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Effect of Intravenous and Intraperivenous Injections of Sclerosants (Sodium Tetradecyl Sulfate and Hydroxy Polyethoxy Dodecan) on the Rat Femoral Vein*

E. Morsiani[1], A. P. Rimondi[2], P. Gorini[1], L. Fogli[1], L. Cappellari[1], and S. Gullini[3]

[1] Istituto di Patologia Chirurgica dell'Università di Ferrara, Arcispedale S. Anna, Corso Giovecca, 203, I-44100 Ferrara, Italy
[2] Istituto di Anatomia e Istologia Patologica dell'Ospedale Nuovo, Rovigo, Italy
[3] Servizio di Gastroenterologia ed Endoscopia Digestiva dell'Arcispedale S. Anna, Ferrara, Italy

Summary. The sclerosant effect of injected tetradecyl sulfate of sodium (STS) and hydroxy polyethoxy dodecan (HPD) was studied in the rat femoral vein. Intravenous (i.v.) and intravenous plus perivenous (i.v. + p.v.) injections of both sclerosants and physiologic saline were compared as to vein lumen occlusion, fibrosis, phlogosis, and damage to the artery and surrounding nervous and muscular tissues.

The study was carried out in 30 rats treated by STS, in 30 treated by HPD, and 15 animals were injected with saline. The neurovascular bundle and adjacent muscle were removed at 48 h, 7 and 30 days and examined histologically. I.v. injections of STS produced a solid occlusion of the vein in a significant number of cases, after 30 days ($P < 0.01$). A statistically significant number of solid occlusions of the femoral vein resulted after i.v. + p.v. injection of STS and HPD, at 48 h, 7 and 30 days ($P < 0.05$; $P < 0.01$). There was no significant difference between STS and HPD after i.v. + p.v. injection. After i.v. + p.v. we recorded a marked inflammation of muscle with signs of focal necrosis, at 48 h and 7 days.

Our study indicated that i.v. + p.v. injection of STS and HPD provided a high degree of efficacy as regards vein occlusion. On the other hand, i.v. + p.v. injection induced a severe inflammation and necrosis of the tissues surrounding the sclerosed vein.

Extrapolating our results to the endoscopic sclerotherapy for esophageal variceal bleeding, we conclude that paravariceal injection of sclerosants is a

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Offprint requests to: E. Morsiani, MD (address see above)

dangerous procedure, even though efficacious to reduce variceal hemorrhage, owing to the high risk of iatrogenic ulcers and esophageal perforation caused by muscular and mucosal necrosis.

Key words: Experimental study – Sclerosants – Tetradecyl sulfate of sodium – Hydroxy polyethoxy dodecan – Varices

Introduction

Sclerosants are widely used in the treatment of varicose veins, hemorrhoids, and some angiomatous malformations. More recently, endoscopic sclerotherapy of esophageal varices has been introduced for elective and emergency treatment of hemorrhage due to portal hypertension [11, 17, 30].

Many sclerosants have been used, but two of the most widely employed are sodium tetradecyl sulfate (STS), and hydroxy polyethoxy dodecan (HDP) [5, 10, 20, 22]. There are some studies comparing the sclerosing effects on varicose veins of different agents in human and in experimental animal models [3–6, 12, 15]. Few preliminary reports suggest that the most damaging agent may be the most efficacious [15, 28]; however, the choice of the sclerosant still remains debated [7].

In the endoscopic sclerotherapy, the most important of the technical variations is the precise site of injection [9]. Many endoscopists attempt to inject the sclerosant directly into the varices [8, 17, 30, 31], others inject only paravariceally to stimulate the production of fibrosis [20, 21], but the most part inject indiscriminantly, intra- and paravariceally [13, 29].

The aim of this work was to study in the rat femoral vein, the effects of STS and HPD after i.v. and intraperivenous injections.

