol gel was made in our Hospital Pharmacy (Caen, France) according to the recommendations of Good Manufacturing Practices [27]. The solution was kept in the refrigerator until procedure to maintain the highest viscosity, which helps the management of injection.

Sclerosing procedure (Fig. 2)

Before the procedure, blood was sampled to follow indicators of hemolysis and systemic effects (haptoglobin, lactic deshydrogenase [LDH], bilirubin, urea and creatinine). Patients with important or severe LIC (D-dimers ≥1 μg/mL) had preoperative Low Molecular Weight Heparin (100 anti-Xa/kg, 10 days before and 10 days after the procedure) [7, 29]. A bolus of antibiotics was given at the beginning of the procedure. All procedures were performed by the same experienced interventional radiologists (JT & FH). The volume of the connecting tube between the 21G butterfly needle (Terumo, Guyancourt, France) and the syringe was measured (around 0.42 mL). Under fluoroscopic guidance, direct puncture of the VM was performed and a strong blood back-flow was obtained. When venous channels were too small to obtain a good back-flow, a smaller butterfly needle was used (23G) to target the vascular lumen only. Water-soluble contrast agent was injected to map the malformation and to visualize potential large draining veins, which should not be sclerosed. Emulsification of ethylcellulose-ethanol and hydrophobic Lipiodol® (Laboratoire Guerbet, Roissy Charles de Gaulle, France) was performed immediately before injection, using one 3 ways stopcock and two 1 mL syringes. A homogeneous emulsion containing small drops of Lipiodol® in the alcoholic gel was obtained with a 1 min mixing. Ten-to-twenty percent of Lipiodol® was sufficient to obtain an emulsion, which could be visualized under fluoroscopy. Injection of the sclerosant was easy, because it is more liquid than Ethibloc®, but thicker than absolute ethanol.

The volume of injected ethylcellulose-ethanol never exceeded 1 mL per puncture site. Due to the fast precipitation of ethylcellulose when in contact with the

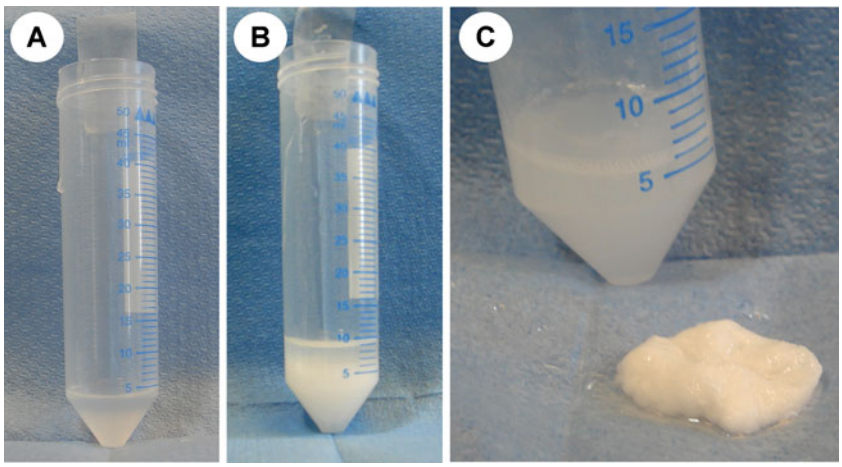

Fig. 1 Ethylcellulose-ethanol: high thickening potential in aqueous media within 150 s: **a** ethylcellulose-ethanol (5 mL); **b** with 5 mL of added saline and **c** ethylcellulose clot after 150 s

