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Case Series: Management of Adult Onset Cervical Lymphangioma by Sclerotherapy with Polidocanol (hydroxypolyathoxydodecan).

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Abstract -
Introduction
Lymphangiomas are uncommon congenital malformations usually present in children and are rare in adults. These malformations of the lymphatic system consist of cysts of varying size. Although benign, they can lead to compression and infiltration of adjacent structures. Surgical excision has been the mainstay of treatment, although total excision of the lymphangioma can be a major challenge and may be associated with complications.
Therefore, a variety of nonsurgical methods have been proposed to reduce the surgical morbidity and to decrease the recurrence rate. Percutaneous sclerotherapy of lymphangioma involves the injection of sclerosing substances into the lymphangioma cysts. In the past, different sclerosants and sclerosant techniques have been developed. However Polidocanol has never been used for lymphangioma, although a few articles have been published in which polidocanol has been used for treatment of haemangioma.
Materials and Methods
Being a rare congenital malformation, we were fortunate to see five cases of adult lymphangioma in last three years. All the five cases of cervical lymphangioma were treated with polidocanol, a sclerosant, followed by application of pressure bandage for two weeks. The patients were followed up at monthly intervals for six months.
Results
Lymphangioma subsided completely after a fortnight without any significant adverse reactions.
Conclusion
From our study we concluded that lymphangiomas can subside completely by administration of the sclerosing agent Polidocanol, thereby decreasing the need for a surgical intervention. Also it proved to be a cost effective procedure avoiding the need for sedation and the risk of post-operative complications.
Lymphangiomas have been treated with sclerotherapy as first line treatment, often with satisfying results. Polidocanol has not been studied extensively in Lymphangiomas. Further studies are required to assess the utility of Polidocanol as a sclerosant in lymphangiomas and also to evaluate its long term results.
Keywords: *Cystic hygroma Lymphangioma Sclerotherapy Polidocanol*

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I. Introduction:

Lymphangioma also referred to as Cystic Hygroma is an aberrant proliferation of lymphatic vessels resulting from abnormal development of the lymphatic system[1,2],about 60% of which present at birth and 80-90% manifest by the age of 2 years[3].They are usually congenital malformations seen in children, however rarely presenting in adults. Lymphangiomas have been classified into 3 groups (A) lymphangioma simplex composed of capillary sized thin walled lymphatic channels, (B) cavernous lymphangioma and (C) cystic lymphangioma/hygroma composed of cysts of few mm to several cm in diameter[4], although different varieties frequently coexist. They can also be classified into septate (multiloculated) or non-septate single cavity (non-loculated). Presentation of lymphangioma in adulthood is rare and the cause is uncertain, although trauma and upper respiratory tract infection have both been suggested as possible triggers for onset[5,6]. In our cases, there was no identifiable cause and onset was insidious and progress gradual. Most commonly these malformations occur in the head and neck region, although they have been described in a variety of other anatomical locations. Surgical excision has been the traditional modality of treatment, however the presence of important structures in

the vicinity of the lymphangioma and infiltration into the surrounding tissue planes makes the dissection difficult[3,7] leading to a high recurrence rate. Therefore, there is a search for effective and safe alternative methods of treatment. To date there have been fewer than 150 reports of adult cervicofacial lymphangiomas in literature and the optimum management of these lesions is still a matter of debate. We present 5 cases of lymphangioma in adults treated successfully by percutaneous sclerotherapy with polidocanol.

Figure 1: Adult Cervical Lymphangioma

II. Review of literature:

Several sclerosants have been used for conservative management of venous & lymphatic malformations. The table (Table 1) below summarizes the different types of sclerosing agents in use.

Table 1: Types of Sclerosing Agents with their Mechanism Of Action

Detergents (Disrupt vein cellular membrane)	
-	Sodium tetradecyl Sulfate
-	Polidocanol
-	Sodium Morrhuate
-	Ethanolamine Oleate
Osmotic Agents (Damage the cell by shifting the water balance)	
-	Hypertonic sodium chloride solution
-	Sodium Chloride Solution with dextrose
Chemical Irritants (Damage the Cell wall)	
-	Chromated Glycerin
-	Polyiodinated iodine
-	Alcoholic solution of zein
-	OK 432
-	Bleomycin

The choice of the sclerosant depends on the availability and experience of the treating physician.