Material and Methods

Male and female Sprague-Dawley rats, weighing 310 ± 24 g (Charles River Italy, Calco, CO) were used. They were housed in single plastic cages, in a controlled air-humidity and temperature room, with free access to tap water and pellet food (MIL, S. Morini, S. Polo D'Enza, RE). The animals were randomly divided into three groups. Before treatment, the rats were anesthetized with ether by inhalation. The femoral vein was exposed by skin incision over the lower thigh, and the injection was made into the femoral vein: (i.v.) or into and around (i.v. + p.v.) its distal and proximal part. Thirty rats were injected i.v. with 0.3 ml 1% HPD[1] on one side, and with 0.3 ml 1% HPD i.v. plus 0.1 ml 1% HPD p.v. on the other side (group 1). Thirty rats were given 0.3 ml 1% STS[2] i.v. on one side, and 0.3 ml 1% STS i.v. plus 0.1 ml 1% STS p.v. on the other side (group 2). Fifteen control animals were injected with saline, i.v. on one side, and i.v. + p.v. on the other side, at the same doses as described above (group 3). The mean exposures to injected substances were 4 s during i.v. and 7 s during i.v. + p.v. Rats were killed 48 h, 7 days, and 30 days after injection, by exsanguination under ether anesthesia. After killing, each injected vein was excised with the adjacent nerve, artery, and muscle; fixed in 10% buffered formalin; and processed for histology. Transverse paraffin section 5 μm thick, were cut at 1-mm intervals, and at each level one section was stained with HE, with PAS, with

[1] Aethoxysklerol: Fa. Kreussler, D-6200 Wiesbaden 12, FRG
[2] Trombovar: It. Lab. Bouty S.p.A., via Vanvitelli, 6, I-20100, Milan, Italy

Table 1. Number of veins treated with HPD, STS, and saline by each technique of injection

Injection technique	1% HPD	1% STS	0.9% saline
Intravenous (i.v.)	30[a]	30[a]	15[b]
Intravenous plus perivenous (i.v. + p.v.)	30[a]	30[a]	15[b]

[a] Ten veins were examined after 48 h, ten after 7 days, and ten after 30 days from injections
[b] Five veins were examined after 48 h, five after 7 days, five after 30 days from injections

elastic-Van Gieson and Shikata, and with Orcein. The number of veins injected with sclerosants and with saline is given in Table 1. The sections were examined by one person with no access to the histological fragments coding. Examination of the sections was carried out to detect the entity of thrombosis, fibrosis, and phlogosis in the femoral veins. Vein wall necrosis, damage to the nervous and muscular tissue, entity of perivenous oedema, and the lesions to the venous endothelium and internal elastic membrane (IEM) were also recorded. These parameters were scored from 0 to 3, according to the severity of the pathologic findings. The percentage of occlusion of the vein lumen in transverse sections, was calculated at X20, with an eye-piece micrometer for each animal, on sections cut at a 2-cm standard distance from the site of injection. The length of the vein thrombosis was estimated for each rat, as sum of the percentages of occlusion of the lumen in consecutive transverse sections, taking as 100% the complete occlusion of the vein segment under examination, starting from the injection site. All values were expressed as mean ± SD. Statistical analysis of the results was carried out by the χ^2 test and the Fisher exact test. Comparisons between the groups were performed by the non-parametric Wilcoxon test, taking a significance of 5%.

Results

Forty-eight hours after injections of sclerosants, the perivenous tissue showed inflammatory cells, chiefly mononuclear and fibroblasts, whereas the dilated veins contained only acellular thrombus. At 7 days, the thrombus and perivenous tissue showed granulation tissue and collagen, and the veins were filled with young connective tissue (Fig. 1). At 30 days, the injected veins were much smaller and characterized by complete occlusion of the lumen by fibrous tissue, leaving only narrow capillary channels (Fig. 2). These early histological changes were very similar in the veins injected with HPD and STS i.v. and i.v. + p.v.