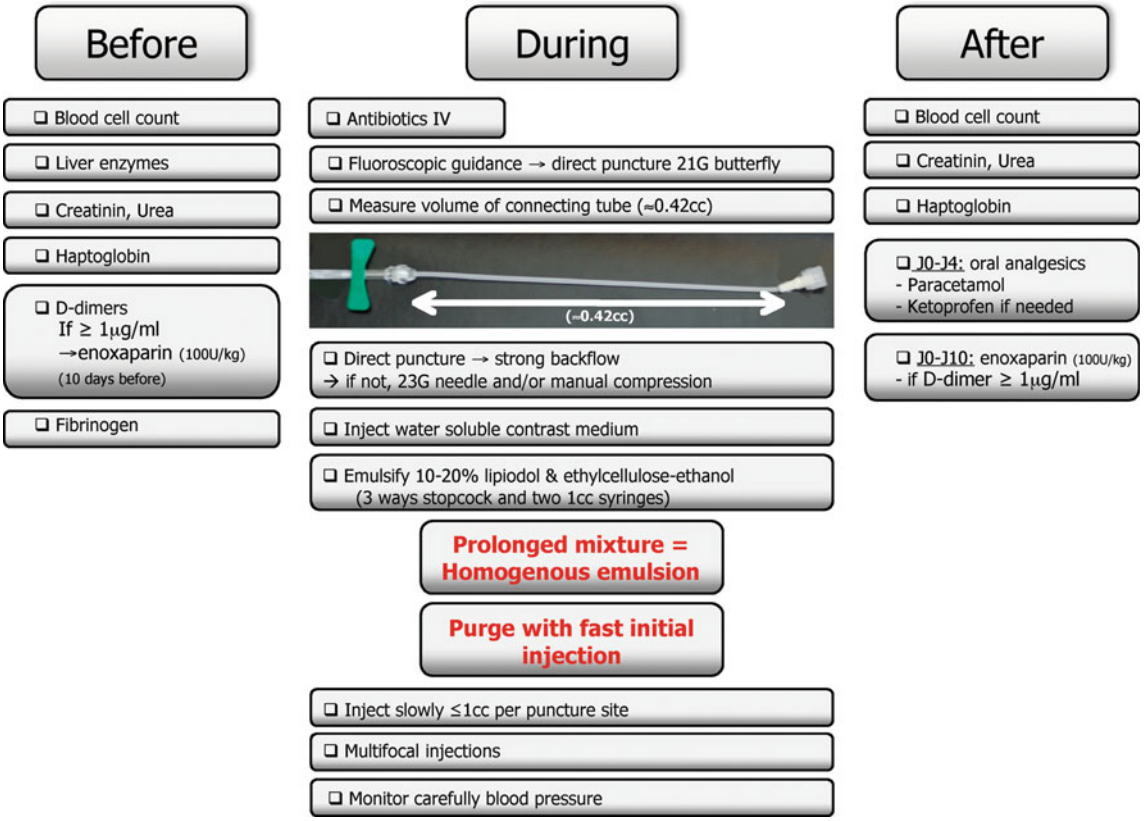

Fig. 2 Scheme of the procedure for ethycellulose-ethanol

blood in the malformation, sclerosing large malformations from a single needle puncture was not possible. Additional puncture sites were needed, each with maximum 1 mL of the emulsion. To avoid flocculation of the sclerosing emulsion in the catheter, the water-soluble contrast solution injected at the beginning of the procedure, was purged with a fast initial injection of ethylcellulose-ethanol up to the "junction" of the needle (0.42 mL). Subsequently, the injection of ethycellulose-ethanol was performed slowly. Careful monitoring of haemodynamic and vital parameters, during and after the procedure, were performed for all patients. To reduce pain secondary to the inflammatory reaction, oral analgesic therapy with paracetamol was prescribed for 4 days, when necessary. When the inflammatory reaction was more severe, oral ketoprofen 3 g/day for 4 days was added. In Brussels, peroperative hyperhydration and intravenous dexamethasone, as for absolute ethanol, were systematically prescribed and blood alcohol levels were measured [31–33]. All patients with general anesthesia were admitted for 12–24 h.

Statistical analysis

Statistical analysis were performed with SPSS 15.0. Seventy-three sclerosis were necessary to determine the prevalence of systemic adverse events with a precision of 5% (assuming the prevalence would be close to 5%). Patients' characteristics were described with n size and percentage for nominal data, and with mean and standard deviation for continuous data. Improvement in comparison to previous sclerosis and adverse events were described with prevalence and 95% confidence interval. Volumes injected per sclerosis were described with median and range. The Wilcoxon matched-pairs signed-ranks test was used to assess changes in pain at the VAS scores obtained before and after treatment. Fisher's exact test was used to compare rates between groups. Significance tests were two-sided, with a type 1 error set at 0.95.

