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Austrian Institute for
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Systematic Review

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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Content

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List of abbreviations

AE..... Adverse event
CR ..... Complete Response
ECT..... Electrochemotherpy
ISSVA..... International Society for the Study of Vascular Anomalies
LPFS ..... Local progression-free survival
OS..... Overall survival
PR..... Partial Response
PD ..... Progressive Disease
QoL ..... Quality of life
RCT..... Randomised controlled trial
RECIST ..... Response Evaluation Criteria in Solid Tumours
SAE..... Serious adverse event
SD..... Stable Disease

Executive Summary

Introduction

Health Problem

vascular anomalies are rare diseases

Vascular anomalies are disorders of the endothelium that affect capillaries, arteries, veins, or lymphatic vessels. They are categorized as vascular tumours (with increased cell proliferation) and vascular malformations (congenital developmental defects). One hundred twenty-one different diseases are subsumed under this generic term. The overall prevalence of vascular anomalies is approximately 4.5%, of which the majority are hemangioma, a vascular tumour that usually regresses spontaneously. The other vascular anomalies are much less common.

symptoms: asymptomatic to functionally limiting and life-threatening

Symptoms of vascular anomalies vary depending on size, location, and histology and range from asymptomatic, cosmetically disturbing, to painful, functionally limiting, or even life-threatening. Therefore, diagnosis and therapy can differ greatly between entities and patients. Therapeutic options include both local therapies (e.g., surgery, sclerotherapy, topical drugs, laser, radiotherapy) for benign/locally destructive vascular tumours and vascular malformations and systemic therapy options (e.g., chemotherapy, immunotherapy) for malignant tumours. Vascular anomalies have in common that there are usually few evidence-based treatment options and recommendations due to the rarity of the conditions.

few evidence-based treatment options

Description of the Technology

electroporation: cell membranes temporarily more permeable = increased effect of bleomycin

Electrochemotherapy is based on reversible electroporation, in which cell membranes are exposed to electrical pulses. This method is intended to increase the permeability of hydrophilic molecules, which normally have difficulty penetrating the membrane, thus enhancing the chemotherapeutic agents' effect. Bleomycin is the most frequently administered drug in this context. After bleomycin is administered locally or systemically, short, weak electrical pulses are delivered around or directly into the lesion using surface plates or needle electrodes. Electrochemotherapy used for vascular malformations is also called electrosclerotherapy.

electrochemotherapy for vascular anomalies = Electrosclerotherapy

Electrosclerotherapy is currently not reimbursed in Austria

Bleomycin electrosclerotherapy is currently not included in the Austrian service catalogue for the indication of vascular anomalies. According to the submitted documents, the associated codes (EC040, EF020) do not reflect procedural, personnel, or material costs.

Research question

synthesis of evidence for comparative clinical effectiveness & safety

Is bleomycin electrosclerotherapy in patients with vascular anomalies more effective and equally safe or equally effective and safer in terms of disease progression, recurrence rate/progression-free survival, survival, symptom control, and improvements in health-related quality of life (HRQoL), as well as postinterventional adverse events and serious adverse events (AEs, SAEs), compared with standard treatment?

Methods

systematic literature search

A systematic literature search was performed to answer the research questions on the effectiveness and safety of bleomycin electrosclerotherapy in vascular anomalies. In addition, a hand search was performed, and the manufacturer was contacted.

RoB & GRADE

Studies were selected independently by two authors. Study data were extracted by one author and cross-checked by two authors. The risk of bias (RoB) of the included studies was systematically assessed using the IHE checklist for case series. The quality of evidence was assessed according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) by one author and controlled by a co-author.

Domain efficacy

endpoints for recommendation on the efficacy

The following endpoints were considered critical to the evaluation of efficacy:

Response rate/change in size, recurrence rate/progression-free survival, survival, pain, other disease-related symptoms (swelling, impaired exercise capacity, wounds, skin discoloration), and quality of life.