A comparative study of the sections showed that after i.v. injection, a statistically significant number of almost complete occluded veins, more than 80% of the lumen [5], was found only after STS at 30 days (Table 2). After i.v. + p.v. injection, the number of occluded veins was significant at 48 h and 7 days, with no difference between the two sclerosants. After 30 days from i.v. + p.v., only the veins treated with STS resulted significantly occluded ($P < 0.01$). The percentage of occlusion of the vein lumen by fibrous tissue, calculated in cross-sectional areas, ranged between $47 \pm 27.7\%$ after i.v. injection of STS and $84.3 \pm 26.3\%$ after i.v. + p.v. injection of STS ($P < 0.05$; Table 3). Calculation of the length of the thrombus, expressed as percentage of occlusion of the vein lumen in consecutive transverse sections, showed a maximum of $81.6 \pm 26\%$ after i.v. + p.v. injection of STS at 48 h, and a significant difference between

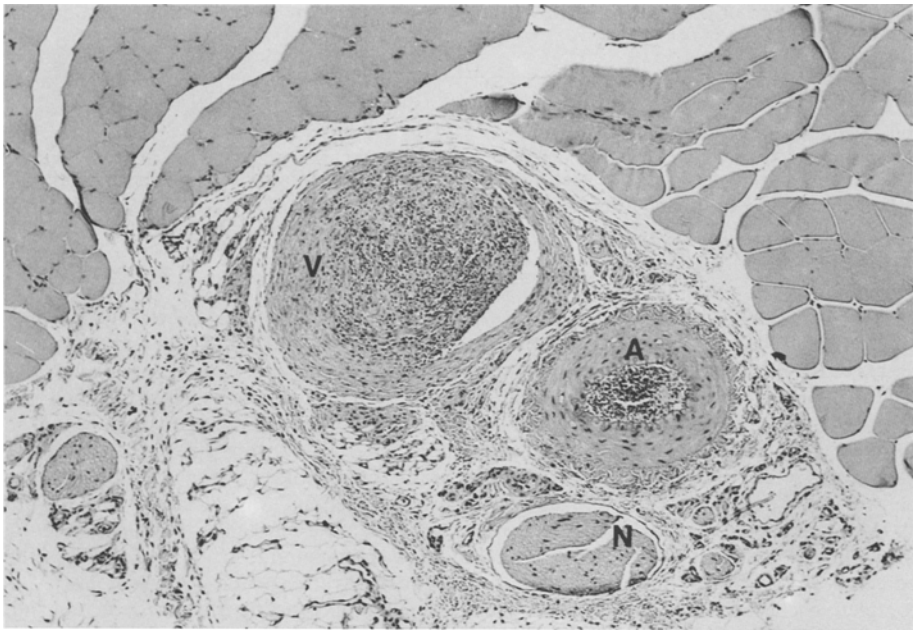

Fig. 1. Rat femoral vein *(V)*, artery *(A)* and nerve *(N)*, 7 days after i.v. injection of 1% STS. The vein is distended and occluded by thrombus, and filled with young connective tissue, particularly at the periphery; HE, × 100

