

Bleomycin for Head and Neck Venolymphatic Malformations: A Systematic Review

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ABSTRACT: *Background:* Venolymphatic malformations are rare benign vascular lesions of the head and neck. Sclerotherapy has become the first-line therapy of these lesions with bleomycin being a sclerosing agent commonly used. *Purpose:* To perform a systematic review of the published literature to synthesize evidence on the safety and efficacy of bleomycin for the treatment of head and neck venolymphatic malformations. *Data sources:* A systematic review of the literature (January 1995–May 2019) was performed in PubMed, Embase, and Cochrane Library databases to identify studies on sclerotherapy of venolymphatic malformations of the head and neck. *Study selection:* A total of 32 studies with participants met the inclusion criteria among which 1121 patients were included in the systematic review. *Data analysis:* Two reviewers independently screened and extracted data and assessed the risk of bias. The primary outcome was the subjective or objective reduction of lesion size as well as minor and major complications. *Data synthesis:* The bleomycin/pingyangmycin sclerotherapy achieved subjective or objective lesion size reduction in 96.3% (95% CI 94.1%–98.5%) of patients. Minor complications were observed in 16.2% and major complications in 1.1%. *Conclusion:* Bleomycin is a highly effective treatment of venolymphatic malformations of the head and neck with a low rate of major adverse events. This study represents an update on the “available” evidence, but only low-to-moderate quality studies were available. *Limitations:* This study reviewed 32 studies performed in different parts of the world, but there was heterogeneity of the study designs and interventions.

RÉSUMÉ : *Utilisation de la bléomycine dans le cas de malformations veinolymphatiques de la tête et du cou : une analyse systématique.* *Contexte :* Les malformations veinolymphatiques sont de rares lésions vasculaires bénignes de la tête et du cou. La sclérothérapie est devenue un traitement de première ligne de ces lésions, la bléomycine étant à cet égard un des agents sclérosants couramment utilisés. *Objectif :* Effectuer une analyse systématique de la littérature scientifique publiée en vue de produire une synthèse des preuves de la sécurité et de l'efficacité de la bléomycine dans le traitement des malformations veinolymphatiques de la tête et du cou. *Origine des données :* Nous avons effectué une revue systématique de littérature (de janvier 1995 à mai 2019) à l'aide des bases de données Pubmed, Embase et Cochrane Library afin d'identifier des études portant sur la sclérothérapie des malformations veinolymphatiques de la tête et du cou. *Sélection à la base de l'étude :* Au total, 32 études et 1121 participants ont satisfait à nos critères d'inclusion. *Analyse de données :* Deux examinateurs indépendants ont filtré et extrait des données en plus d'évaluer les risques de biais. Le principal résultat évalué a été la réduction, subjective ou objective, de la taille de ces lésions en plus d'une diminution des complications d'ordre mineur ou majeur. *Synthèse des données :* La sclérothérapie à l'aide de la bléomycine et de la pingyangmycine a permis de réduire la taille de ces lésions, tant d'un point de vue objectif que subjectif, chez 96,3 % des patients (IC 95 % 94,1-98,5 %). Des complications mineures ont été observées dans 16,2 % des cas tandis que des complications majeures l'ont été dans seulement 1,1 % des cas. *Conclusion :* La bléomycine s'est révélée un traitement des malformations veinolymphatiques de la tête et du cou hautement efficace offrant un faible taux d'événements indésirables majeurs. À noter toutefois que cette étude ne représente qu'une mise à jour de données « disponibles » et que seules des études de qualité faible à moyenne étaient disponibles. *Limites de cette étude :* Notre étude a passé en revue 32 publications antérieures de différentes parties du monde. Il n'est donc pas surprenant que nous ayons noté une hétérogénéité des modèles d'étude et des interventions cliniques.