Domain safety

endpoints for recommendation on safety

The following endpoints were considered critical to the evaluation of safety:

Pain, skin toxicity, and all (serious) adverse events (AEs, SAEs).

Results

Available evidence

no controlled studies identified

evidence: 8 case series involving 151 patients (pts)

Eight studies met the inclusion criteria. No controlled studies were identified. Therefore, an assessment of efficacy was not possible. The included studies are two retrospective and six prospective case series with a total of 151 patients, all of which were used to evaluate safety. Three studies investigated bleomycin electrosclerotherapy in patients with Kaposi sarcoma, two studies in patients with angiosarcoma and one study each in patients with vascular malformations, venous malformations and hypertrophic capillary malformations. Accordingly, the inclusion and exclusion criteria of the included studies are heterogeneous.

Clinical efficacy

no efficacy studies identified

No data on efficacy from controlled trials were available for bleomycin electrosclerotherapy.

Safety

safety: no controlled studies

No controlled study was identified. Overall, the reporting of adverse events and complications in the included studies was inconsistent, and statistical analyses were rarely performed.

no SAEs

Serious Adverse Events (SAEs): Six included studies reported on SAEs. No SAEs occurred in the six studies with 128 patients. One study reported fever and nausea associated with treatment, but the number of patients affected was not reported.

Pain: Pain was reported in all included studies. Not all studies provided information on the pain assessment tools used or the actual number of patients with pain (descriptive data). In the four studies that reported the number of patients with pain, 15 of 90 patients (16.6%) reported post-operative pain. In two studies, more patients reported pain before treatment than at follow-up. In one study, pain during treatment was assessed using a 7-point Likert scale. Patients rated, on average, 4.7 points for pain during treatment.

post-operative pain: 15 of 90 pts

Skin toxicity: Skin toxicity was reported in all included studies, although exact numbers were not always reported. Overall, 40 of 107 (37.3%) patients in five studies suffered from skin toxicity. One study reported skin toxicity but did not provide patient-specific results. The most common adverse event was **skin ulceration**, reported in 17 of 97 patients (17.5%) in five studies, followed by **erythema/swelling** in 16 of a total of 127 (12.5%) patients in six studies. **Hyperpigmentation** was reported in seven of 127 (5.5%) patients in six studies, and **infections** were reported in eight of 127 (6.2%) patients in six studies. Four studies reported on **bleeding**. Post-treatment bleeding was reported in two of 88 patients (2.2%). The number of patients who bled after the procedure decreased in two studies. **Skin necrosis** was reported in two of 127 patients (1.5%) in six studies. No statistical analyses of skin toxicity, including bleeding, were performed, and overall skin toxicity was mostly mild and healed spontaneously.

skin toxicity: 40 of 107 pts
skin ulceration: 17 of 97 pts
erythema/swelling: 16 of 127 pts
Hyperpigmentation: 7 of 127 pts
Infections: 8 of 127 pts
Post-operative bleeding: 2 of 88 pts
Skin necrosis: 2 of 127 pts

In one of the included studies involving five patients with hypertrophic capillary malformations, lesions in three comparable regions were selected in each patient and randomly assigned to one of three treatment arms (bleomycin electrosclerotherapy, bleomycin alone, no therapy). Because of the study design and size (pilot study), this study was considered a case series, although it compared different treatment modalities. After electrosclerotherapy, mild hyperpigmentation was reported in two patients (40%) and superficial skin necrosis in one patient (20%). In the regions treated with bleomycin alone, single patients reported mild erythema (20%), hematoma (20%), and hyperpigmentation (20%). No adverse events were reported for the regions that received no treatment.

Upcoming evidence

A search for ongoing trials or planned controlled trials was conducted in three clinical trial registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) in March 2023. Two single-arm studies of bleomycin electrosclerotherapy treating vascular malformations were identified (NCT05494710 and DRKS00031072). Because these studies are uncontrolled studies, it will most likely not contribute to current safety findings.

