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Sclerotherapy for Venous Malformations of Head and Neck: Systematic Review and Meta-Analysis

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We performed a systematic review and meta-analysis of studies performing sclerotherapy for treatment of venous malformations (VMs) of the face, head and neck. It is our hope that data from this study could be used to better inform providers and patients regarding the benefits and risks of percutaneous sclerotherapy for treatment of face, head and neck VMs. We searched PubMed, MEDLINE, and EMBASE from 2000–2018 for studies evaluating the safety and efficacy of percutaneous sclerotherapy of neck, face and head VMs. Two independent reviewers selected studies and abstracted data. The primary outcomes were complete and partial resolution of the VM. Data were analyzed using random-effects meta-analysis. Thirty-seven studies reporting on 2,067 patients were included. The overall rate of complete cure following percutaneous sclerotherapy with any agent was 64.7% (95% confidence interval [CI], 57.4–72.0%). Sodium tetradecyl sulfate had the lowest complete cure rate at 55.5% (95% CI, 36.1–74.9%) while pingyangmycin had the highest cure rate at 82.9% (95% CI, 71.1–94.7%). Overall patient satisfaction rates were 91.0% (95% CI, 86.1–95.9%). Overall quality of life improvement was 78.9% (95% CI, 67.0–90.8%). Overall permanent morbidity/mortality was 0.8% (95% CI, 0.3–1.3%) with no cases of mortality. Our systematic review and meta-analysis of 37 studies and over 2,000 patients found that percutaneous sclerotherapy is a very safe and effective treatment modality for treatment of VMs of the head, neck and face.

Key Words: Venous malformations; Venous; Head and neck; Sclerotherapy

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INTRODUCTION

Venous malformations (VMs) are slow flow developmental anomalies of the veins which do not proliferate and normally do not involute.[1-37] These lesions can develop anywhere in the body, including structures of the face, head and neck. Due to the delicate interplay between aesthetics, function, and anatomy in this region, management of these lesions with any treatment modality can be challenging.

Over the past several decades, sclerotherapy with various agents has been demonstrated to be effective for face, head and neck VMs.[1,6,13,38-40] However, the evidence for treatment of these

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lesions is often based off of smaller case series which makes generalizing results to the greater population difficult. Furthermore, comparative studies examining the efficacy and safety of various sclerotherapy agents are few and far between. The goals of this systematic review and meta-analysis were to 1) understand the overall safety and efficacy rates of percutaneous sclerotherapy for treatment of VMs in the face, head and neck and 2) compare safety and efficacy rates of commonly used sclerotherapy agents. It is our hope that data from this study could be used to better inform providers and patients regarding the benefits and risks of percutaneous sclerotherapy for treatment of face, head and neck VMs.

MATERIALS AND METHODS

Literature search

The systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[37] A comprehensive literature search of the databases PubMed, Ovid MEDLINE, and Ovid EMBASE was designed and conducted by an experienced librarian with input from the authors. The search duration was 2 months. The key words "sclerotherapy," "vascular malformations," "venous malformations," "arteriovenous malformation," "hemangioma," "lymphatic malformation, "head," "neck," "facial," "oropharyngeal," and "orbital" were used in "AND" and "OR" combinations. The search was limited to articles published from 2000 to 2018. Inclusion criteria were the following: 1) English or Italian language, 2) case series reporting greater than 5 patients, 3) studies reporting image guided percutaneous sclerotherapy, 4) studies reporting exclusively face, head and neck VMs or subdividing outcomes and complications by anatomical region, and 5) studies classifying VMs appropriately using the International Society for the Study of Vascular Anomalies. Exclusion criteria were: 1) case series reporting fewer than 5 patients, 2) case reports, 3) vascular malformation not of the head and/or neck region (e.g., sclerotherapy for varicose veins in legs), and 4) studies not classifying lesions according to the International Society for the Study of Vascular Anomalies criteria. International Society for the Study of Vascular Anomalies criteria on imaging and clinical exam for VMs on imaging include 1) septated lobulated T2 hyperintense and T1 hypointense mass without mass effect, 2) phleboliths which are characteristically hypointense on T1/T2, 3) presence of fluid-fluid levels, 4) no flow voids on spin echo sequences, 5) the lesion infiltrates tissue planes, 6) no arterial or early venous enhancement, and 7) diffuse enhancement on delayed images.[41] On clinical exam, VMs appear as faint blue, soft and easily compressible non-pulsatile masses. The lesions characteristically enlarged with Valsalva maneuver and in dependent positions and decompress with local compression.

In studies with overlapping patient populations written by the same author/institution, we only included the largest or most complete dataset. In cases where outcomes were separated out by the type of sclerotherapy agent used, we abstracted outcomes separately for each agent in order to perform our subgroup analyses. Two authors determined inclusion and exclusion criteria for the studies in the literature search with differences resolved by the senior author.

Outcomes and data extraction

For each study, we extracted the following baseline information: number of patients, mean or median age and gender, number of malformations treated, location of malformations, sclerosing agent and its mean volume used, mean number of treatment sessions, and mean length of radiographic and clinical follow-up. The primary outcome of this study is the efficacy of sclerotherapy which includes complete cure of the vascular malformation (resolution of the VM on physical exam), partial cure of the vascular malformation (partial decrease in VM size), lack of benefit following sclerotherapy, improvement in quality of life (QoL), and patient satisfaction. Secondary outcomes are adverse events after sclerotherapy, including respiratory complications, skin necrosis/scars, any permanent morbidity/mortality, local temporary complications). Permanent morbidity and mortality were defined as mortality or any permanent neurological deficit. Local temporary complications included erythema, swelling, and pain.

For our subgroup analysis by sclerotherapy agent, we separated outcomes by agent. We were able to abstract data for the following individual agents: bleomycin, ethanol, sodium tetradecyl sulfate (STS), ethanolamine and pingamycin.