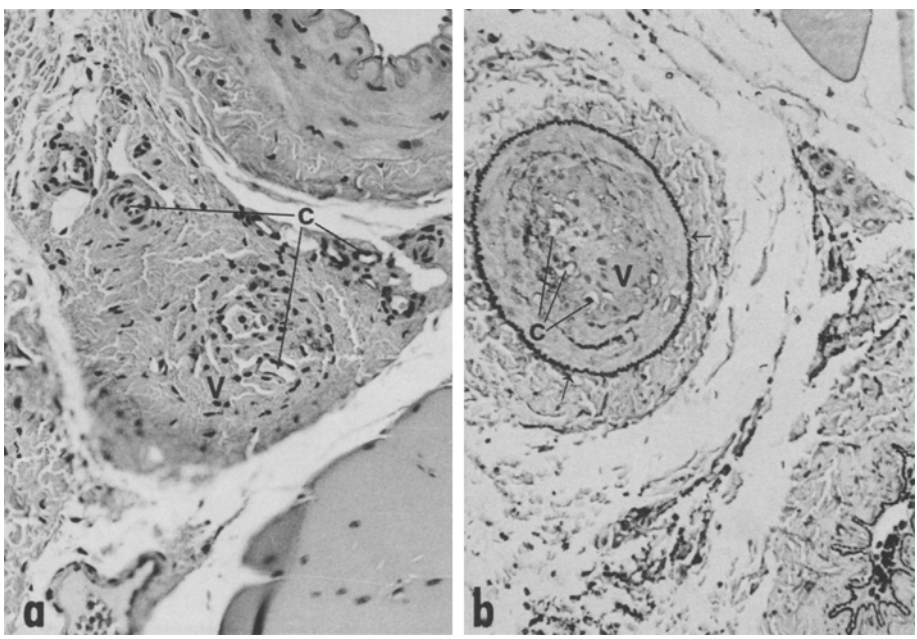

Fig. 2a, b. Rat femoral veins *(V)* 30 days after i.v. + p.v. injection of 1% STS. **a** The vein has completely shrunk, leaving only narrow capillary channels *(C)*; HE, × 150. **b** Complete occlusion of the vein lumen by fibrous tissue, leaving only narrow capillary channels *(C)*; a small interruption of the IEM *(arrow)* is also evident; Shikata, × 200

Table 2. Comparison between the veins treated with 1% HPD, 1% STS, and saline, by i.v. and i.v. + p.v. injection. The number of veins with at least 80% of occlusion of the lumen in transverse sections are reported

Time after injection	1% HPD i.v.		1% STS i.v.		Saline i.v.	
	No. occluded veins	Total injected veins	No. occluded veins	Total injected veins	No. occluded veins	Total injected veins
48 h	7	10	7	10	—	5
7 days	6	10	4	10	—	5
30 days	7	10	9[b]	10	—	5

Time after injection	1% HPD i.v. + p.v.		1% STS i.v. + p.v.		Saline i.v. + p.v.	
	No. occluded veins	Total injected veins	No. occluded veins	Total injected veins	No. occluded veins	Total injected veins
48 h	8[a]	10	9[b]	10	—	5
7 days	9[b]	10	7	10	—	5
30 days	3	10	8[a]	10	—	5

Comparison between the total number of injected veins and the number of occluded veins gave: [a] $P < 0.05$, [b] $P < 0.01$ (χ^2 test). No differences between HPD i.v. and STS i.v., and between HPD i.v. + p.v. and STS i.v. + p.v. (non-parametric Wilcoxon test)

Table 3. Comparison between the mean percentages of occlusion of the vein lumen in cross-sectional areas, after i.v. and i.v. + p.v. injection of 1% HPD, 1% STS, and saline. The number of sections examined is reported

Time after injection	No. of sections	1% HPD i.v. (%)	No. of sections	1% STS i.v. (%)	No. of sections	Saline i.v. (%)
48 h	23	60 ± 37.9	20	61.4 ± 35.5	10	—
7 days	20	71.6 ± 44	22	47 ± 27.7[a]	10	—
30 days	21	62.9 ± 32.5	20	65 ± 26.7	9	—

Time after injection	No. of sections	1% HPD i.v. + p.v. (%)	No. of sections	1% STS i.v. + p.v. (%)	No. of sections	Saline i.v. + p.v. (%)
48 h	20	85 ± 23.3	22	82.2 ± 22.8	11	8.3 ± 4.5
7 days	20	84 ± 17.2	20	84.3 ± 26.3[a]	10	—
30 days	22	73.3 ± 46.2	20	83.1 ± 35.5	10	—

Comparison between the percentages of occlusion of the injected veins at different times: [a] STS i.v. vs STS i.v. + p.v. $P < 0.05$ (non-parametric Wilcoxon test)