Results

Seventeen male and twenty-seven female patients were included (Table 1). The mean age at procedure was 22.7 years ±15.5 (range from 1 to 69 years). The mean number of procedures per patient was 1.8±1.4 (range: 1–9). All patients, except four who had local anesthesia, had general anesthesia. Ten patients had been previously treated with other sclerosing agents: 8 with absolute ethanol, one with sodium tetradecyl sulfate (Trombovar®, Innotech International Laboratory, Arcueil, France), and one with lauromacrogol (Aethoxisclerol®, Kreussier

Pharma, Paris, France). Thirty-one malformations (70.4%) were located in areas at risk for neurologic or functional complications. Thirty-eight patients (86.4%) had pain, 28 (63.6%) of which during daily activities and/or efforts, hormonal and temperature changes. The remaining ten were unable to specify aggravating factors. Thirty-five patients (79.6%) had functional impairment during daily activities and 41 patients (93.2%) had aesthetic prejudice.

The median injected volume was 1.00 mL per session (range: 0.10–9.00 mL). Small malformations (<10 cm^2) were treated with a median dose of 0.70 mL (range: 0.10–2.50 mL), and larger ones (>10 cm^2) with a median dose of 1.00 mL (range: 0.30–9.00 mL). One patient who presented with a Klippel Trenaunay syndrome of the upper limb and trunk had a large lymphatic cyst of the chest (>30 cm2) treated with 9 mL in one session with multiple puncture sites. All patients experienced immediate post-sclerotherapy local oedema. Systemic ethanol contamination was not detected.

Of the 38 patients with pain, fifteen had complete relief of pain (39.4%, 19 procedures) and 23 had less pain after the treatment (60.5%, 47 procedures). The mean VAS scores were 5.20±2.81 before and 1.52±1.25 after, which was statistically highly significant ($p<0.001$).

Thirty-one patients had functional improvement (88.6%, 56 procedures). This was obtained less frequently with LMs, GVMs, and KT (33.3%) compared to VMs (97.3%, $p<0.001$). Thirty-three patients (80.5%, 66 procedures) had aesthetic improvement, whereas 8 (19.5%, 9 procedures) did not. Six patients (13.63%, 8 procedures) had a very good acceptance, 9 patients (20.4%, 13 procedures) a good acceptance, 24 patients (54.54%, 53 procedures) a quite good acceptance and 5 patients (11.36%, 65 procedures), no change/bad acceptance of the outcome. All seven patients who had been previously sclerosed with absolute ethanol, noted less postprocedurial swelling. Investigator's evaluation was very good for 8 patients (18.18%, 10 procedures), good for 9 patients (20.45%, 12 procedures), quite good for 23 patients (52.27%, 52 procedures) and no change/bad for 4 patients (9.09%, 5 procedures). Overall result-scores were excellent (9–10) for 10 patients (23%), good (7–8) for 21 patients (48%), fair (5–6) for 8 patients (18%) and mediocre (0–4) for 5 patients (11%). Eleven patients (18%) experienced local side-effects ($n=14$ procedures): necrosis without discharge of ethylcellulose after 9 procedures (11.39%), necrosis with discharge of ethylcellulose after 4 procedures (5.06%), and one small (0,5 cm) palpable residue after 1 procedure (1.26%). All these side-effects occurred on malformations in areas with higher risk for local complications. No systemic side-effect, such as haemoglobinuria, haemolysis, renal failure, myocarditis or collapse, was observed.

Discussion

Venous malformations are slow-flow lesions, which are difficult to treat. Sclerotherapy is the endovascular treatment of choice. The efficacy of the therapy depends on the strength and the distribution of the sclerosing agent, and the contact time with the endothelium. Large malformations are rarely completely occluded with a single procedure without local or systemic side effects. Multiple sessions are necessary. Each intervention is performed according to functional and/or aesthetic complaints.