Study risk of bias

We modified the Newcastle-Ottawa Quality Assessment Scale to assess the methodologic quality of the studies included in this meta-analysis. This tool is designed for use in comparative studies; however, because the studies did not include a control group, we assessed study risk of bias

based on selected items from the tool, focusing on the following questions: 1) Did the study include all patients or consecutive patients versus a selected sample?, 2) Was the study retrospective or prospective?, 3) Was clinical follow-up satisfactory, thus allowing ascertainment of all outcomes?, 4) Were outcomes clearly reported?, and 5) Were there clearly defined inclusion and exclusion criteria?

Statistical analysis

We estimated from each cohort the cumulative prevalence and 95% confidence interval (CI) for each outcome. Event rates were pooled across studies with a random-effects meta-analysis. Heterogeneity across studies was evaluated using the I^2 statistic. An I^2 value of >50% suggests substantial heterogeneity. We also extracted a 2×2 table to calculate P values for the comparisons among the results. For the purpose of statistical comparisons we chose bleomycin sclerotherapy as the reference group, since it is the sclerosing agent most commonly used in the USA. Meta-regression was not used in this study. Statistical analyses were performed using OpenMeta[Analyst] (http://www.cebm.brown.edu/openmeta/; Biostat, Englewood, NJ, USA).

RESULTS

Literature search

The initial literature search yielded 1,211 articles. On review of the abstracts and titles, we excluded 1,126 articles. Eighty-five articles were selected for full-text screening, of which 37 met inclusion criteria.[1-37] The remaining 48 articles were excluded for reasons including 1) failure to separate outcomes by anatomic location (9 articles), 2) inclusion of lymphatic or venolymphatic malformations rather than pure VMs (14 articles), 3) use of confusing or unclear terminology making it difficult to ascertain whether lesions were VMs or hemangiomas (12 articles), and 4) mixture of VMs, AVMs and lymphatic malformations (13 articles). All studies included in the analysis had at least one or more outcome measure available for one or more of the patients groups analyzed. Fig. 1 shows the flow chart according to the PRISMA statement.[37]

These 37 studies included a total of 2,067 patients. The smallest study included 10 patients and the largest included 358 patients. Mean age was 24.9 years. There was a female predilection (1:1.2). The mean number of malformations per patient was 1.08 and they were all located in the head and/or neck region. The highest number of treated malformations per study was 358, while the least was 10. The mean number of treatment sessions per patient was 2.4. The mean length of radiographic and clinical follow-up from the time of the first treatment was 16.61 months and 18.04 months respectively.

Most included studies used a single sclerosing agent for each vascular malformation, while the remainder used a combination of them. Five studies reported outcomes of bleomycin sclerotherapy, 10 studies reported outcomes of ethanol sclerotherapy, 7 studies reported outcomes of STS sclerotherapy, 4 studies reported outcomes of ethanolamine

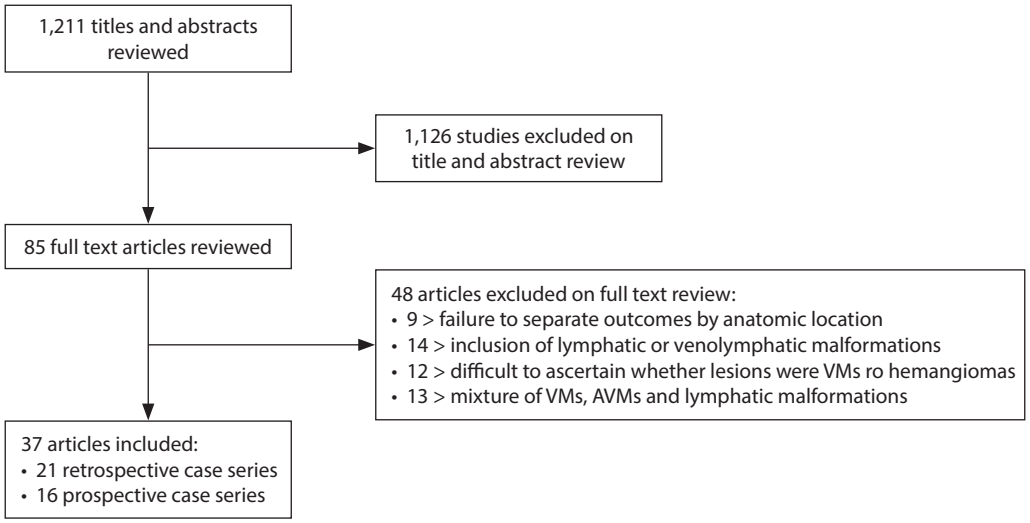

Fig. 1. PRISMA flow diagram. VMs, venous malformations; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Table 1. Summary of studies[1-37]