2 ongoing single-arm studies

Discussion

The current evidence on bleomycin electrosclerotherapy is mainly based on prospective and retrospective single-arm case series with small sample sizes. The studies have a number of serious limitations. Therefore, the results of this systematic review should be interpreted with caution regarding internal and external validity.

evidence based on small case series; limited internal & external validity

No evidence was available to evaluate efficacy. Regarding the safety of bleomycin electrosclerotherapy, serious adverse events are rare, and other side effects are usually mild and self-limiting. A comparison with the safety profile of other treatments was not possible because of the study designs of the included trials.

serious adverse events rare, side effects often mild & self-limiting

high-quality guidelines needed

Treatment of rare vascular anomalies is mostly not evidence-based due to the lack of robust clinical trials, and high-quality guidelines are lacking. A German S3 guideline for vascular malformations has been registered and is expected to be completed in 2024. However, conducting studies and collecting robust data is generally challenging in the field of rare diseases.

Conclusion

no robust clinical comparative data available → no solid conclusions Possible; controlled studies needed

In summary, no clear conclusion can be drawn as to whether bleomycin electrosclerotherapy leads to better results than current treatment standards, as no robust comparative studies are available. In individual cases, i.e., when current treatment options are exhausted or not applicable, bleomycin electrosclerotherapy seems to be a potentially safe treatment option due to its preliminary safety profile and lack of evidence-based standard therapies. However, the safety profile is also highly uncertain due to the limited evidence of the available studies.

inclusion is currently not recommended

Due to the methodological shortcomings of the available evidence and the lack of controlled evidence, the inclusion of bleomycin electrosclerotherapy in the catalogue of benefits is currently not recommended.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Vaskuläre Anomalien sind Störungen des Endothels von Kapillaren, Arterien, Venen oder Lymphgefäßen. Der Begriff wird in vaskuläre Tumore (mit erhöhter Zellproliferation) und vaskuläre Malformationen (angeborene Entwicklungsdefekte) unterteilt und subsumiert 121 verschiedene Gefäßerkrankungen. Die Prävalenz der vaskulären Anomalien liegt insgesamt bei etwa 4,5%, wobei der überwiegende Teil auf das Hämangiom, einen sich in der Regel spontan zurückbildenden Gefäßtumor, zurückzuführen ist. Die anderen vaskulären Anomalien sind weitaus seltener.

121 verschiedene vaskuläre Anomalien & viele sind selten

Die Symptome der vaskulären Anomalien sind je nach Größe, Lokalisation und Histologie unterschiedlich und reichen von asymptomatisch, kosmetisch störend bis zu schmerzhaft, funktionell einschränkend oder sogar lebensbedrohlich, weshalb Diagnostik und Therapie sich zwischen Entitäten und Patient*innen stark unterscheiden können. Therapeutische Möglichkeiten umfassen sowohl lokale Therapieformen (z. B. Operation, Sklerotherapie, topische Arzneimittel, Laser, Radiotherapie) bei benignen/lokal destruktiven Gefäßtumoren und vaskulären Malformationen, als auch systemische Therapieoptionen (z. B. Chemotherapie, Immuntherapie) bei bösartigen Tumoren. Gemein ist den vaskulären Anomalien, dass es aufgrund der Seltenheit der Erkrankungen meist nur wenige evidenzbasierte Behandlungsoptionen und –Empfehlungen gibt.