Keywords: Venolymphatic malformations, Bleomycin, Venous malformations, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

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INTRODUCTION

Venolymphatic malformations are the most common vascular malformations and a majority is present in the head and neck.^{1–5} They are rare benign vascular lesions present at birth but usually presents in late childhood or early adulthood. Total surgical resection of these malformations is often not possible and

recurrence is frequent besides the functional and esthetic sequelae from surgical resection. For this, sclerotherapy has become the first-line therapy of these lesions with bleomycin being a sclerosing agent commonly used in the region of the head and neck.

Bleomycin, or pingyangmycin (also known as bleomycin A5), is a cytotoxic agent used for the systemic treatment of various types of

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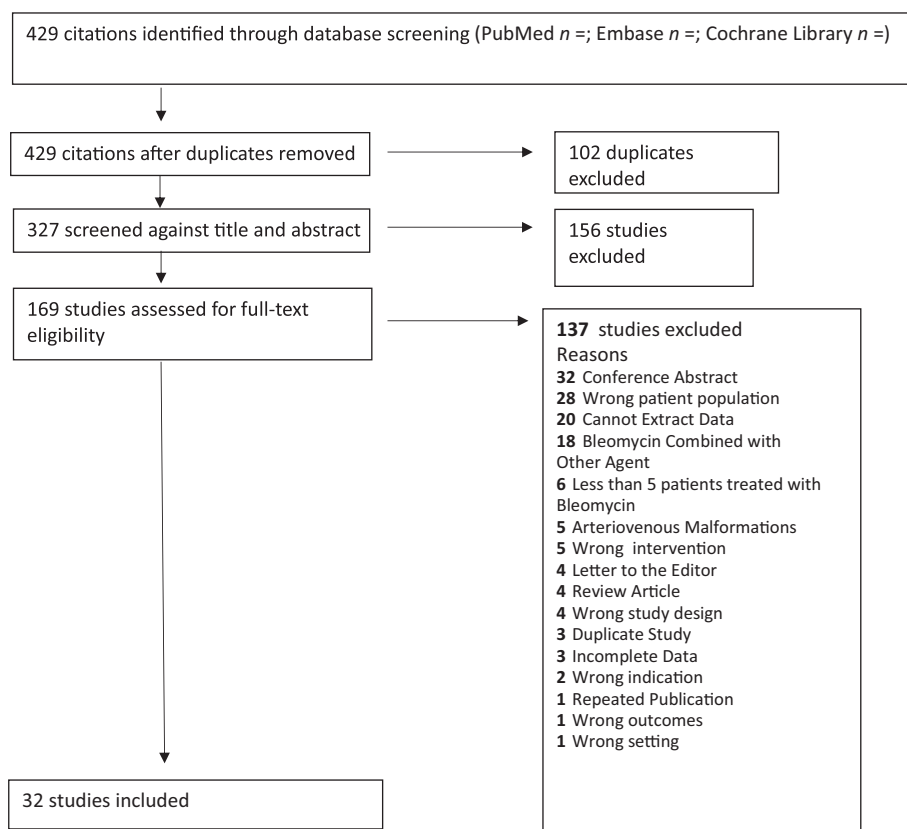


Figure 1: Flowchart of selection of studies. Embase n = 259; Medline n = 134; Scopus n = 162.

malignancies including lymphoma and cutaneous squamous cell carcinoma.^{6–10} It is also injected intralesionally for the treatment of subcutaneous tumors like warts and keloids.^{8,9} In venolymphatic malformation, the intralesional injection of bleomycin induces sclerosis^{11,12} through endothelial damage and fibrosis.^{13,14} Bleomycin has been considered very safe for this indication with the rare complications reported with the use of bleomycin include hyperpigmentation, necrosis, and pulmonary fibrosis.^{15–17}

Most of the published studies are smaller single-center studies, which can be used for any significant and meaningful conclusion or guidelines. Earlier systematic reviews included venolymphatic malformation anywhere in the body.^{10,55–57} The purpose of our study was to perform a systematic review of the published literature to synthesize the evidence on the safety and efficacy of bleomycin for the treatment of venolymphatic malformations in the head and neck region only.