Various sclerosants in use are as follows :

1. Polidocanol(hydroxypolyathoxydodecan).-Has not been studied extensively in lymphangiomas. Use in lymphangioma has been reported only in a single study by Jain et al.[8]

Clinical Pharmacology-

- Polidocanol (hydroxypolyathoxydodecan) is a non ionic detergent, consisting of two components, a polar hydrophilic (dodecyl alcohol) and an apolar hydrophobic (polyethylene oxide) chain.
- Polidocanol has the following structural formula:
  $C_{12}H_{25}(OCH_2CH_2)_nOH$ Polyethylene glycol monododecyl ether
- Mean extent of polymerization (n): Approximately 9
- Mean molecular weight: Approximately

Mechanism of Action (for venous malformations)

- Polidocanol is a sclerosing agent that locally damages the endothelium of blood vessels. When injected intravenously, polidocanol induces endothelial damage. Platelets then aggregate at the site of damage

and attach to the venous wall. Eventually, a dense network of platelets, cellular debris, and fibrin occludes the vessel. Finally, the occluded vein is replaced with fibrous tissue[9].

- Due to its anesthetic effect, the injection is almost painless.

Pharmacodynamics –

- The damaging effect on the endothelium of blood vessels of polidocanol is dependent on concentration and volume.

Pharmacokinetics-

- 12 hours after intravenous injection, about 90% of the polidocanol administered will have been eliminated from the blood. In a study, the following values were determined after a single intravenous dose: protein binding 64%, terminal elimination half-life 4 hours, volume distribution 24.5l, total clearance 11.7l/hr, renal clearance 2.43l/hr and biliary clearance 3.14l/hr[9].

Indications and Usage-

- Polidocanol is indicated to sclerose varices, venectasias (spider veins), heamorrhoids, anal fissures, haemangiomas and lymphangiomas.

Dosage and administration- dose should not exceed 2mg/kg body weight per day.

Adverse effects-

- Accidental intra-arterial injection can cause severe necrosis, ischemia or gangrene.
- Anaphylaxis -Severe allergic reactions have been reported following polidocanol use, including anaphylactic reactions, some of them fatal. Severe reactions are more frequent with use of larger volumes (greater than 3 ml)[9]. Therefore, care should be taken in intravenous needle placement and the smallest effective volume at each injection site should be used. The dose should not be exceeded.

2. OK- 432- In 1986, Ogita et al[10] treated a lymphangioma through intralesional injection of OK-432 for the first time. Since the first description of OK-432 many reports have focused on the use of OK-432 as first-line treatment for lymphangiomas[11]. Surgical excision is considered not to be more difficult after OK-432 therapy.[12]
3. Doxycycline- The efficiency of this broad spectrum antibiotic in lymphangioma therapy was demonstrated by Molitch et al[13] for the first time. Cordes et al[14] also demonstrated marked regression of lymphangiomas after percutaneous injection of doxycycline. Burrows et al[15] stated that Doxycycline seems to be more effective in the treatment of microcystic lymphangiomas than OK-432.This was also endorsed by Shiels et al[16].
4. Ethanol- This is widely available, cheap and has powerful sclerosing properties. However Alomari et al[17] demonstrated that ethanol sclerotherapy leads to more complications than therapy with other sclerosants.
5. Bleomycin- Its usefulness in lymphangioma therapy was first analyzed in 1977 by Yura et al.[18]Zhong et al[19] reported successful treatment in 97% of cases without serious complications. The serious complications of bleomycin which are dose dependent are pulmonary fibrosis and interstitial pneumonia.
6. Ethibloc- Ethibloc consists of an alcohol (60%) solution of zein (corn-protein) and is a biodegradable and thrombogenic agent. Emran et al[20] found satisfactory results after Ethibloc sclerotherapy in 84% of macrocystic and 77% of mixed lymphangiomas. Baud et al[21] found Ethibloc particularly appropriate for the treatment of large lymphangiomas.