Table 4. Comparison between the mean percentages of occlusion of the vein lumen in consecutive transverse sections (length of the thrombus), after i.v. and i.v. + p.v. injection of 1% HPD, 1% STS, and saline. The number of sections examined is reported

Time after injection	No. of sections	1% HPD i.v. (%)	No. of sections	1% STS i.v. (%)	No. of sections	Saline i.v. (%)
48 h	163	42.1 ± 17.3[a]	185	50.7 ± 30.5[c]	87	—
7 days	198	53 ± 23.1	180	38.6 ± 10.5[d]	100	—
30 days	190	46 ± 18.3	198	45.4 ± 17.1	96	—

Time after injection	No. of sections	1% HPD i.v. + p.v. (%)	No. of sections	1% STS i.v. + p.v. (%)	No. of sections	Saline i.v. + p.v. (%)
48 h	190	58.1 ± 26.9[b]	190	81.6 ± 26[b,c]	90	26.4 ± 12
7 days	200	48.5 ± 16.6[e]	189	70 ± 19.9[d,e]	89	—
30 days	198	55 ± 19	196	49.5 ± 17.6	96	—

Comparison between the total number of injected veins and the number of occluded veins gave: [a] $P < 0.05$, [b] $P < 0.01$ (χ^2 test). No differences between HPD i.v. and STS i.v., and between HPD i.v. + p.v. and STS i.v. + p.v. (*non-parametric* Wilcoxon test)

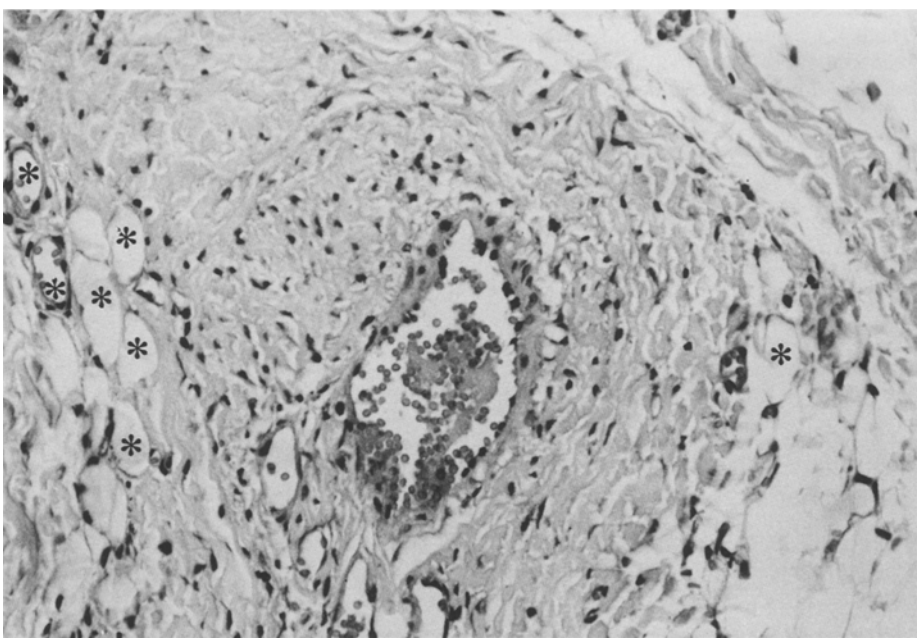

Fig. 3. Rat femoral vein 30 days after i.v. + p.v. injection of 1% HPD. The center of the thrombus is occupied by a patent channel. Fibrosis is present both inside and outside of the original vein wall. There are a number of dilated perivenous capillaries (✻); HE × 300

Table 5. Morphological findings in the muscle tissue after i.v. and i.v. + p.v. injection of 1% STS and 1% HPD