MRI is a useful examination to determine the size of the malformation and its infiltration to adjacent tissues. However, the size of the lesion does not correlate with signs and symptoms [11, 31]. Moreover, MRI and all other imaging procedures are incapable of measuring the exact volume of the malformation and thus radiological quantification cannot be used to accurately evaluate the reduction in size after treatment. However, experimental methods are being developed [34].

A successful sclerotherapy must be safe and effective, with a good reproducibility and repeatability. Absolute ethanol (95%) is known as the best sclerosing agent, but it is associated with high morbidity due to diffusibility [16]. To minimize egress of ethanol, manual compression or tourniquet is often used. In some areas, such as hands, feet, face and mouth, leakage of ethanol is dangerous, as it can cause direct damage (skin and nerves). Moreover, the important postprocedure swelling can induce vascular and nervous compression. Hence, even experienced practitioners hesitate to treat lesions in these areas. This study was performed mostly on such lesions, small-to-medium in size, which functionally and cosmetically disturbed the patients (Figs. 3a-b and 4a-b)

To keep the injected alcohol within the malformation, we used gelified ethanol. It has a higher viscosity than absolute ethanol and therefore it is easier to inject. As soon as it encounters an aqueous media, a framework of ethylcellulose develops, quickly within 150 s (Fig. 1), trapping ethanol in the lesion and increasing the time at contact with the vascular endothelium. Hence, small quantities are sufficient to obtain a good sclerosing effect. On the basis of prolonging surface contact, another team developed a foam, made of polidocanol and carbon dioxide. Although foam is more efficient than solution, detergents are less efficient than ethanol as sclerosing agents, and the gas bubbles disappear more rapidly than ethylcellulose [24, 35, 36].

We added a contrast agent to our sclerosing solution to better monitor the procedure. Lipiodol®, an oily contrast agent was chosen, because the ethylcellulose-ethanol-Lipiodol® mixture and hence the lesion, can be visualized as radio-opaque droplets during and after the procedure (Figs. 3d and 4c-d). Suh and coworkers also used Lipiodol® [37]. They found it increased safety when using

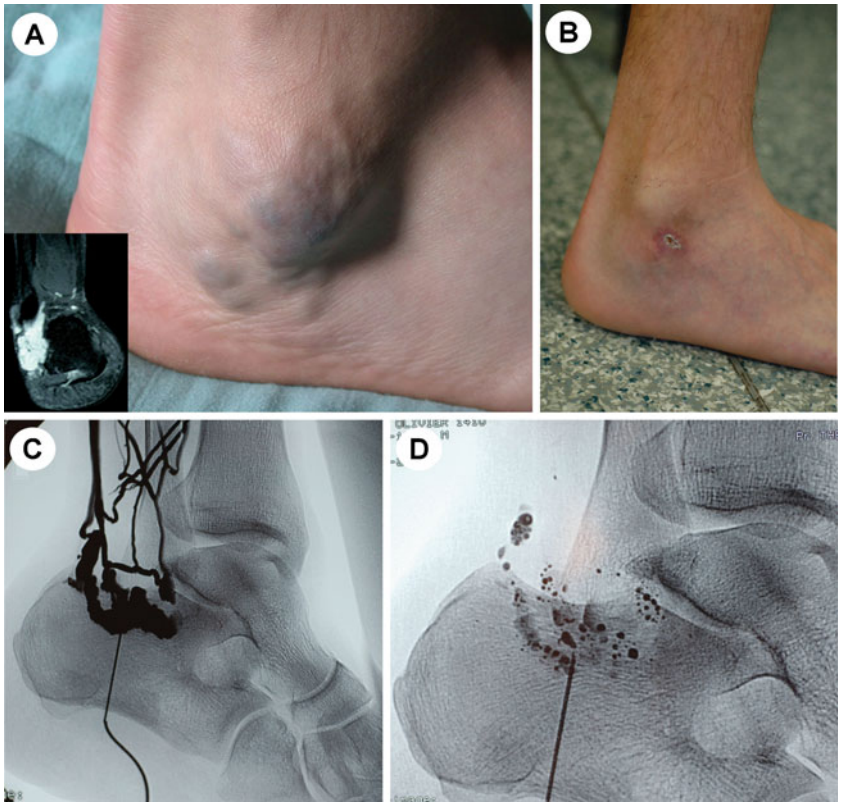

Fig. 3 **a** VM of ankle (patient #13) with T2-weighted MRI (*inlet*); **b** Results 2 months after 2 sclerotherapy procedures; **c** peroperative venogram; **d** visible Lipiodol® droplets at end of sclerotherapy

absolute ethanol for the management of venous malformations. Their median dose of ethanol (6 mL) was lower than that commonly used.