Table 2: Dose, Action and Adverse Effects of Sclerosing Agents

Sclerosing agent	Dose	Mechanism	Complications/Adverse effects
Polidoconol (Aethoxysclerol)	1ml for each cm of the diameter of the lesion[8]	Vascular injury by altering the surface tension around endothelial cells	Erythema, Induration around the skin
Sotradecol 3% (Sodium Tetradecyl Sulfate)	2ml[22]	Vascular injury by altering the surface tension around endothelial cells	Inflammatory reaction, swelling, edema, mild allergic reaction, chronic facial pain.
Sodium Morrhuate 5% (Scleromate)	0.1ml[23]	Vascular injury by altering the surface tension around endothelial cells	Pain, haemorrage , keratopathy
Acetic acid acid 40% to 50%	4.6% to 50% of the suctioned volume[24]	Dessicating action on proteins by inducing coagulation necrosis.	Pain, Tingling sensations
Fibrin sealant (Tissucol)	10% to 50% of the suctioned volume[25]	Adhesive that seals tissue surfaces; Local hemostatic	Itching and erythema
O K -432 (Picibanil)	0.01mg/ml. Max 20ml[26-28]	Cellular and Cytokine Mediated production of cytokines related to sclerotic changes; Direct cytotoxic effects.	Swelling, erythema, pain and fever

Bleomycin	1mg/ml; max 15-20mg 0.25-0.6mg/kg Body weight[28-33]	Injury and detachment of endothelial cells, lumen narrowing and occlusion, inflammation	Flu-like symptoms, erythema, edema, pigmentation of the skin, transient hair loss, pulmonary toxicity.
Ethibloc (Alcoholic Solution of Zein)	1-20ml not exceeding 15% of the lesion capacity[20-22]	Intravascular thrombosis, necrosis and fibrotic reaction	Scars, erythema, edema, pain fever, aesthetic defects
Doxycycline	5-20mg/ml Max 20-100ml 100% of the suctioned volume[10,13-15,3]	Inflammatory process leading to fibrosis and involution of the cysts, inhibition of matrix-metalloproteinases.	Pain on injection, erythema, edema and dental staining
Absolute Ethanol	0.5-1mg/ml Max 1ml/kg body weight[35,36]	Endothelial damage, thrombosis of vessels, sclerotic reaction.	Nerve injuries, ischemia, skin necrosis, hypotension, respiratory depression, cardiac arrhythmia.
Ethanolamine Oleate 5% (Ethamolin)	1.5-5ml Max 20ml	Vascular Injury by altering the surface tension around endothelial cells	Allergic reactions: Anaphylaxis, urticaria

Materials and Methods -

We conducted a study to observe the effect of polidocanol on adult onset lymphangioma. As it is a rare congenital disease, we were fortunate to have 5 patients referred from different centres, who were willing to undergo treatment with polidocanol as an alternative to surgical excision.

All the 5 patients referred to us were male and in the age group of 15-28 years.
A complete history was taken and proper clinical examination was done noting down the site, size, shape, colour, presence of any pulsations, temperature and tenderness, margins of the swelling, consistency, reducibility, fluctuation test, transillumination test, fixity to skin.
All patients were then investigated. Routine Blood tests, Ultrasound Neck and Fine needle aspiration cytology were done to make a confirmation of the diagnosis and also to rule out any involvement of the adjacent structures.

Method
Informed consent of all the 5 patients was taken prior to the procedure along with ethical clearance from the institute.
All five patients underwent treatment with polidocanol, a sclerosing agent. Under aseptic precautions using 18 Gauge needle, cystic fluid was aspirated percutaneously. In two cases ultrasound guided aspiration was done as it was close to vessels of the neck. Then 2ml of polidocanol was injected intralesionally at the same site without removing the needle. Pressure bandage was applied, which was removed after 2 weeks and patient was followed at monthly intervals for 6 months for any adverse reactions and recurrence.
The amount of fluid aspirated was noted and the fluid was also sent for examination.

Result
In all 5 patients swelling completely subsided after a fortnight without any significant immediate/delayed local or systemic adverse reactions. Ultrasound scan done 2 months after sclerosant treatment also confirmed the same.