Case	Time after sclerosis	1% STS i.v.		1% STS i.v. + p.v.	
1	48 h	–		++	(phlogosis and necrosis)
2	48 h	–		++	(phlogosis and necrosis)
3	48 h	–		++	(phlogosis and necrosis)
4	48 h	–		+++	(phlogosis and necrosis)
5	48 h	–		++	(phlogosis and necrosis)
6	48 h	+	(phlogosis)	++	(phlogosis and necrosis)
7	48 h	–		++	(phlogosis and necrosis)
8	48 h	–		±	
9	48 h	–		+++	(phlogosis)
10	48 h	++	(phlogosis)	++	(phlogosis)
1	7 days	–		±	
2	7 days	–		++	(phlogosis and necrosis)
3	7 days	–		+++	(phlogosis and necrosis)
4	7 days	–		+	(phlogosis and necrosis)
5	7 days	–		±	
6	7 days	–		+++	(phlogosis)
7	7 days	–		+++	(phlogosis)
8	7 days	–		+++	(phlogosis and necrosis)
9	7 days	–		++	(phlogosis and necrosis)
10	7 days	–		++	(phlogosis and necrosis)
Case	Time after sclerosis	1% HPD i.v.		1% HPD i.v. + p.v.	
1	48 h	–		++	(phlogosis)
2	48 h	–		+++	(phlogosis)
3	48 h	+	(phlogosis)	++	(phlogosis)
4	48 h	–		+	(phlogosis)
5	48 h	–		±	
6	48 h	–		++	(phlogosis and necrosis)
7	48 h	–		++	(phlogosis and necrosis)
8	48 h	+	(phlogosis)	++	(phlogosis and necrosis)
9	48 h	–		+	(phlogosis and necrosis)
10	48 h	–		++	(phlogosis)
1	7 days	–		++	(phlogosis and necrosis)
2	7 days	–		++	(phlogosis and necrosis)
3	7 days	–		+++	(phlogosis and necrosis)
4	7 days	–		+++	(phlogosis)
5	7 days	–		±	
6	7 days	–		++	(phlogosis)
7	7 days	–		++	(phlogosis)
8	7 days	+	(phlogosis)	++	(phlogosis)
9	7 days	–		++	(phlogosis)
10	7 days	–		±	

STS and HPD at 7 days ($P < 0.05$; Table 4). Perivenous fibrosis was present in 100% of the animals at 7 and 30 days, with no difference between STS and HPD, and the two techniques of injection. On the contrary, 100% of the veins showed signs of perivenous inflammation at 48 h, and resolution of phlogistic infiltration at 30 days. Nerve lesions were present in five of ten veins treated by HPD, and in four of ten veins treated with STS, after 48 h from i.v. + p.v. injection. Segmental arterial wall damage was present in five of ten veins treated with HPD, and in six of ten veins treated by STS, after 48 h from i.v. + p.v. injection. Damage of the IEM was present after i.v. + p.v. injection of STS at 48 h and 7 days ($\chi^2 = 3.60$; $p < 0.05$). However, short interruption or doubling of the IEM were present in six of ten veins treated by HPD and in six of ten veins treated with STS, after 7 and 30 days from i.v. injection. After i.v. + p.v. injections we could notice the presence of dilated perivenous capillaries in 100% of the veins treated by HPD, and in eight of ten veins treated with STS, at 7 days. The presence of a large amount of dilated perivenous capillaries persisted in 50% of the veins injected i.v. + p.v. after 30 days (Fig. 3). I.v. + p.v. injection of STS and HPD resulted in severe necrosis of the muscle with massive infiltration of polymorphs in almost all the animals examined after 48 h and 7 days (Table 5).

I.v. injection of saline resulted in moderate signs of perivenous edema at 48 h, and at 7 and 30 days the veins appeared completely normal. The i.v. + p.v. injection of saline produced marked signs of perivenous edema and inflammation at 48 h, and three of five veins appeared partially occluded by thrombosis. After 7 days, only a low grade of perivenous inflammation was seen, without signs of vein occlusion, and after 30 days all the injected veins resulted completely normal (Tables 2–4).