The overall injected dose of ethanol can never exceed 1 mg/kg of patient's weight. The volume of absolute alcohol to be injected is estimated on the basis of pre-

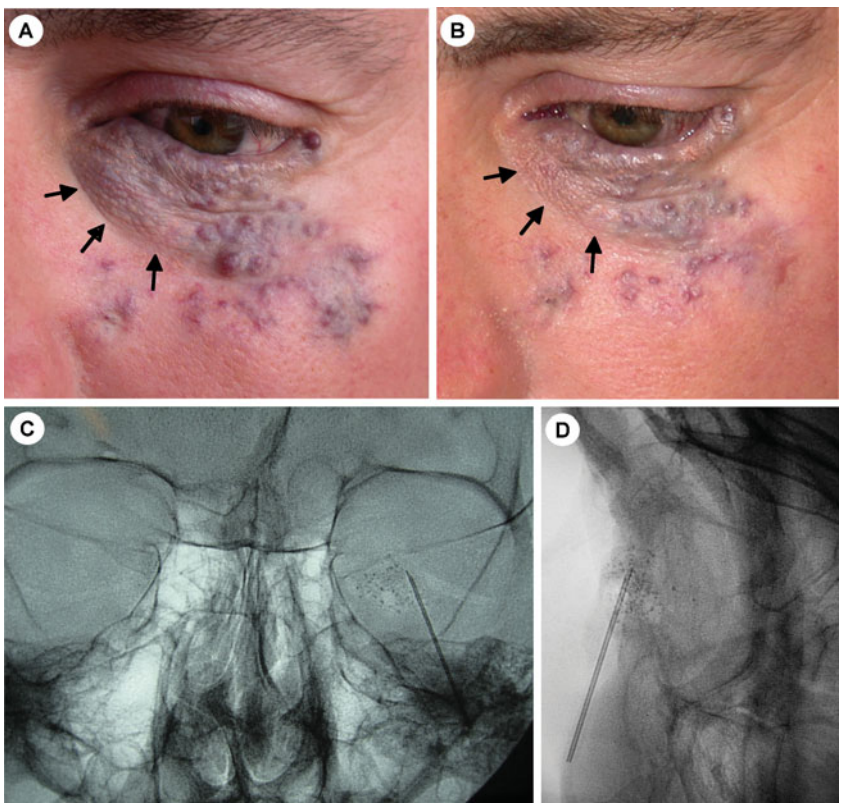

Fig. 4 **a** Periocular VM with compression of lacrymal duct (*arrows*) (patient # 17); **b** Results 3 months after 1 sclerotherapy procedure; **c** and **d** Visible Lipiodol® droplets at end of procedure (**c**: front view, **d**: lateral view)

injection phlebography Fig. 3c-d. Moreover, the injected dose of gelified-ethanol should never exceed 1 mL/injection site, since the ethylcellulose framework forms quickly. However, numerous injections can be performed depending on the size of the venous malformation. With this procedure, we reduced the incidence of local side effects from that observed in the pilot study [27].

The therapeutic results with gelified ethanol were at least as good as those reported for absolute ethanol [10, 31, 35–38]. However, evaluation in the literature is commonly based on clinicians' general acceptance only. Berenguer and co-workers stressed that interobserver concordance is never 100% and used in their retrospective study of craniofacial VMs three defined grading topics (patient's overall satisfaction, panel evaluation of esthetic improvement on the basis of pre and post treatment photographs, and review of radiologic images) to obtain a higher concordance [11]. To increase objectiveness, we further developed their scheme and used multiple assessments for grading combining equally 5 criteria (VAS, evaluation of functional and esthetic impairment, patients' and investigators' general acceptance), and summed a final Result-score (0–10). In order to have the maximal score, the patient needed to have improvement in all items (Table 2). Even with this stringent and detailed grading, our results with gelified ethanol were as good as those of our initial study, as those by Berenguer and co-workers using absolute ethanol, and as others evaluating with more general criteria [10, 12, 38–41].