No.	Study	No. of patients	Mean/ median age (years)	M:F	No. of malformations treated	Location of malformations (if specific)	Sclerosing agent	Mean volume used (mL)	Mean No. of treatment sessions	Mean length of radiographic follow-up (months)	Mean length of clinical follow-up (months)
1	Akan et al.[1] (2017)	13	30	1:12	66	Oropharynx	Ethanol	6	1.8	NR	11
2	Alakailly et al.[2] (2015)	13	18.2	1:3.3	14	NR	STS	NR	1.4	9	9
3	Alexander et al.[3] (2016)	37	21.7	14:23	37	NR	STS, ethanolamine	NR	1.5	20.8	20.8
4	Baek et al.[4] (2011)	22	30.3	1:1.2	NR	NR	Ethanol	8.5	1.7	NR	13
5	Bajpai and Bajpai[5] (2012)	8	17	1:1	NR	NR	Bleomycin	NR	1.1	12	30
6	Bajpai and Bajpai[5] (2012)	8	15	1:1	NR	NR	STS	NR	5	NR	30
7	Bourgouin et al.[6] (2018)	33	43	1:1	46	Oropharynx	STS	NR	2.9	9	3
8	Castren et al.[7] (2016)	75	35.9	1:1.2	75	NR	STS, polidocanol, bleomycin, ethanol doxycyclin	NR	2	NR	18
9	Chen et al.[8] (2015)	11	36	1:1	NR	NR	NR	21	4		6
10	Chen et al.[9] (2010)	18	11.8	1:1.25	NR	Face, neck	OK-432 , PYM	NR	NR	NR	8.4
11	Chen et al.[10] (2008)	19	15	1:1	NR	Orbital	PYM	NR	NR	23	23
12	Choi et al.[11] (2002)	29	22	10:19	29	Cheek, lip, submandibular, temporalis muscle, scalp, parotid, orbit, oropharynx	Ethanolamine	NR	2	8.5	8.5
13	Colletti et al.[12] (2017)	69	34	NR	69	NR	STS	7.75	2.1	NR	NR
14	Costa et al.[13] (2011)	53	51.5	1:1.2	66	Oral, maxillofacial	Ethanolamine	NR	1		
15	Jia et al.[14] (2014)	33	23.8	15:18	33	Orbital, periorbital	PYM	NR	2	7.9	7.9
16	Kim et al.[15] (2004)	10	5.4	1:1.5	NR	NR	Bleomycin	NR	4.3	NR	NR
17	Kim et al.[15] (2004)	35	21	1:1	NR	NR	OK-432	8.5	1.8	NR	11
18	Kim et al.[15] (2004)	29	22	1:1.9	NR	NR	Ethanolamine	NR	NR	NR	NR
19	Kishi et al.[16] (2014)	23	32	1:1.5	35	NR	Ethanol	NR	NR		
20	Lamba et al.[17] (2012)	15	25	10:5	15	Face, neck	Ethanol	21	1.2	7.6	7.6
21	Lee et al.[18] (2009)	87	17.5	40:47	NR	NR	Ethanol	38	3.5	35	35
22	Li et al.[19] (2010)	20	17.14	10:10	21	Maxillofacial	PYM, Ethanol	18,9 (PYM), 12.5 (ethanol)	2.4	13.5	13.5

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Table 1. Continued

No.	Study	No. of patients	Mean/ median age (years)	M:F	No. of malformations treated	Location of malformations (if specific)	Sclerosing agent	Mean volume used (mL)	Mean No. of treatment sessions	Mean length of radiographic follow-up (months)	Mean length of clinical follow-up (months)
23	Liu et al.[20] (2009)	23	21	12:11	23	Cheek, parotid, infraorbital, scalp, chin, submandibular, oral	PYM, Ethanol	22 (PYM), 2.8 (ethanol)	2.5	2.5	20.3
24	Meng et al.[21] (2014)	43	20.5	26:17	43	Tongue, pharynx, parotid	PYM, Ethanol	NR	NR	24	24
25	Orlando et al.[22] (2014)	51	23	14:37	51	Face, tongue, neck, lip	Ethanol	2.5	7	18	18
26	Ribeiro et al.[23] (2018)	17	41.6	6:11	34	NR	Ethanolamine	NR	2.8	6	6
27	Rosbe et al.[24] (2010)	10	20.3	4:06	12	Masseter	STS	NR	1	28	28
28	Sachin et al.[25] (2013)	358	NR	NR	358	NR	Butyl cyanoacrylate, polyvinyl alcohol, STS, bleomycine	NR	NR	4.7	56.4
29	Shigematsu et al.[26] (2019)	18	34.3	6:12	18	Eyes	Bleomycin	34.5	3	43	43
30	Siniluoto et al.[27] (1997)	34	28	14.24	34	NR	STS	11.8	2.2	NR	nr
31	Songsaeng et al.[28] (2015)	33	25.1	6:27	43	NR	Bleomycin, ethanol	NR	3	14.7	14.7
32	Spence et al.[29] (2011)	17	40	7:09	17	Face, tongue, parotid	Ethanol	8.1	1.7	6	6
33	Spence et al.[29] (2011)	17	32.4	5:12	17	Face, tongue, parotid	Bleomicyn	NR	3.4	6	6
34	Spence et al.[30] (2010)	31	34.4	14:17	32	Face, orbital, parotid, oropharinx	Bleomicyn	NR	3.5	5.2	5.2
35	Stimpson et al.[31] (2012)	12	7	7:05	12	Oropharynx	STS	NR	3	28	28
36	Su et al.[32] (2010)	60	22.6	26:34	60	Face, neck	Ethanol	11.2	1.8	8	8
37	Wang et al.[33] (2017)	21	25.4	12:09	72	Oropharynx, head, neck	Ethanol	79.6	1.5	9.1	9.1
38	Wang et al.[34] (2010)	23	19	13:10	23	Parotid, oral, neck, face	Ethanol	73	1.5	25	25
39	Zhao et al.[35] (2004)	260	NR	131:159	260	Oral, face	PYM, sodium morrhuate	NR	1.7	NR	NR
40	Zheng et al.[36] (2009)	297	20.6	159:138	297	Oral, maxillofacial, head, neck	PYM	NR	3.5	36	36
41	Zhi et al.[37] (2008)	82	12	26:56	82	Maxillofacial	PYM	NR	2.9	24	24

No., number; M, male; F, female; NR, not reported; STS, sodium tetradecyl sulfate; PYM, pingyangmycin.