Symptome: asymptomatisch bis funktionell einschränkend und lebensbedrohlich

Diagnostik & Therapie unterschiedlich

fehlende hochwertige Leitlinien = kein Goldstandard

Beschreibung der Technologie

Die Elektrochemotherapie basiert auf der reversiblen Elektroporation, bei der die Zellmembranen elektrischen Impulsen ausgesetzt werden. Mit dieser Methode soll die Permeabilität für hydrophile Moleküle, die die Membran normalerweise nur schwer durchdringen können, erhöht und somit die Wirkung von Chemotherapeutika verstärkt werden. Bleomycin ist dabei das am häufigsten verabreichte Medikament. Weiters wird bei der Elektrochemotherapie eine niedrigere Bleomycindosis benötigt.

reversible Elektroporation: Zellmembranen vorübergehend durchlässiger = verstärkte Wirkung von Bleomycin

Die Elektrochemotherapie wird in einem chirurgischen Setting durchgeführt. Möglich ist die Durchführung in Vollnarkose oder lokaler Anästhesie mit oder ohne Sedierung. Nachdem Bleomycin lokal oder systemisch verabreicht wurde, werden mit Hilfe von Oberflächenplatten oder Nadelelektroden kurze, schwache elektrische Impulse um die Läsion herum oder direkt in die Läsion abgegeben.

chirurgisches Setting mit lokaler Anästhesie oder Vollnarkose

Die Elektrochemotherapie wird bereits in der Dermatologie zur Behandlung kutaner Metastasen jeglicher Histologie sowie von primärem Hautkrebs eingesetzt. Die Elektrochemotherapie von vaskulären Malformationen wird als Elektrosklerotherapie bezeichnet.

Elektrochemotherapie bei Vaskulären Anomalien = Elektrosklerotherapie

Fragestellung

Ist die Bleomycin-Elektrosklerotherapie im Vergleich zur Standardbehandlung bei Patient*innen mit vaskulären Anomalien wirksamer und gleich sicher oder gleich wirksam und sicherer in Bezug auf den Krankheitsverlauf, Rezidivrate, Überleben/progressionsfreies Überleben, Symptomkontrolle und

Forschungsfrage

Verbesserungen der gesundheitsbezogenen Lebensqualität (HRQoL) sowie postinterventionelle Nebenwirkungen und schwerwiegende unerwünschte Ereignisse (SAE)?

Methoden

systematische Literatursuche in 4 Datenbanken

Die Beantwortung der Forschungsfragen bezüglich der Wirksamkeit und Sicherheit von Bleomycin-Elektrosklerotherapie bei vaskulären Anomalien erfolgte anhand einer systematischen Literatursuche in folgenden Datenbanken: Medline via Ovid, Embase, The Cochrane Library, INAHTA Datenbank. Die Suche beschränkte sich auf kein Publikationsjahr oder Studiendesign, jedoch auf Artikel, die in englischer oder deutscher Sprache veröffentlicht wurden. Zusätzlich wurde eine Handsuche durchgeführt und der Hersteller kontaktiert.

RoB- & GRADE-Bewertung

Die Studienauswahl erfolgte unabhängig durch zwei Autor*innen. Studiendaten wurden von einem Autor extrahiert und von zwei Autor*innen kontrolliert. Das Risiko einer Verzerrung (risk of bias; RoB) der eingeschlossenen Studien wurde systematisch mit Hilfe der IHE-Checkliste für Fallserien bewertet. Die Bewertung der Qualität der Evidenz nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) wurde von einem Autor vorgenommen und von einem Co-Autor kontrolliert.

Klinische Wirksamkeit

Endpunkte für Empfehlung hinsichtlich der Wirksamkeit

Zur Bewertung der Wirksamkeit der Bleomycin-Elektrosklerotherapie wurden randomisierte kontrollierte Studien und prospektive nicht randomisierte kontrollierte Studien einbezogen. Folgende Endpunkte wurden als *entscheidend* für die Bewertung der Wirksamkeit eingestuft:

Ansprechrate/Größenänderung, Rezidivrate/progressionsfreies Überleben, Überleben, Schmerzen, andere krankheitsbedingte Symptome (Schwellungen, eingeschränkte körperliche Leistungsfähigkeit, Wunden, Hautverfärbungen) und Lebensqualität.