Table 3: Clinical Examination Details

	Site in neck	Size cm x cm	Temp	Tenderness	Consistency	Fluctuation test	Transillumination test	Fixity to skin
Patient 1.	RPT	7x5	Not raised	Absent	Soft	Positive	Positive	Present
Patient 2	LPT	6x4	Not raised	Absent	Soft	Positive	Positive	Present
Patient 3	RAT	4X3	Not raised	Absent	Soft	Positive	Positive	Present
Patient 4	LPT	5X4	Not	Absent	Soft	Positive	Positive	Present

			raised					
Patient 5	LAT	4X4	Not raised	Absent	Soft	Positive	Positive	Present

RPT: Right post triangle. LPT: Left post triangle. RAT: Right ant triangle. LAT: Left ant triangle

Figure 2: Before Injecting with Polidocanol

Figure 3: After Injecting with Polidocanol

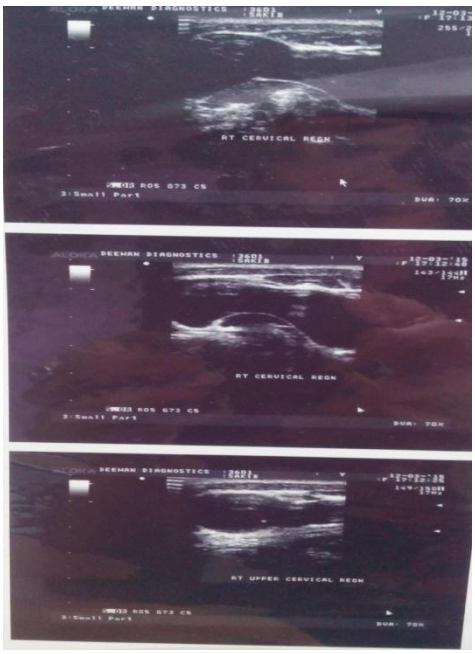

Figure 4: Ultrasound Images of Lymphangioma

III. Discussion

Lymphangiomas are congenital malformations of the lymphatic system that consist of cysts of varying size. Although they are benign, they can undergo progressive growth with compression and infiltration of adjacent structures. Surgical excision has been the cornerstone of treatment, although total excision of the lymphangioma can be a major challenge and may be associated with complications. Therefore, a variety of nonsurgical methods have been proposed to reduce the surgical morbidity and to decrease the recurrence rate. Percutaneous sclerotherapy is the injection of a chemical solution (sclerosant) into a vein or lymphangioma cyst, which damages the endothelial lining and causes vessel occlusion and the development of fibrous tissue. To achieve a satisfying result it is necessary to attain maximal contact of sclerosant with cystic endothelium while minimizing extravasation into surrounding tissue. Sclerotherapy is an established procedure for the treatment of varicose veins, low-flow vascular malformations, symptomatic hemangiomas, benign vascular tumors and telangiectasias.

Polidocanol (POL) and sodium tetradecyl sulfate (STS) have a very low incidence of allergic

reactions, produce a low incidence of pigmentation and other adverse cutaneous effects and fewer complications if extravasated[37]. Other agents, including sodium morrhuate, ethanolamine oleate, OK-432 (picibanil), bleomycin and intravenous doxycycline, have been used as sclerosing agents, predominantly for venous malformations[38]. Hypertonic saline (20% or 23.4% solution) was previously popular for sclerosis of telangiectatic leg veins, but it causes pain and burning and, almost invariably, causes significant necrosis if extravasated[38].Another sclerosant, 72% chromatedglycerin[39](Scleremo) is very popular in Europe for the treatment of small vessels.

In the past, different sclerosants and sclerosant techniques have been developed. Although several sclerosants have been used in the treatment of lymphangiomas, the relative advantages of one over the other are unclear. Sclerotherapy has not been widely practiced in India as yet. This being a conservative and simple procedure, reduces the cost and morbidity associated with surgery.

IV. Conclusion

From our study we concluded that lymphangioma subsided completely by injecting Polidocanol intralesionally, thereby decreasing the need for a surgical intervention. Also it proved to be a cost effective procedure avoiding the need for sedation and postoperative complications.

The management of lymphangiomas remains challenging. Till date many patients with lymphangiomas have been treated with sclerotherapy as first line treatment, often with satisfying results. Added advantage is that sclerotherapy makes subsequent surgical excision easier by reducing the size of the lesion. The advantages of one sclerosant over another are still unclear. The optimal sclerosing agent is one that induces panendothelial destruction and possesses no systemic toxicity. Sclerotherapy is mainly recommended for macrocystic lymphangiomas and requires careful planning with multiple sittings. However, our present study has a relatively low sample size, so further studies using larger sample size are required to be conducted to assess the utility of polidocanol on lymphangiomas and also to evaluate long term results.