Gelified ethanol may not be indicated for all vascular anomalies. Three of the five patients with bad Result-scores were treated for a non-VM lesion. One had a GVM, one had a LM and one had a KT, treated on her large macrocystic lymphatic component. As another GVM, LM and two LVMs responded well, further studies are necessary.

Slow-flow malformations are rarely life-threatening, hence, safe procedures are mandatory [42]. Although absolute ethanol is used by experienced practitioners, the range of local and systemic complications varies between 7.5 and 28% of patients [11, 20, 31]. Life-threatening systemic complications include haemoglobinuria, which may lead to renal tubular necrosis, as well as cardiovascular collapse, which has been reported for minimum 6 cases, at least two of which led to death [13, 15, 19, 31]. The pathophysiology of the latter is unknown, but pulmonary artery vasospasm and direct toxicity to the cardiac conduction system have been hypothesized [19, 43]. The two statistically significant factors affecting the pulmonary artery pressure are a peroperative increase in systemic blood pressure, and the total volume of ethanol injected per procedure. The mild elevation of systemic blood pressure is probably related to pain due to sympathetic stimulation by ethanol injection, even under general anesthesia [19]. We think that systemic side effects do not occur with ethylcellulose-ethanol, as less alcohol is used, even if multiple injections are performed. Moreover, the rapid thickening of ethylcellulose in aqueous media, makes the use of a tourniquet unnecessary, eliminating the risk of cardiac toxicity associated with its release [15].

Gelified ethanol minimizes local complications without reducing efficacy of treatment. The procedure is less painful and postprocedurial swelling is less important, as noted by all patients who had undergone previous scleroses with other agents. Contrary to sclerotherapy using absolute ethanol, small lesions can be treated under local anesthesia (nerve block). We performed six such procedures on superficial VMs located on upper lip (n=3), nose (n=1), mouth (n=1) and the arm (n=1).

Ethylcellulose, which is always palpable after sclerosis, spontaneously dissolves within 3–6 months, in contrast to Ethibloc®, which necessitated a surgical removal of the residue. Only one of our patients with a VM of the mucosa of her lower lip (patient #33) complained of functional disturbance by the persistence of a small ethylcellulose residue, which was subsequently surgically removed. This patient had had 1 mL of ethylcellulose-ethanol injected into her 2 cm^2 VM, an amount "*a posteriori*" too important in regard to the localization and size of the lesion. This exemplifies the importance of careful dosing of gelified ethanol to avoid generating a prolonged disturbing nodule.

Twelve patients (n=13/79 procedures, 16%) had cutaneous necrosis with (n=4 patients, 4 procedures) or without (n=6 patients, 9 procedures) discharge of ethylcellulose. They all occurred in areas with higher risk for local side effects, when using absolute ethanol, i.e. face, mouth, hands and feet. The discharged ethylcellulose, an aseptic cotton-like material, should not be misdiagnosed as pus. To accelerate healing, the material should be manually removed. Since the initial study, the frequency of secondary surgery to repair local side effects has been reduced from 20% (n=10/48 procedures) to 1% (n=1/79 procedures) [27].Thus, our 8-year-experience with this sclerosing agent, allowed us to optimize results using smaller doses per puncture, multifocal injections and more accurate monitoring with Lipiodol®.

In conclusion, this study suggests that, per mL used, radio-opaque gelified ethanol is at least as effective a sclerosing agent as absolute ethanol. Yet, none of the systemic complications associated with absolute ethanol are observed, as only a low dose of ethanol is injected. Indications for sclerotherapy can be widened to areas with higher risk for local side effects from absolute ethanol, such as hands and the periocular region, as gelified ethanol is less diffusible. Careful injection procedure is though necessary, because an excessive amount of ethylcellulose

per puncture site can cause local side effects. Finally, radio-opaque gelified ethanol allows outpatient procedures, as it is safe and its use is feasible under local anaesthesia.

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