Sicherheit

Endpunkte für Empfehlung hinsichtlich der Sicherheit

In Bezug auf die Sicherheit wurden prospektive einarmige Studien (Fallserien), prospektive register-basierte Studien und andere Beobachtungsstudien (z. B. retrospektive Fallserien) in den vorliegenden Bericht aufgenommen. Folgende Endpunkte wurden als *entscheidend* für die Bewertung der Sicherheit eingestuft: Schmerzen, Hauttoxizität und alle (schwerwiegenden) unerwünschten Ereignisse (AEs, SAEs).

Ergebnisse

Verfügbare Evidenz

keine kontrollierten Studien verfügbar; Evidenz: 2 retrospektive & 6 prospektive Fallserien; Insgesamt 151 Patienten

Acht Studien erfüllten die Einschlusskriterien. Es wurden keine kontrollierten Studien identifiziert, weshalb eine Bewertung der Wirksamkeit nicht möglich war. Die inkludierten Studien sind zwei retrospektive und sechs prospektive Fallserien mit insgesamt 151 Patient*innen, welche zur Bewertung der Sicherheit herangezogen wurden. Drei Studien untersuchten die Bleomycin-Elektrosklerotherapie bei Patient*innen mit Kaposi-Sarkom, zwei Studien bei Patient*innen mit Angiosarkom und jeweils eine Studie bei Patient*innen mit vaskulären Malformationen, venösen Malformationen und hypertrophen kapillären Malformationen. Dementsprechend heterogen sind auch die Ein- und Ausschlusskriterien der inkludierten Studien.

Klinische Wirksamkeit

Für die Bleomycin-Elektrosklerotherapie lagen keine Wirksamkeitsdaten aus kontrollierten Studien vor.

kein Vergleich mit Standardtherapie oder konservativer Therapie möglich

Sicherheit

Sicherheit: keine Vergleiche der Endpunkte möglich

Es wurde keine kontrollierte Studie identifiziert, weshalb kein Vergleich zwischen der Bleomycin-Elektrosklerotherapie und einer Standardbehandlung in Bezug auf die Sicherheit der Technologie gezogen werden konnte. Insgesamt war die Berichterstattung über unerwünschte Ereignisse und Komplikationen in den inkludierten Studien uneinheitlich, und statistische Analysen wurden nur selten durchgeführt.

keine SAEs

Schwerwiegende unerwünschte Ereignisse (SAEs): Sechs inkludierte Studien berichteten über SAEs. In den sechs Studien mit 128 Patient*innen traten keine SAEs auf. Eine Studie berichtete über Fieber und Übelkeit in Zusammenhang mit der Behandlung, die Anzahl der betroffenen Patient*innen wurde aber nicht genannt.

hauptsächlich deskriptive Daten

postoperativer Schmerz 15 von 90 Patient*innen (Pts) (4 Studien)

Schmerzen: In allen inkludierten Studien wurde über Schmerzen berichtet. Nicht alle Studien machten Angaben zu den benutzten Instrumenten zur Schmerzerfassung oder zur tatsächlichen Anzahl der Patient*innen mit Schmerzen (deskriptive Daten). In den vier Studien, die Angaben zur Anzahl der Patient*innen mit Schmerzen machten, gaben 15 von 90 Patient*innen (16,6 %) Schmerzen nach der Behandlung an. In zwei Studien gaben vor der Behandlung mehr Patient*innen Schmerzen an als bei der Nachuntersuchung. In einer Studie wurden die Schmerzen während der Behandlung anhand einer 7-Punkte-Likert-Skala bewertet. Die Patient*innen bewerteten die Schmerzen während der Behandlung im Durchschnitt mit 4,7 Punkten.