References :

[1]. Bloom DC, Perkins JA, Manning SC. Management of lymphatic malformations. CurrOpinOtolaryngol Head Neck Surg 2004; 12: 500–4. PMid:15548907.

[2]. Naidu SI, McCalla MR. Lymphatic malformations of the head and neck in adults: a case report and review of the literature. Ann OtolRhinolLaryngol 2004; 113: 218–22.PMid:15053205.

[3]. Okada A, Kubota A, Fukuzawa M, et al. Injection of Bleomycin as a primary therapy ofcysticlymphangioma. J PediatrSurg 1992,27:440-443.

[4]. Tanigawa N, Shimomatsuya T, Takahashi K, et al. Treatment of cystic hygroma andlymphangioma with the use of bleomycin fat emulsion.Cancer 1987, 60:741:749.

[5]. Schefter RP, Olsen KD, Gaffey TA. Cervical lymphangioma in the adult. Otolaryngol Head Neck Surg1985; 93: 65–69. PMid:3920626.

[6]. Antoniades K, Kiziridou A, Psimopoulou M. Traumatic cervical cystic hygroma. Int J Oral Maxillofacial Surg2000; 29: 47–8. doi:10.1034/j.1399-0020.2000.290111.x.

[7]. Orford J, Barker A, Thonell S, et al. Bleomycin therapy for cystic hygroma. J PediatrSurg 1995, 30:1282-1287

[8]. Jain R, Bandhu S, Sawhney S, Mittal R. Sonographically guided percutaneous sclerosis using 1% polidocanol in the treatment of vascular malformations. J Clin Ultrasound 2002;30:416–423

[9]. Merz Aesthetics, Inc. Asclera (polidocanol) injection for intravenous use prescribing information. Franksville, WI; 2010 Mar.

[10]. Ogita S, Tsuto T, Tokiwa K, Takahashi T. Intracystic injection of OK-432: a new sclerosing therapy for cystic hygroma in children. Br J Surg 1987;74:690–691.

[11]. Eivazi B, Ardelean M, Ba¨umler W, et al. Update on hemangiomas and vascular malformations of the head and neck. Eur Arch Otorhinolaryngol 2009;266:187–197

[12]. Luzzatto C, Midrio P, Tchaprassian Z, Guglielmi M. Sclerosing treatment of lymphangiomas with OK-432. Arch Dis Child 2000;82:316–318.

[13]. Molitch HI, Unger EC, Witte CL, vanSonnenberg E. Percutaneous sclerotherapy of lymphangiomas. Radiology 1995;194:343–347

[14]. Cordes BM, Seidel FG, Sulek M, Giannoni CM, Friedman EM. Doxycycline sclerotherapy as the primary treatment for head and neck lymphatic malformations. Otolaryngol Head Neck Surg2007;137:962–964

[15]. Burrows PE, Mitri RK, Alomari A, et al. Percutaneous sclerotherapy of lymphatic malformations with doxycycline. Lymphat Res Biol 2008;6:209–216.

[16]. Shiels WE II, Kang DR, Murakami JW, Hogan MJ, Wiet GJ. Percutaneous treatment of lymphatic malformations. Otolaryngol Head Neck Surg 2009;141:219–224.

[17]. Alomari AI, Karian VE, Lord DJ, Padua HM, Burrows PE. Percutaneous sclerotherapy for lymphatic malformations: a retrospective analysis of patient-evaluated improvement.J VascIntervRadiol 2006;17:1639–1648

[18]. Yura J, Hashimoto T, Tsuruga N, Shibata K. Bleomycin treatment for cystic hygroma in children. Nippon Geka Hokan 1977;46:607–614.

[19]. Zhong PQ, Zhi FX, Li R, Xue JL, Shu GY. Long-term results of intratumorous bleomycin-A5 injection of head and neck lymphangioma.OralSurg Oral Med Oral Pathol Oral RadiolEndod 1998;86:139–144.

[20]. Emran MA, Dubois J, Laberge L, Al-Jazaeri A, Bu¨ tter A, Yazbeck S. Alcoholic solution of zein (Ethibloc) sclerotherapy for treatment of lymphangiomas in children. J PediatrSurg 2006;41:975–979.