Discussion

In spite of diversity of the used techniques, the endoscopic sclerotherapy has shown to be effective in arresting variceal bleeding. The type of sclerosant and the selection of the injection site, i.e., intra-, para-, intraparavariceal, are under discussion [7, 9]. It is generally assumed that the injected sclerosant induces a damage of the venous endothelium leading to thrombosis. However, this is probably not the only mechanism whereby bleeding is controlled, since paravariceal injection is just as effective as intravariceal [18, 20]. Paravariceal sclerotherapy was introduced as prophylactic treatment to reduce the esophageal variceal hemorrhage [21]. By this way of injection, the varices themselves are not sclerosed to preserve their portal decompression function [20, 21]. Besides simultaneous paravariceal and intravariceal injections showed to be an efficacious method to reduce bleeding from the esophageal varices [29].

In our study, we compared the effects of two sclerosants, STS and HPD, by i.v. and i.v. + p.v. injection into the rat femoral vein to evaluate the differences between the two agents and the two techniques of injection. I.v. + p.v. injection of both sclerosants resulted more efficacious in producing vein occlusion. Fur-

thermore, STS was found to be much better than HPD when given by i.v. Apparently, there was no difference in producing inflammation and fibrosis of the vein wall between the two agents at different time, and the only morphological difference was the damage to IEM after STS injection. This is partly in discordance with similar experimental work in rat, that demonstrated only a more marked capacity of STS to produce ulceration after intradermal or subcutaneous injection in comparison with HPD [5].

The perivenous inflammation and subsequent fibrosis were similar after i.v. and i.v. + p.v. in spite of the more pronounced thrombosis after i.v. + p.v. injection. This could be explained partly by extravasation of the sclerosing agents after i.v. injection [2, 23]. After i.v. injection, the loss of endothelium probably results in a diffusion of sclerosant to the surrounding tissue and may thereby provoke changes as in the i.v. + p.v. injection [16, 24]. On the other hand, studies in the rat femoral vein showed that p.v. injection of STS caused only a little occlusion of the lumen, whereas i.v. injection produced a marked or complete occlusion [4]. We could see that the association of p.v. to i.v. injection potentiated the thrombogenic effect of both sclerosants. The mechanism by which p.v. injection can share to thrombogenic occlusion remains unclear, since it is well known that the destruction of the endothelium and the contact between blood and intimal collagen fibrin starts the mechanism of thrombus production [19]. Our results also confirmed that not only varicose, but also healthy veins, can be occluded be exposure to sclerosants, depending on the entity of the vein wall damage [4].

We like others could see a severe damage to the surrounding nervous and muscular tissue after i.v. + p.v. injection [26]. Particularly, we recorded a marked infiltration of polymorphs and necrosis in the muscle and arterial wall after 48 h and 7 days. Extrapolating our experimental findings in rat to the human variceal sclerotherapy, we believe that paravariceal injection can lead to dangerous esophageal wall damage, with the possibility of ulceration and hemorrhage. These severe complications can affect the patients even when the endoscopist believe the injection to be intravariceal, by extravasation of sclerosant [23–25].

In conclusion, our work demonstrated a marked thrombogenic effect of the combined i.v. and p.v. injections. However, i.v. + p.v. injection lead to severe inflammation and necrosis of the surrounding tissues and to a marked fibrosis. Severe inflammatory reaction and sometimes focal necrosis of the smooth muscle in the esophageal wall after paravariceal sclerotherapy has been indicated as a dangerous effect of this treatment [14, 27, 29]. Our study confirmed the observations on the side effects of paravariceal and intraparavariceal injections of sclerosants in man, and lead us to conclude that careful evaluation of the sclerosing technique and its histopathologic consequences is needed before performing an endoscopic treatment.

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