METHODS

We used standard systematic review methods advocated by the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.^{18–20}

Inclusion Criteria

Study type: Any prospective or retrospective case series or clinical trials.

Patient type: Studies that enrolled patients of any age with the diagnosis of head and neck venolymphatic malformation.

Intervention: Sclerotherapy with bleomycin or pingyangmycin (a bleomycin analog) alone, or in combination with other sclerosing agents or techniques.

Outcome measures: Subjectively or objectively documented lesion size reduction, major or minor complications. Subjective size reduction was defined as reduction appreciated either by the patient or the physician documenting it. Objective size reduction was defined when size reduction was documented on any cross-sectional imaging tests. Major complications were defined as extensive necrosis, oral or respiratory obstruction, and pulmonary fibrosis. Minor complications were largely self-limiting such as transient pain, edema, hematoma, ecchymosis, atrophy, hypertrophy, infection, superficial necrosis, and hyperpigmentation.

Follow-up period: Unrestricted.

Publication types: Search was unrestricted but non-English language studies were excluded from the final review. This was mainly due to the lack of resources for translation. All publications from across the world were included. Only study articles published in peer-reviewed literature were included.

Exclusion criteria: Non-English language studies and studies with less than five patients were excluded.

Search strategy: A computerized search of PubMed, Embase, and Cochrane Library was done using index terms and keywords (see Appendix 1) from January 1995 until May 2019. In addition to online database searching, reference lists of all included studies and previous reviews were also screened.

Data collection and analysis: Two researchers independently used Covidence for the primary and secondary screening (title/abstract and full text, respectively) and data extraction (Figure 1)

to streamline the production of standard intervention reviews. The titles and abstracts were screened and were categorized as “Yes,” “No,” and “Maybe.” For those categorized as “Yes” and “Maybe,” a full-text review was done to assess the inclusion of the studies. Data were then extracted from the included studies using a standard extraction form with characteristics of the trials, participants, interventions, and outcomes.

Covidence was also used for the Risk of Bias assessment using Cochrane risk of bias criteria. Cochrane risk of bias criteria included assessment of sequence generation; allocation concealment; blinding of participants and study personnel; blinding of outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Data on all relevant variables were collected (Table 1).

Meta-analysis: A meta-analysis was not possible because of the heterogeneity of the study designs and interventions performed.

Grading of evidence: Overall quality of evidence was graded by interpretation of the quantitative synthesis using recommendations of the GRADE working group.²¹ The risk of bias, the completeness and context of available evidence, and the size and consistency of observed effects were considered in the grading of evidence.

RESULT

The flow diagram of systematic literature search and study selection is depicted in Figure 1.

Trial Design

Twenty-eight retrospective cohort studies, two prospective cohort studies, one case-control, and one randomized control study were included. In the randomized control trial, the analysis was based on intention to treat. Nineteen studies reported on venolymphatic lesions of the head and neck in general, 7 on lesions located in the orbital region, and 6 on lesions in the orofacial area. Most studies used a combination of imaging modalities for the diagnosis of venolymphatic malformations – 17 studies used ultrasound, 11 studies used CT, 20 studies used MRI while no imaging test was used in 6 studies.

Trial Participants

A total of 1121 patients with venolymphatic malformations of the head and neck were included, with a mean of 35 patients per study (SD: 17 patients, range – 6–297 patients) of whom 45.1% were females. The mean patient age was 14.4 years (range – 9 days–72 years). Reported symptoms included cosmetic issues, skin discoloration, progressive increase in size, pain, hemorrhage, fever, and erythema. The orbital lesions presented with blurry vision, scotoma, proptosis, pain, diplopia, palpable mass, ecchymosis, bleeding, motility disturbance, ptosis, eyesight obstruction, and eyelid dysfunction. Oral lesions presented with swallowing and chewing difficulties, oral obstruction, hemorrhage, functional problems (breathing, suction, and speech), distorted dentition, and discomfort. Only a few studies reported the actual percentage of patients presenting with these symptoms.