[21]. Baud AV, Breton P, Guibaud L, Freidel M. Treatment of low-pressure vascular malformations by injection of Ethibloc. Study of 19

cases and analysis of complications. [Article in French] Rev StomatolChirMaxillofac 2000;101:181–188.
[22]. PoonyathalangA, PreechawatP, JiarakongmunP, Pongpech S. Sclerosing therapy for orbital lymphangioma using sodium tetradecyl sulfate. Jpn J Ophthalmol 2008;52:298–304
[23]. Schwarcz RM, Ben Simon GJ, Cook T, Goldberg RA. Sclerosing therapy as first line treatment for low flow vascular lesions of the orbit. Am J Opthalmol 2006;141:333–339
[24]. Won JH, Kim BM, Kim CH, Park SW, Kim MD. Percutaneous sclerotherapy of lymphangiomas with acetic acid. J VascIntervRadiol 2004;15:595–600.
[25]. Castanon M, Margarit J, Carrasco R, Vancells M, Albert A, Morales L. Long-term follow-up of nineteen cystic lymphangiomas treated with fibrin sealant. J PediatrSurg 1999;34:1276–1279.
[26]. Larrane J, Keski-Nisula L, Rautio R, Rautiainen M, Airaksinen M. OK-432 (Picibanil) therapy for lymphangiomas in children. Eur Arch Otorhinolaryngol 2002;259:274–278.
[27]. Gigue`re CM, Bauman NM, Sato Y, et al. Treatment of lymphangiomas with OK-432 (Picibanil) sclerotherapy: a prospective multi-institutional trial. Arch Otolaryngol Head Neck Surg2002;128:1137–1144.
[28]. Okazaki T, Iwatani S, Yanai T, et al. Treatment of lymphangioma in children: our experience of 128 cases. J PediatrSurg 2007;42:386–389.
[29]. Orford J, Barker A, Thonell S, King P, Murphy J. Bleomycin therapy for cystic hygroma. J PediatrSurg 1995;30:1282–1287.
[30]. Baskin D, Tander B, Bankaoglu M. Local bleomycin injection in the treatment of lymphangioma. Eur J PediatrSurg 2005;15:383–386.
[31]. Sanlialp I, Karnak I, Tanyel FC, Senocak ME, Bu¨yu¨ kpamukc ¸u N. Sclerotherapy for lymphangioma in children. Int J PediatrOtorhinolaryngol 2003;67:795–800
[32]. StringelG.Hemangiomas and lymphangiomas. In: Ashcraft KW, editor. Pediatric Surgery. 3rd edition. Philadelphia, London, New York, St. Louis, Sydney, Toronto: W.B. Saunders Company; 2000. pp 965–986.
[33]. Zulfiqar MA, Zaleha AM, Zakaria Z, Amin T. The treatment of neck lymphangioma with intralesional injection of bleomycin. Med J Malaysia 1999;54:478–481..
[34]. Nehra D, Jacobson L, Barnes P, Mallory B, Albanese CT, Sylvester KG. Doxycycline sclerotherapy as primary treatment of head and neck lymphatic malformations inchildren. J PediatrSurg 2008;43:451–460.
[35]. Puig S, Aref H, Brunelle F. Double-needle sclerotherapy of lymphangiomas and venous angiomas in children: a simple technique to prevent complications. AJR Am J Roentgenol 2003;180:1399–1401.
[36]. Mason KP, Michna E, Zurakowski D, Koka BV, Burrows PE. Serum ethanol levels in children and adults after ethanol embolisation or sclerotherapy for vascular anomalies. Radiology 2000;217:127–132.
[37]. Lee AJ, Evans CJ, Allan PL, Ruckley CV, Fowkes FG. Lifestyle factors and the risk of varicose veins: Edinburgh Vein Study. J ClinEpidemiol 2003;56:171-9.
[38]. Feied CF. Sclerosing solutions. In: Fronek H, Editor. The fundamentals of phlebology, venous disease for clinicians. 2nd ed. USA: American College of Phlebology Publishing 207 Ch.5. p23
[39]. Kern P, Ramelet AA, Wutschert R, Bounameaux H, Hayoz D. Single-blind, randomized study comparing chromated glycerin, polidocanol solution, and polidocanol foam for treatment of telangiectatic leg veins. DermatolSurg 2004;30:367-72