Hauttoxizität 40 von 107 Pts
Hautulzerationen 17 von 97 Pts
Erythemen/Schwellungen 16 von 127 Pts
Hyperpigmentierung 7 von 127 Pts
Infektion 8 von 127 Pts
Postoperative Blutungen 2 von 88 Pts
Hautnekrosen 2 von 127 Pts

Hauttoxizität: In allen inkludierten Studien wurde über Hauttoxizität berichtet, wobei nicht immer konkrete Zahlen berichtet wurden. Insgesamt litten 40 von 107 (37,3 %) Patient*innen in fünf Studien unter Hauttoxizität. Eine Studie berichtete über Hauttoxizität, lieferte jedoch keine auf Patient*innen bezogenen Ergebnisse. Die häufigste Nebenwirkung waren **Hautulzerationen**, die in fünf Studien bei 17 von 97 Patient*innen (17,5 %) berichtet wurden, gefolgt von **Erythemen/Schwellungen** bei 16 von insgesamt 127 (12,5 %) Patient*innen in sechs Studien. **Hyperpigmentierung** wurde bei sieben von 127 (5,5 %) Patient*innen in sechs Studien berichtet und Infektionen wurden bei acht von 127 (6,2 %) Patient*innen in sechs Studien berichtet. Vier Studien berichteten über **Blutungen**. Blutungen nach der Behandlung wurden bei zwei von 88 Patient*innen (2,2 %,) berichtet. In zwei Studien nahm die Zahl der Patient*innen, die nach dem Eingriff bluteten, ab. **Hautnekrosen** wurden in sechs Studien bei zwei von 127 Patient*innen (1,5 %) berichtet. Es wurden keine statistischen Analysen zur Hauttoxizität, einschließlich Blutungen, durchgeführt, und insgesamt war die Hauttoxizität meist leicht und heilte spontan ab.

In einer der inkludierten Studien, an der fünf Patient*innen mit hypertrophen kapillären Malformationen teilnahmen, wurden bei jedem der Patient*innen drei vergleichbare Regionen innerhalb der Läsionen ausgewählt und nach dem Zufallsprinzip in einen der drei Behandlungsarme (Bleomycin Elektrosklerotherapie, Bleomycin alleine, keine Therapie) zugeteilt. Nach der Elektrosklerotherapie wurden bei zwei Patient*innen (40 %) eine leichte Hyperpigmentierung und bei einem Patienten (20 %) eine superfizielle Hautnekrose festgestellt. In den mit Bleomycin allein behandelten Regionen be-

richteten einzelne Patient*innen über leichte Erytheme (20 %), Hämatome (20 %) und Hyperpigmentierung (20 %). Für die Regionen, die keine Behandlung erhielten, wurden keine unerwünschten Ereignisse berichtet.

Laufende Studien

2 laufende einarmige Studien

Eine Suche nach laufenden Studien oder geplanten kontrollierte Studien wurde in drei klinischen Studienregistern (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) im März 2023 durchgeführt. Zwei einarmige Studien zur Bleomycin-Elektrosklerotherapie bei der Behandlung von Gefäßfehlbildungen wurde identifiziert (NCT05494710 und DRKS00031072). Da es sich um weitere, unkontrollierte Studien handelt, werden sie höchstwahrscheinlich nicht zu den derzeitigen Erkenntnissen über die Sicherheit beitragen.

Kostenerstattung

in Ö ist Elektrosklerotherapie derzeit nicht im LKF Katalog abgebildet

Die Bleomycin-Elektrosklerotherapie ist derzeit nicht im österreichischen Leistungskatalog für die Indikation der vaskulären Anomalien enthalten. Die zugehörigen Kodes (EC040, EF020) spiegeln nach den eingegangenen Einreichunterlagen nicht die Verfahrens-, Personal- und Sachkosten wider.