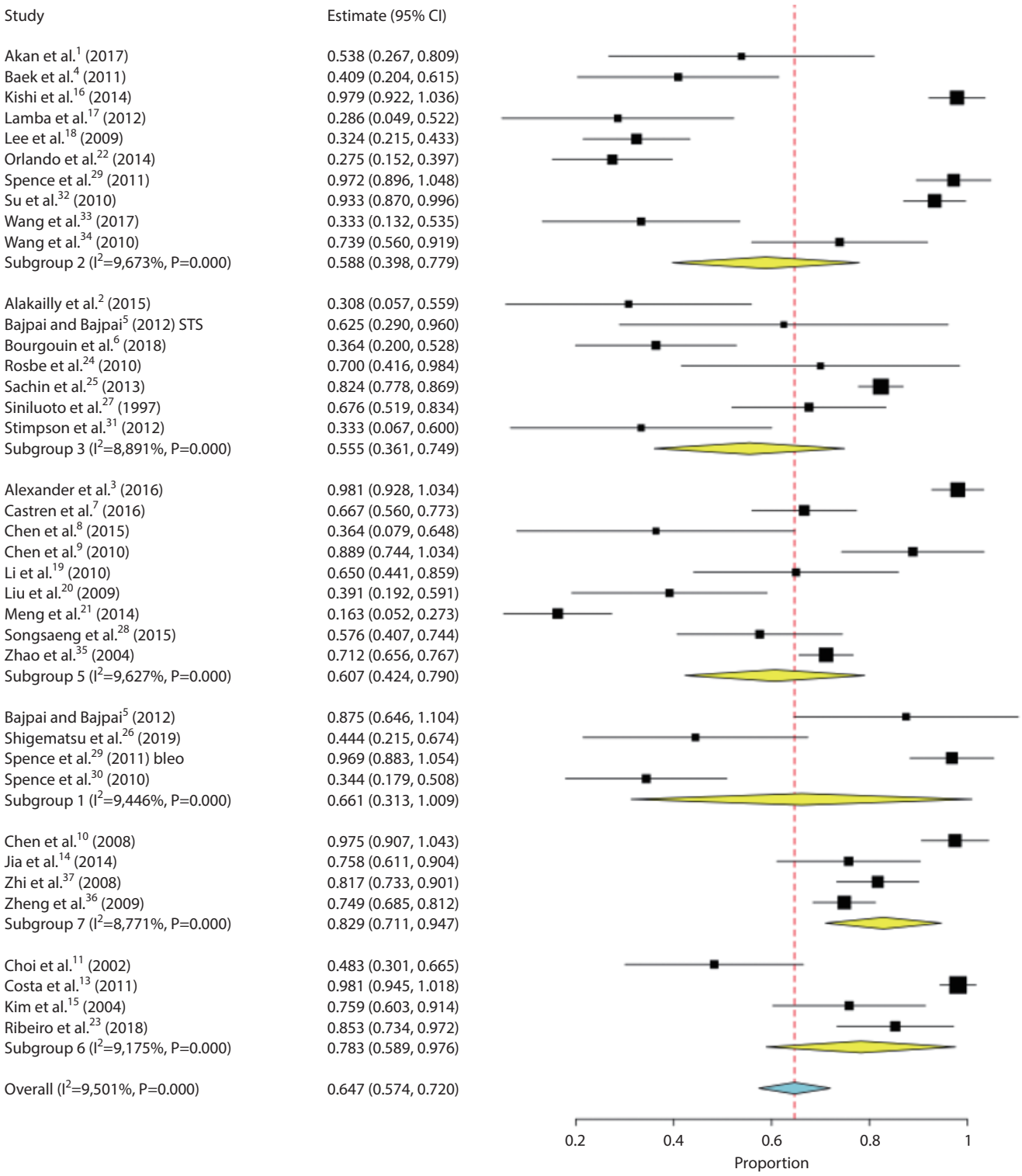

Fig. 2. Forest plot: complete cure rates. Subgroup 1, bleomycin; subgroup 2, ethanol; subgroup 3, sotradecol; subgroup 5, mixed/other; subgroup 6, ethanolamine; subgroup 7, pingyangmycin. CI, confidence interval.

sclerotherapy, and 4 studies reported outcomes of pingamycin sclerotherapy. In 11 studies either multiple agents were used and we could not separate outcomes by agent or other sclerosing agent including OK-432 were used. A summary of included studies is provided in Table 1.

Efficacy outcomes

Overall complete cure rates were reported in 1,736 patients. The overall rate of complete cure following percutaneous sclerotherapy with any agent was 64.7% (95% CI, 57.4–72.0%). STS had the lowest complete cure rate at 55.5% (95% CI,