Interventions

Bleomycin was used as a sclerosing agent in 562 patients and pingyangmycin in 559 patients. The operators were

neuroradiologist or radiologist in 8 studies, a surgeon in 6 studies, and not specified in 18 studies. Besides sclerotherapy sessions with bleomycin/pingyangmycin 33 patients received surgical treatment, 30 patients laser therapy, 9 patients absolute ethanol sclerotherapy, and 22 patients sodium tetradecyl sulfate sclerotherapy. It is unclear how many of these patients received the additional treatment before or after undergoing treatment with bleomycin. The type of analgesia/anesthesia performed was reported in 726 patients. Local anesthesia was administered in 393 patients (54.1%), sedation in 50 patients (6.8%), and general anesthesia in 77 patients (10.6%) while some type of analgesia/anesthesia without further detail was administered in 176 patients (24.2%). In 30 patients (4.1%), sclerotherapy was administered without any anesthetic/analgesic treatment. The imaging guidance used for treatment guidance was reported in 523 patients – ultrasound in 141 patients (26.9%), fluoroscopy in 164 patients (31.3%), and in 43 patients (8.2%), the imaging used was not specified. In 175 patients (33.4%), sclerotherapy was administered without any image guidance.

The mean number of sclerotherapy sessions per patient was 3.36 (range – 1–9). The mean concentration of bleomycin/pingyangmycin used was 1.6 mg/ml (range – 0.5–4 mg/ml). The maximum dose administered per session ranged from 0.2 to 1 mg/kg. The total maximum dose administered ranged from 0.033 to 6 mg/kg with a mean of 20.5 mg (min. = 1 mg, max. = 96.5 mg). Lower doses were usually used in children.

Outcome

Bleomycin/pingyangmycin sclerotherapy achieved subjective or objective lesion size reduction in 96.3% (95% CI 94.1%–98.5%) of patients (Table 1). Minor complications were observed in 16.2% (95% CI 10.5%–21.7%) of cases. Major complications were seen in four patients (1.1%, 95% CI 0%–2.5%) of whom one was death (0.3%, 95% CI 0%–0.8%). The circumstances of this last complication could not be deduced.³³ The other major complications included abscess in one patient and two patients needing surgical decompression after bleomycin injection for orbital lymphangiomas to improve eyelid position.^{39,40} The mean duration of follow-up from the last treatment was 17 months (range – 1 month to 7 years). The imaging modality on follow-up was reported only in 817 patients. Ultrasound was used in 288 patients (35.2%), MRI in 143 patients (17.5%), and in 343 patients (41.9%), the imaging modality used was not specified. In 304 patients (37.2%), no imaging was performed on follow-up.

Risk of Bias in Included Studies

The risk of bias was assessed for allocation, blinding, incomplete outcome data, selective reporting, and other sources. The risk of bias summary for each risk of bias item for each included study is shown in Figure 2. This is shown in a risk of bias graph where the judgments about each risk of bias item are presented as percentages across all included studies (Figure 3). The risk of bias was used for grading the evidence from this review.

DISCUSSION

Summary of Main Results

Our systematic review assessed the efficacy and safety of bleomycin sclerotherapy for venolymphatic malformations in the