Diskussion

Evidenz: kleine Fallserien

Die derzeitige Evidenz zur Bleomycin-Elektrosklerotherapie basiert hauptsächlich auf prospektiven und retrospektiven einarmigen Fallserien mit kleinen Stichprobengrößen. Diese Studien weisen eine Reihe von schwerwiegenden Einschränkungen auf. Die Ergebnisse dieser systematischen Übersichtsarbeit sollten daher hinsichtlich der internen und externen Validität mit Vorsicht interpretiert werden.

eingeschränkte interne und externe Validität

schwerwiegende unerwünschte Ereignisse selten, Nebenwirkungen oft leicht & selbstlimitierend

Für die Bewertung der Wirksamkeit lag keine Evidenz vor. Was die Sicherheit der Bleomycin-Elektrosklerotherapie anbelangt, so sind schwerwiegende unerwünschte Ereignisse selten und andere Nebenwirkungen in der Regel leicht und selbstlimitierend. Ein Vergleich mit dem Sicherheitsprofil einer konservativen Therapie war aufgrund der Studiendesigns der inkludierten Studien nicht möglich.

bedarf nach hochwertige Leitlinien

Die Therapie der seltenen vaskulären Anomalien ist aufgrund des Mangels an aussagekräftigen klinischen Studien meist nicht evidenzbasiert und hochwertige Leitlinien fehlen. Eine deutsche S3-Leitlinie für vaskuläre Malformationen ist registriert und wird voraussichtlich 2024 fertiggestellt. Die Durchführung von Studien und das Erheben von robusten Daten ist im Bereich der seltenen Erkrankungen jedoch generell eine Herausforderung.

Schlussfolgerung

hoher Bedarf nach kontrollierten Studien

Zusammenfassend kann keine eindeutige Aussage darüber getroffen werden, ob die Bleomycin-Elektrosklerotherapie zu wesentlich besseren Ergebnissen führt als aktuelle Behandlungsoptionen, da keine belastbaren komparativen Studien vorliegen. Im Einzelfall, d. h. wenn aktuelle Behandlungsoptionen ausgeschöpft oder nicht anwendbar sind, scheint die Bleomycin-Elektrosklerotherapie aufgrund ihres vorläufigen nicht auffälligen Sicherheitsprofils und Ermangelung an evidenzbasierten Standardtherapien, eine potentielle sichere Behandlungsoption darzustellen. Aufgrund der begrenzten Evidenz der vorliegenden Studien (keine kontrollierten Studien) ist jedoch auch das Sicherheitsprofil mit hoher Unsicherheit verbunden.

Aufgrund des Mangels an robusten Daten reicht die derzeitige Evidenz nicht aus, um zu beweisen, dass die Bleomycin-Elektrosklerotherapie bei Gefäßanomalien wirksamer und ebenso sicher, oder ebenso wirksam und sicherer ist als eine Vergleichsmethode (z. B. Operation oder Sklerotherapie). In den retrospektiven und prospektiven Fallserien wurden keine größeren Sicherheitsbedenken berichtet. Aus diesem Grund wird die Bleomycin-Elektrosklerotherapie vorerst nicht für die Aufnahme in den österreichischen Krankenhausleistungskatalog empfohlen. Eine Re-Evaluierung ist für 2028 empfohlen.

ohne kontrollierte Studien keine Schlussfolgerungen über Wirksamkeit & Sicherheit möglich

Aufnahme in den Leistungskatalog wird derzeit nicht empfohlen

1 Background

1.1 Overview of the disease, health condition and target population[1]

1.1.1 Vascular anomalies[2,3]

verschiedene vaskuläre Anomalien & viele sind selten

Vascular anomalies are disorders of the endothelium that affect capillaries, arteries, veins, or the lymphatic system. According to the International Society for the Study of Vascular Anomalies (ISSVA) [1], vascular anomalies are categorized as vascular tumours with increased cell proliferation and vascular malformations with mesenchymal and angiogenetic disorders resulting from developmental defects. One hundred twenty-one different diseases are subsumed under this generic term. The overall prevalence of vascular anomalies is approximately 4.5%, of which the majority is due to haemangioma, a vascular tumour that usually regresses spontaneously. The other vascular anomalies are much less common [2, 3].

Vascular tumours[4,5,6,7,8,9]

Vascular tumours may be classified as benign, locally aggressive/borderline and malignant [1]. There are various tumour types with multiple histological and clinical manifestations (Table 1-1) [4].