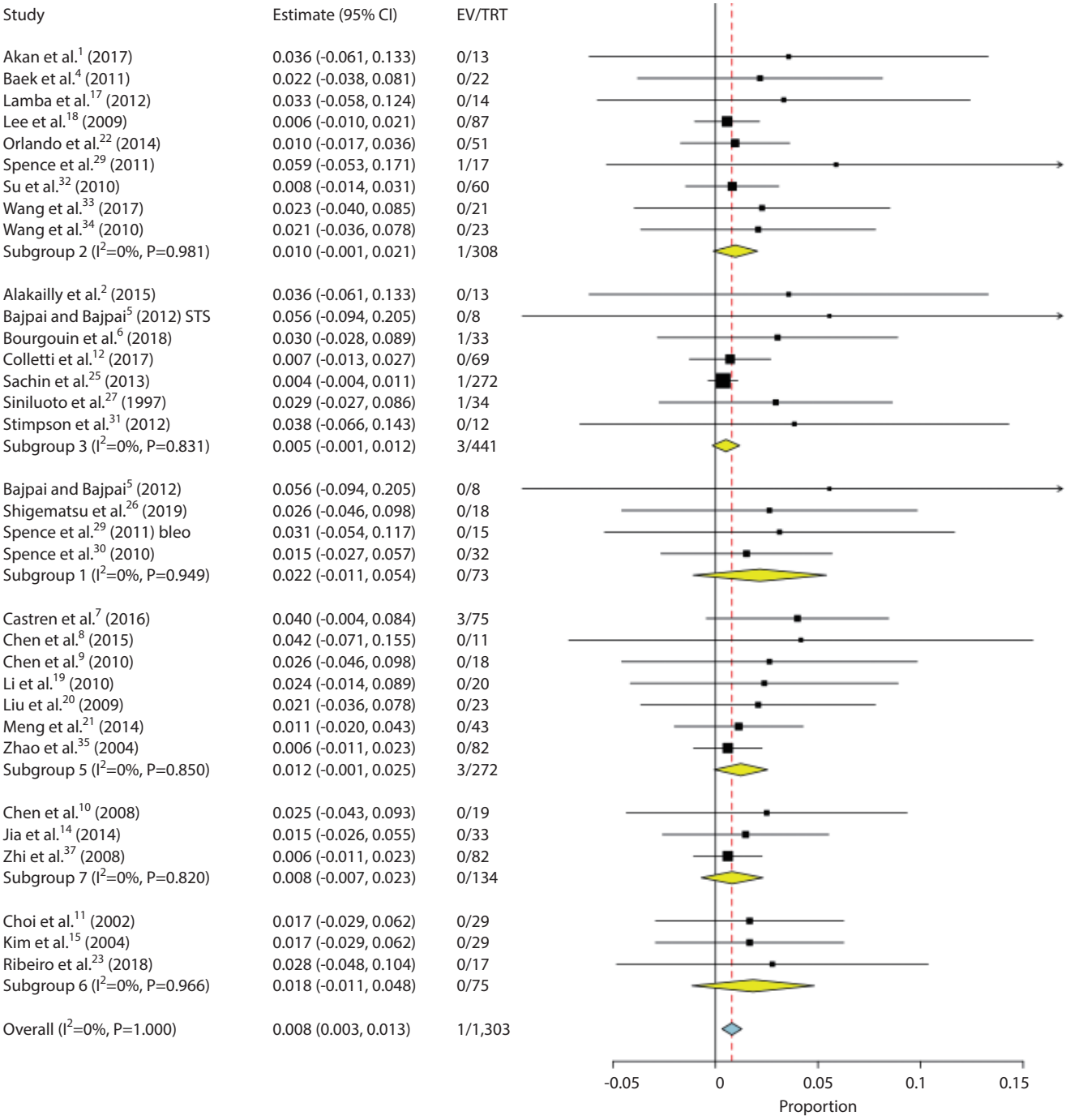

Fig. 3. Forest plot: permanent morbidity and mortality rates. Subgroup 1, bleomycin; subgroup 2, ethanol; subgroup 3, sotradecol; subgroup 5, mixed/other; subgroup 6, ethanolamine; subgroup 7, pingyangmycin. CI, confidence intervall; EV, number of events; TRT, number of treated patients.

36.1–74.9%) while pingyangmycin had the highest cure rate at 82.9% (95% CI, 71.1–94.7%). Fig. 2 shows the complete cure rates forest plot. Overall partial cure rates were reported in 1,703 patients. The overall rate of partial cure following percutaneous sclerotherapy with any agent was 28.0% (95% CI, 22.1–34.0%). Partial cure rates ranged from 16.2% (95% CI, 4.7–27.6%) for pingyangmycin to 35.3% (95% CI, 19.1–51.5%) with ethanol. The overall rate of no benefit following percutaneous sclerotherapy was reported in 1,736 patients and was 4.5% (95% CI, 3.0–6.1%). STS sclerotherapy had the highest rate of no benefit (14.9%; 95% CI, 4.3–25.4%) while pingyangmycin had the lowest rate of no benefit (0.6%;