Table 1: Summary of all included studies

Authors	Country	Year of publication	Number of patients	Location	Treatment	Max Concentration (mg/ml)*	Major complications	Minor complications (%)	Mean duration of follow-up (months)	Subjective/objective lesion reduction (%)
Ahmad et al. ²²	Pakistan	2019	24	Head and neck	Bleomycin, sodium tetradecyl sulfate	1	–	0	13.7	100
Bajpai et al. ²³	India	2012	8	Oral and maxillofacial	Bleomycin	2	–	25	24 (min.)	100
Baskin et al. ²⁴	Turkey	2005	7	Head and neck	Bleomycin	1.5	–	0	6	100
Chaudry et al. ²⁵	USA	2014	27	Head and neck	Bleomycin, doxycycline	1	–	0	32	962
Chen et al. ²⁶	China	2017	15	Airway	Pingyangmycin	2	–	60	16.6	100
Chen et al. ²⁷	China	2008	19	Orbit	Pingyangmycin	1.3	–	5.2	23	100
Da Ros et al. ²⁸	France	2017	16	Orbit, maxillofacial, tongue	Bleomycin	1.9	–	18.7	26	87.5
Hanif et al. ²⁹	USA	2018	10	Orbit	Bleomycin	–	–	20	7.5	75
Hou et al. ³⁰	China	2010	75	Cervicofacial region	Pingyangmycin	1.6	–	2.6	10.3	100
Jia et al. ³¹	China	2014	33	Orbital–periorbital	Pingyangmycin	1.5	–	12.1	7.9	100
Karavelioglu et al. ³²	Turkey	2010	12	Cervicofacial	Bleomycin	–	–	–	64.1	100
Kim et al. ³³	Korea	2004	10	Head and neck	Bleomycin, surgery	1	1	–	17	90
Li et al. ³⁴	China	2010	20	Maxillofacial	Pingyangmycin, absolute ethanol	2	–	35	13.5	100
Luo et al. ³⁵	China	2013	16	Oral–maxillofacial	Pingyangmycin, triamcinolone acetonide	0.6	–	0	24	100
Mai et al. ³⁶	China	2013	18	Tongue	Pingyangmycin	1	–	16.7	36	100
Mathur et al. ³⁷	India	2005	10	Head and neck	Bleomycin	2	–	0	9	100
Nuruddin et al. ³⁸	Bangladesh	2019	12	Orbit	Bleomycin	–	–	16.7	3	100
Porwal et al. ³⁹	India	2018	8	Head and neck	Bleomycin	1.5	1	37.5	12	87.5
Raichura et al. ⁴⁰	India	2017	13	Orbit	Bleomycin	–	2	30.7	19.7	92.3
Regmi et al. ⁴¹	Nepal	2017	30	Head and neck	Bleomycin	3	–	33	10	100
Shigematsu et al. ⁴²	USA	2018	18	Eyelid	Bleomycin	3	–	0	2 (min.)	100
Sindel et al. ⁴³	Turkey	2018	34	Eyelid	Bleomycin	1	–	44.1	24	100
Spence et al. ⁴⁴	Canada	2010	31	Face	Bleomycin	1	–	19.2	5.2	93.7
Sung et al. ⁴⁵	Korea	1995	10	Head and neck	Bleomycin	1	–	0	18.3	90
Wu et al. ⁴⁶	China	2016	21	Face	Pingyangmycin	1	–	9.5	33	90.5
Xu et al. ⁴⁷	China	2014	32	Cervical	Pingyangmycin	2.7	–	3.1	18	100
Yang et al. ⁴⁸	China	2011	65	Cervicofacial	Bleomycin, surgery	2	–	21.5	16	100
Yue et al. ⁴⁹	China	2014	13	Orbit	Pingyangmycin	4	–	23	13.3	100
Yura et al. ⁵⁰	Japan	1977	6	Cervicofacial	Bleomycin	1	–	0	n/a	100
Zheng et al. ⁵¹	China	2009	297	Oral–maxillofacial	Bleomycin, laser therapy, and surgical excision	2	–	16.8	12 (min.)	100
Zhong et al. ⁵²	China	1998	200	Head and neck	Bleomycin	2	–	37.5	24 (min.)	97.5
Zulfiqar et al. ⁵³	Malaysia	1999	11	Neck	Bleomycin	1.5	–	0	6	81.8