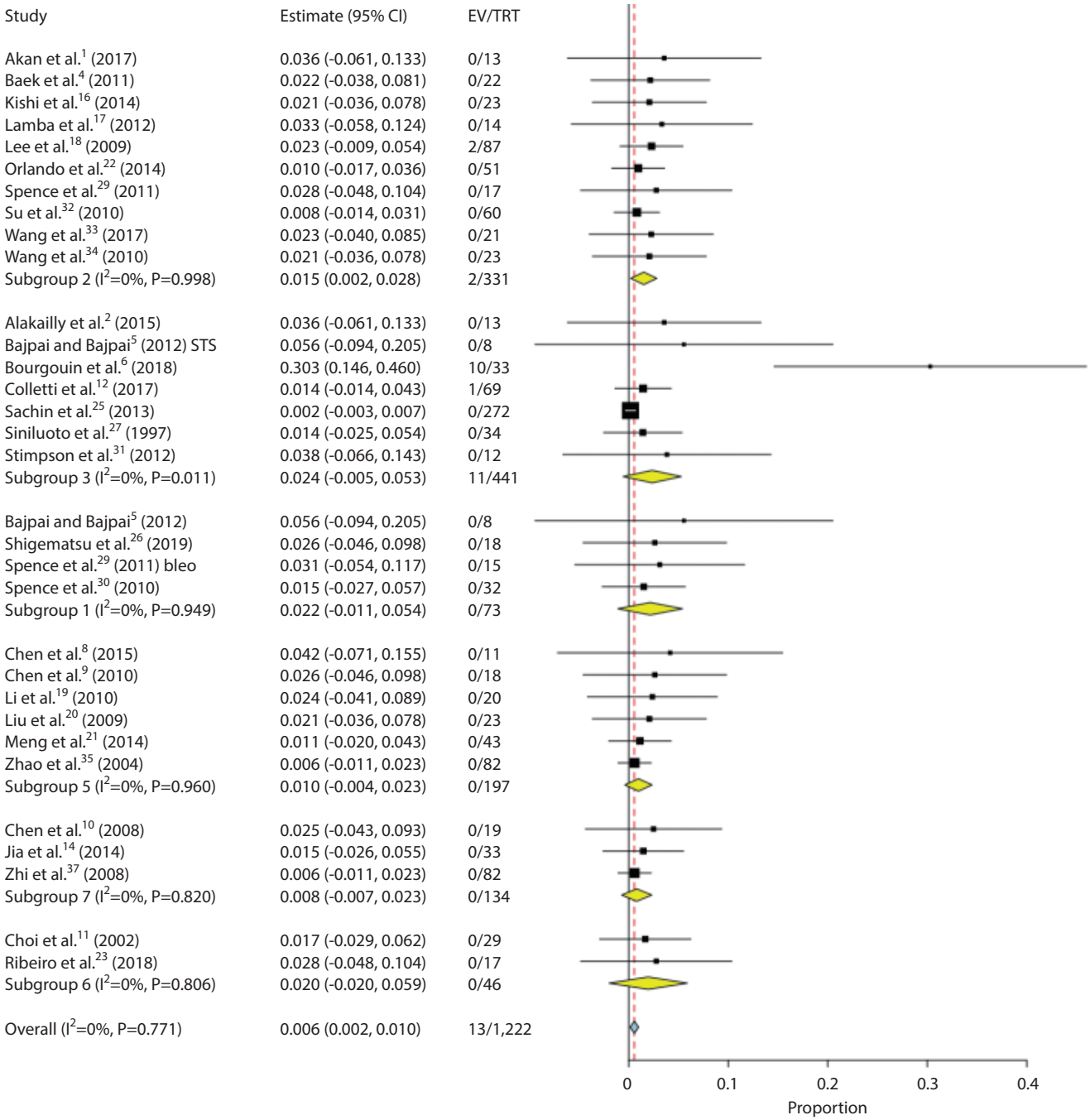

Fig. 4. Forest plot: pulmonary complication rates. Subgroup 1, bleomycin; subgroup 2, ethanol; subgroup 3, sotradecol; subgroup 5, mixed/other; subgroup 6, ethanolamine; subgroup 7, pingyangmycin. CI, confidence interval; EV, number of events; TRT, number of treated patients.

95% CI, 0.0–1.6%). Patient satisfaction was reported in 315 patients. Overall patient satisfaction rates were 91.0% (95% CI, 86.1–95.9%). Patient satisfaction rates ranged from 72.8% (95% CI, 63.6–81.9%) with STS to 96.0% (95% CI, 92.5–99.6%) with ethanol. Improvement in QoL was reported in 243 patients. Overall QoL improvement was 78.9% (95% CI, 67.0–90.8%) ranging from 46.7% (95% CI, 22.4–71.0%) for STS to 98.1% (95% CI, 94.5–100%) with ethanolamine.

Safety outcomes

Overall permanent morbidity and mortality rates were reported in 1,303 patients. The overall rate of permanent mor-

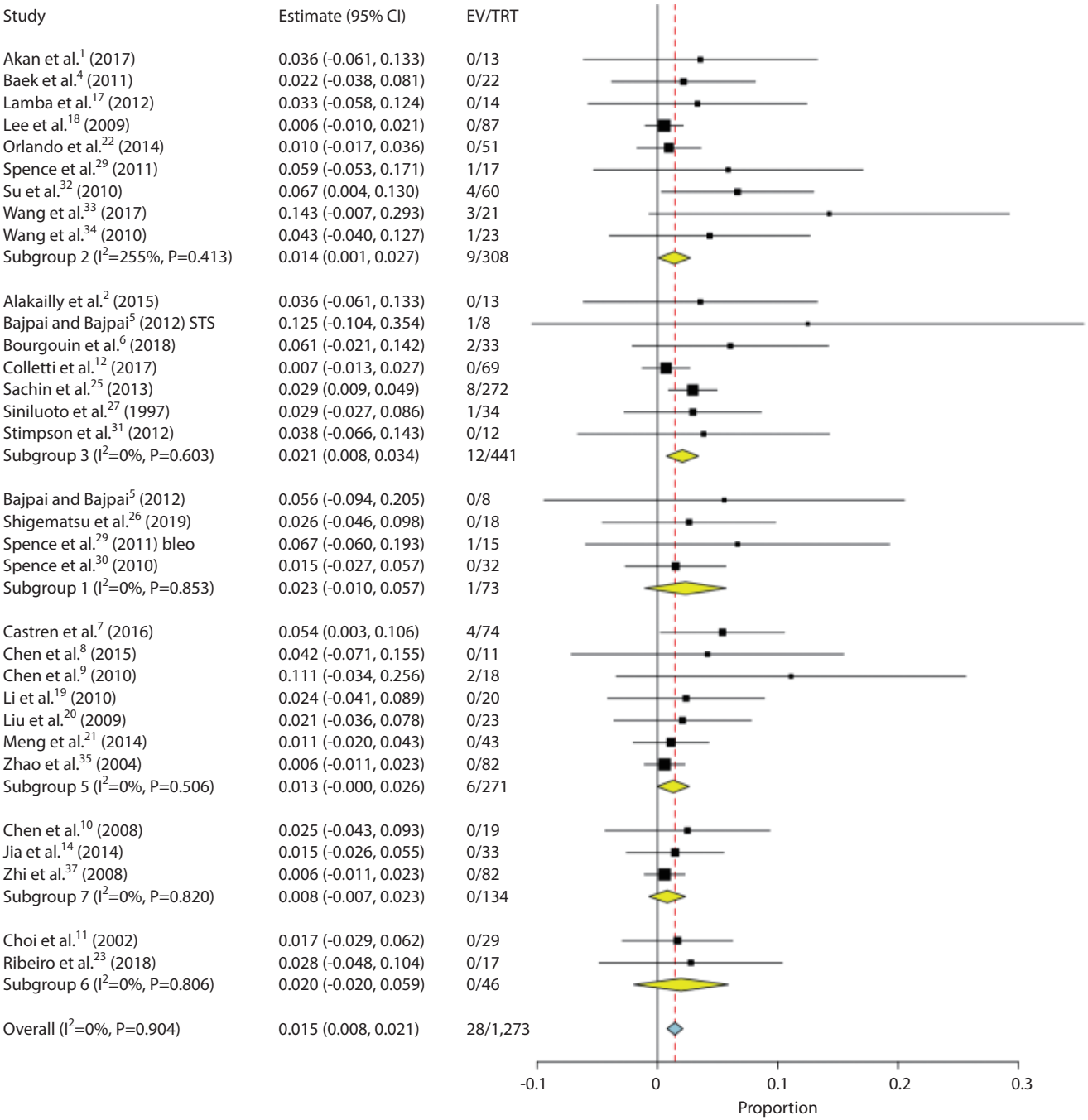

Fig. 5. Forest plot: skin necrosis and scarring rates. Subgroup 1, bleomycin; subgroup 2, ethanol; subgroup 3, sotradecol; subgroup 5, mixed/other; subgroup 6, ethanolamine; subgroup 7, pingyangmycin. CI, confidence interval; EV, number of events; TRT, number of treated patients.