*In the case bleomycin quantity was expressed in International Units (IU), conversion to milligrams (mg) was made according to the formula 1 IU = 1 mg³⁸.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessors	Incomplete outcome data (attrition bias)	Selective outcome reporting	Other bias
Ahmad 2019	Red	Red	Red	Red	Green	Green	Red
Bajpai 2012	Red	Red	Red	Red	Green	Green	Red
Baskin 2005	Red	Red	Yellow	Red	Green	Green	Yellow
Chaudry 2014	Red	Red	Red	Red	Green	Green	Yellow
Chen 2017	Red	Red	Red	Red	Green	Green	Yellow
Chen 2008	Red	Red	Red	Red	Green	Green	Yellow
DaRos 2018	Red	Red	Red	Red	Green	Green	Red
Hanif 2018	Red	Red	Red	Red	Red	Green	Yellow
Hou 2010	Red	Red	Red	Red	Green	Green	Yellow
Jia 2014	Red	Red	Red	Red	Red	Green	Green
Karavelioglou 2010	Red	Red	Red	Red	Red	Red	Yellow
Kim 2004	Red	Red	Red	Red	Red	Red	Yellow
Li 2010	Red	Red	Red	Red	Green	Green	Yellow
Luo 2013	Red	Red	Red	Red	Red	Green	Yellow
Mai 2013	Red	Red	Red	Green	Red	Green	Yellow
Mathur 2015	Red	Red	Red	Red	Red	Green	Yellow
Nuruddin 2019	Red	Red	Red	Red	Red	Green	Yellow
Porwal 2018	Red	Red	Red	Red	Red	Red	Yellow
Raichura 2017	Red	Red	Red	Red	Red	Green	Yellow
Regmi 2017	Red	Red	Red	Red	Red	Red	Yellow
Shigematsu 2019	Red	Red	Red	Red	Green	Green	Yellow
Sindel 2018	Red	Red	Red	Red	Red	Red	Yellow
Spence 2010	Red	Red	Red	Red	Green	Green	Yellow
Sung 1995	Red	Red	Red	Red	Red	Red	Yellow
Wu 2016	Red	Red	Red	Green	Red	Green	Yellow
Xu 2014	Red	Red	Red	Red	Red	Green	Yellow
Yang 2011	Red	Red	Red	Red	Red	Green	Yellow
Yue 2013	Red	Red	Red	Yellow	Red	Green	Yellow
Yura 1997	Red	Red	Red	Red	Red	Yellow	Yellow
Zheng 2009	Red	Red	Red	Red	Green	Green	Yellow
Zhong 1998	Red	Red	Red	Red	Red	Red	Yellow
Zulfiquar 1999	Red	Red	Red	Red	Red	Red	Red

Figure 2: Judgments about each risk of bias item for each included study.

head and neck region. The lesion reduction was found in 93.7% (95% CI 88.5%–98.9%) of subjective or objective lesion size making it a highly effective treatment in the head and neck regions (Table 1). No studies reported the recurrence of these lesions. Minor self-limiting complications occurred in 16.2% (95% CI 10.5%–21.7%) of patients while major complications occurred only in four patients (1.1%, 95% CI 0%–2.5%) including death of one patient (0.3%, 95% CI 0%–0.8%). However, the exact circumstances of death in this one patient were not described.⁴⁵ Our results suggested that bleomycin/pingyangmycin treatment is relatively safe with minimal major non-self-limiting complications.

The included studies did not specify the specific location of the lesions in the head and neck region. The included studies also did not specify whether the lesions were primarily venous or lymphatic or mixed or macro- versus microcystic type. Although these will be of interest to know, our study could not shed light on these issues. It is considered that microcystic lymphangiomas tend to be more resistant to treatment than macrocystic lymphangiomas possibly because there are no obvious cysts to target within the lesion.⁴⁶ The therapeutic effect on large diffuse lesions was poor.⁴⁶

Completeness and Applicability of Evidence

This review synthesized evidence provided by 32 studies from different parts of the world published before May 2019. A high heterogeneity in the dosage, administration protocols, administration techniques, follow-up, and outcome measures after bleomycin sclerotherapy was noted among studies. This review highlights the need and may help in designing a more standardized protocol of bleomycin sclerotherapy and outcome assessment.

Quality of Evidence

The overall quality was low by GRADE approach⁵⁴ since most of the included studies suffered from a high risk of bias (Figure 3).

Potential Bias in the Review Process

Two reviewers (SF and KF) independently screened all the studies to reduce any bias during the screening process. The inclusion of only studies with full publication in peer-reviewed journals led to publication bias. This was done to keep the quality of evidence to the highest possible level. Only studies published in the English language were included due to the lack of translation service for appropriate translation of studies published in languages other than English.

How is this Different from Other Reviews?

This is the most updated review on bleomycin/pingyangmycin sclerotherapy of venolymphatic malformations. Earlier systematic reviews were assessed for venolymphatic malformation anywhere in the body.^{10,55–57} Our study is the first one on head and neck venolymphatic malformation. We excluded high-flow malformations in our study as they are known not to respond very well to bleomycin/pingyangmycin treatment.

AUTHOR’S CONCLUSION

Implication for Practice

The grade of evidence, in favor of bleomycin treatment for head and neck venolymphatic malformations, is only moderate. However, for clinical practice, a randomized clinical trial (RCT) to prove this beyond doubts is warranted.

Implications for Research

In our review, the evidence for the efficacy of bleomycin treatment for subjective or objective lesion reduction of venolymphatic malformations of the head and neck is only moderate. For a higher level of evidence, an RCT is warranted.

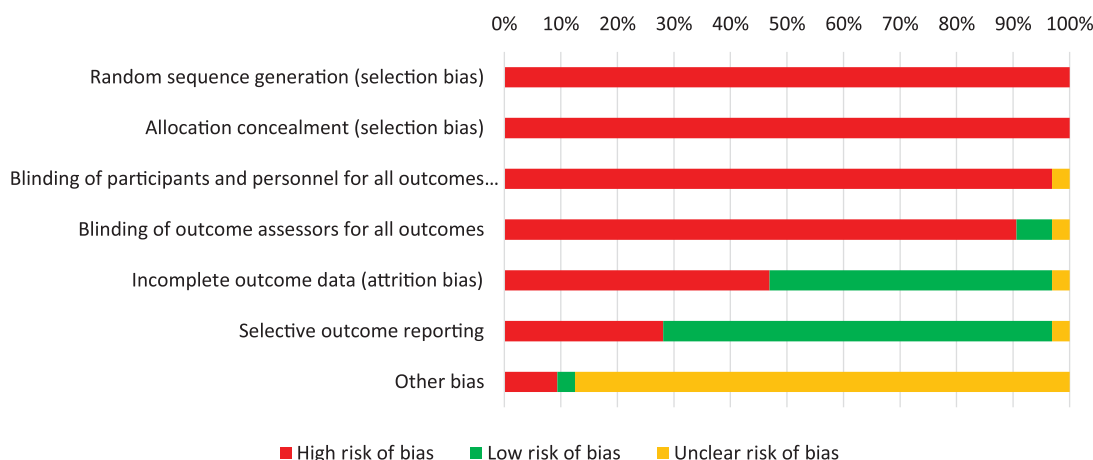


Figure 3: Risk of bias graph, judgments about each risk of bias item presented as percentages across all included studies.

Conclusions

Bleomycin sclerotherapy is effective and relatively safe in the treatment of venolymphatic malformations of the head and neck region.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

STATEMENT OF AUTHORSHIP

SF – Data collection, analysis, and manuscript preparation and review; KF – Data collection and manuscript review; JL – Search and manuscript review; JJSS – Conceptualization, data collection, analysis, and manuscript preparation and review.

ETHICAL APPROVAL

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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