bidity and mortality was 0.8% (95% CI, 0.3–1.3%). The lowest rate was reported with STS, and pingamycin (0.5%, 0.8%) and the highest rate reported was with bleomycin (2.2%; 95% CI, 0.0–5.4%). Fig. 3 shows the permanent morbidity and mortality rates forest plot. Local temporary complication rates were reported in 1,312 patients. The overall rate of local temporary complications was 41.8% (95% CI, 27.0–56.5%). Local temporary complications were highest with ethanolamine (51.0%; 95% CI, 24.7–26.6%) and were lowest with bleomycin (27.0%; 95% CI, 5.4–59.4%). Pulmonary complication rates were reported in 1,222 patients. The overall rate was 0.6% (95% CI, 0.2–1.0%). Pulmonary complication rate was lowest for pingamycin (0.8%; 95% CI, 0.0–2.3%), and was highest for STS (2.4%; 95% CI, 0.5–5.3%). Fig. 4 shows the pulmonary complication rates forest plot. Skin necrosis and scarring rates were reported in 1,273 patients and the overall rate was 1.5% (95% CI, 0.8–2.1%). Rates were highest with bleomycin (2.3%; 95% CI, 1.0–5.7%) and lowest with pingamycin (0.8%; 95% CI, 0.0–2.3%). Fig. 5 shows the skin necrosis and scarring rates forest plot. The efficacy and safety outcomes are summarized in Tables 2 and 3.

Study heterogeneity

I^2 values were >50% indicating substantial heterogeneity for the following outcomes: lack of benefit, improvement in QoL, local temporary complication, overall cure, partial cure, patient satisfaction and systemic side effects. I^2 values were <50% indicating lack of substantial heterogeneity for the following outcomes: permanent morbidity and mortality, pulmonary complications and skin necrosis/scarring.

Table 2. Summary of overall outcomes

	Overall (%) (95% CI)
Complete cure	64.7 (57.4–72.0)
Partial cure	28.0 (22.1–34.0)
No benefit	4.5 (3.0–6.1)
Improvement in QoL	78.9 (67.0–90.8)
Patient satisfaction	91.0 (86.1–95.9)
Pulmonary complication	0.6 (0.2–1.0)
Skin necrosis/scar	1.5 (0.8–2.1)
Any permanent morbidity/mortality	0.8 (0.3–1.3)
Local temporary complication	41.8 (27.0–56.5)

QoL, quality of life; CI, confidence interval.

DISCUSSION

Our systematic review and meta-analysis of percutaneous image guided sclerotherapy for treatment of VMs of the head face and neck found that the overall efficacy rate of sclerotherapy was high with complete and partial cure rates of over 90%. Over 90% of patients reported satisfaction with the results of their sclerotherapy treatments and over 70% reported improvements in QoL. Temporary local complication rates were high, however rates of permanent morbidity and mortality as well as permanent scarring were low. When performing subgroup analyses by agent, we found that agents such as ethanol, pingamycin and ethanolamine were generally associated with the highest rates of cure and patient satisfaction, however these agents were also associated with higher rates of local temporary complications. These findings are important as they provide important information regarding the risks and benefits of percutaneous sclerotherapy for VMs of the head, face and neck.

The efficacy of sclerotherapy for VMs is dependent on both the angioarchitecture of the venous malformation, the sclerosing agent used and the dwell time of the sclerosant within the venous malformation.[42] Angioarchitecture can be easily assessed on contrast venography following percutaneous injection of the lesion. According to Gemmette et al, the 4 morphological subtypes of VMs are as follows: type I, isolated malformation without discernible venous drainage; type II, lesions draining into normal veins; type III, lesions draining into dysplastic veins; type IV, lesion consists primarily of venous ectasia.[42] Types I and II are thought to respond best to sclerotherapy. None of the studies included in our analysis examined outcomes by lesion angioarchitecture, however this undoubtedly is an important factor in determining outcomes.

A summary of the different sclerosing agents is provided in Table 4. Based on our study, it is clear that sclerosants such as ethanol, ethanolamine oleate and pingyangmycin are generally more effective at inducing a complete or partial cure of the VM. However, this comes at the cost of increased risk of permanent morbidity as well as local side effects. Medications such as ethanol, ethanolamine and pingyangmycin act by directly inducing endothelial injury and thrombosis of the VM.[43] Meanwhile, less potent sclerosing agents such as STS and bleomycin work by inducing a nonspecific inflammatory reaction within the VM.[43] Adverse side effects of sclerosing agents also differ by agent and are summarized in Table 4.

Table 3. Summary of outcomes by agents

	Bleomycin		Ethanol		Sodium tetradecyl sulfate		Ethanolamine		Pingamycin	
	% (95% CI)	P-value vs. bleomycin	% (95% CI)	P-value vs. bleomycin	% (95% CI)	P-value vs. bleomycin	% (95% CI)	P-value vs. bleomycin	% (95% CI)	P-value vs. bleomycin
Complete cure	66.1 (31.3–100.9)	Ref.	58.8 (39.8–77.9)	0.004	55.5 (36.1–74.9)	0.005	78.3 (58.9–97.6)	<0.001	85.9 (72.7–99.2)	<0.001
Partial cure	24.5 (1.7–47.3)	Ref.	35.3 (19.1–51.5)	0.18	25.9 (13.1–38.6)	0.08	19.5 (2.1–37.0)	0.05	12.5 (1.0–24.0)	0.03
No benefit	12.9 (0.7–26.6)	Ref.	4.0 (1.2–6.8)	0.003	14.9 (4.3–25.4)	0.02	2.1 (0.2–4.4)	<0.001	2.6 (0.1–5.2)	<0.001
Improvement in QoL		Ref.	89.8 (76.4–3.2)		46.7 (22.4–71.0)		98.1 (94.5–100)			
Patient satisfaction	94.3 (88.3–100.3)	Ref.	96.0 (92.5–99.6)	0.72	72.8 (63.6–81.9)	<0.001	76.5 (62.2–90.7)	0.02		
Pulmonary complication	2.2 (0.0–5.4)	Ref.	1.5 (0.2–2.8)	1.00	2.4 (0.5–5.3)	0.38	2.0 (0.0–5.9)	1.00	0.8 (0.0–2.3)	1.00
Skin necrosis/ scar	2.3 (1.0–5.7)	Ref.	1.4 (0.1–2.7)	0.69	2.1 (0.8–3.4)	0.71	2.0 (0.0–5.9)	1.00	0.8 (0.0–2.3)	0.35
Any permanent morbidity/ mortality	2.2 (0.0–5.4)	Ref.	1.0 (0.1–2.1)	1.00	0.5 (0.1–1.2)	1.00	1.8 (0.0–4.8)	1.00	0.8 (0.0–2.3)	1.00
Local temporary complication	27.0 (5.4–59.4)	Ref.	30.0 (3.3–56.7)	0.61	44.0 (10.6–77.4)	<0.001	51.0 (24.7–26.6)	<0.001	36.2 (19.7–92.1)	0.45

CI, confidence interval; Ref., reference; QoL, quality of life.

Table 4. Summary of commonly used agents

Agent	Mechanism of action	Standard dose	Adverse effects
Ethanol	Endothelial denudation and thrombosis	1 mL/kg, most studies have max of 10–20 mL	Skin necrosis, tachycardia, DVT, PE, pain
Bleomycin	DNA damage. Lipid peroxidation, non-specific inflammatory reaction	1 mg/kg up to 15 mg	Skin pigmentation, fever, mucositis, pulmonary toxicity (rare)
Sodium tetradecyl sulfate	Detergent resulting in lipid damage in vessel wall, inflammatory reaction	0.5–2 mL of 3% solution	Pain, edema, ecchymosis, nerve injury
Ethanolamine oleate	Fatty acid emulsion inducing endothelial damage and thrombosis	2 mL of 50 mg/mL solution	Skin ulceration and necrosis
Pingyangmycin	DNA damage. Lipid peroxidation, non-specific inflammatory reaction	8 mg in a 2 mg/mL solution	Atrophy of subcutaneous tissues, fever, swelling, anaphylactic shock
OK-432	Natural killer cell activator resulting in inflammation and endothelial permeability	0.1 mg dried cocci in 10 mL of normal saline	Fever, pain, edema, inflammation
Doxycycline	Inhibition of matrix metalloproteins and VEGF > decreased angiogenesis	10–20 mg/kg	Severe pain on injection

DVT, deep vein thrombosis; PE, pulmonary embolism; VEGF, vascular endothelial growth factor.

In brief, adverse side effects are generally most severe with ethanol and include nerve injury, skin necrosis, and cardiopulmonary collapse.[43] Side effects are least severe with bleomycin and include mucositis and skin pigmentation.

It is important to point out that a variety of factors should go into the decision regarding which sclerotherapeutic agent to use. Choice of agent should be based on the depth of the venous malformation from the skin surface as well as the ability to limit non-target sclerotherapy and venous thrombosis. Alcohol is generally best used for deeper VMs due to the risk of skin necrosis from extravasation.[4,28,29] Superficial VMs are likely best treated with milder agents such as bleomycin or STS.[5,26,28,29]

The results from our study compare favorably to other modalities of treatment including medical therapy, surgical resection and laser therapy. Conservative management techniques for VMs are centered around pain control, prevention of phlebitis or thrombosis and prevention of bleeding.[43] Pain can generally be managed with anti-inflammatory medications and analgesics. Low dose aspirin can provide pain relief in patients with venous malformation thrombosis.[24,31] Recently the mammalian target of rapamycin inhibitor sirolismus has been trialed for treatment of VMs and has been found to result in symptom improvement in approximately 80% of patients.[44] Surgical excision of VMs is usually part of staged multimodal treatment of VMs.[45] However, surgical excision alone is often considered when lesions are smaller and are not adjacent to vital structures. Surgical excision of large invasive VMs is often very challenging due to the presence of poorly defined tissue planes and proximity to important structures. In such cases, intralesional sclerotherapy can be considered as a useful adjunct to surgery as part of an interdisciplinary approach.[46] Small case series have reported various levels of efficacy with surface and endovenous/interstitial laser therapy for treatment of VMs, most series report efficacy rates ranging from 70–90%. Combined laser and sclerotherapy treatment has also been shown to be effective as part of an interdisciplinary approach.[46]

Limitations

Our study has limitations. This meta-analysis was based primarily off of single-center case series and thus has limitations inherent to single center retrospective studies. There was high risk of bias in 21 series. While we were able to perform subgroup analyses based on sclerotherpeutic agent used, we were unable to perform more granular analyses stratifying outcomes by lesion location. Follow-up in the included studies is limited. Many of our outcomes are subjective and volumetric analyses documenting lesion improvement were not available for a vast majority of the included studies. Nonetheless, our study provides helpful information for both patients and providers who are considering percutaneous sclerotherapy for treatment of VMs and provides guidance for future areas of investigation.

CONCLUSIONS

Our systematic review and meta-analysis of 37 studies and over 2,000 patients found that percutaneous sclerotherapy is a very safe and effective treatment modality for treatment of VMs of the head, neck and face. As expected, mild sclerosing agents such as bleomycin and STS were associated with lower efficacy rates but generally superior safety profiles than stronger sclerosing agents such as ethanol, ethanolamine and pingyangmycin. Further prospective studies are needed to validate our results and determine the optimal treatment strategies for patients with VMs of the head, face and neck.

Fund

None.

Ethics Statement

For this type of study formal consent is not required.

Conflicts of Interest

The authors have no conflicts to disclose.

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