Table 1-1: Vascular tumours according to ISSVA

	Histological entity		
	Benign	**Locally aggressive/borderline**	**Malignant**

Tumour type	■ Infantile hemangioma
	■ Congenital hemangioma
	  ▪ rapidly involuting hemangioma (RICH)
	  ▪ partially involuting hemangioma (PICH)
	  ▪ non-involuting (NICH)
	■ Spindle cell hemangioma
	■ Epitheloid hemangioma
	■ Pyogenic granuloma
	■ Tufted angioma
	■ Others
		■ Kaposiform hemangioendothelioma
		■ Retiform hemangioendothelioma
		■ Papillary intralymphatic angioendothelioma
		■ Composite hemangioendothelioma
		■ Kaposi sarcoma
		■ Others
			■ Angiosarcoma
			■ Epitheloid hemangioendothelioma
			■ Others

[1] This section addresses the EUnetHTA Core Model® domain CUR.

[2] **A0007** – What is the target population in this assessment?

[3] **A0023** – How many people belong to the target population?

[4] **A0024** – How are vascular anomalies and vascular tumours currently diagnosed according to published guidelines and in practice?

[5] **A0004** – What is the natural course of the disease or health condition?

[6] **A0005** – What is the burden of disease for patients with vascular malformations and vascular tumours?

[7] **A0003** – What are the known risk factors for vascular anomalies and vascular tumours?

[8] **A0024** – How are vascular anomalies and vascular tumours currently diagnosed according to published guidelines and in practice?

[9] **A0025** – How are vascular anomalies and vascular tumours currently managed according to published guidelines and in practice?

Diagnostik & Therapie für vaskuläre Tumore unterschiedlich

Vascular tumours require more or less diagnostics and treatments based on whether they are benign or malignant, their location and their symptoms.

The following are exemplary descriptions of some of the more common vascular tumours:

infantiles Hämangiom am häufigsten unter den gutartigen Gefäßtumoren

- **Haemangioma:** by far, infantile haemangioma is the most common among benign vascular tumours. 4-5% of all infants are affected. It usually develops in the first few weeks of life and regresses spontaneously with the patient's age without treatment [4]. According to a German S2k guideline, in complicated cases (e.g. functional impairment, ulceration), first-line therapy is systemic propranolol [5]. Other treatment options include topical treatment with timolol, intralesional triamcinolone, and systemic treatment with prednisolone. Rarely, surgical resection or laser-treatment may be indicated [4].

büschelartiges Angiom: angeborener oder erworbener Gefäßtumor

Kaposiform Hämangioendotheliom: seltener maligner Gefäßtumor der Haut und inneren Organe

- **Tufted angioma and Kaposiform hemangiothelioma:** tufted angiomas are benign tumours usually present in early childhood. They present as vascular lesions with irregular borders and a red to purple colour, typically on the trunk or extremities. It is a rare disease, but the exact prevalence is unclear [6]. Kaposiform hemangiothelioma is locally aggressive, also presenting in early childhood, as a raised, subcutaneous mass with purpuric colour. It usually affects the extremities and can cause musculoskeletal dysfunction with functional impairment or pain. Tufted angiomas and Kaposiform hemangiothelioma have similar histopathologic and clinical profiles. Their diagnosis is based on clinical examination and confirmed via MRI, ultrasound and biopsy. Laboratory evaluation is essential for the diagnosis of the Kasabach-Merritt phenomenon, a possibly life-threatening complication affecting coagulation. There is limited evidence regarding the efficacy of possible treatments. To our knowledge, no treatment guidelines exist. Treatment options include observation in asymptomatic lesions, surgical excision, pulsed dye laser, topical and systemic agents such as sirolmus, corticosteroids, vincristine and sirolimus [6, 7].

Kaposi-Sarkom: bösartig & befällt hauptsächlich die Haut und die Schleimhäute

- **Kaposi sarcoma:** Kaposi sarcoma is a rare disease originating from lymphatic endothelial cells. It is malignant, usually multilocular, and primarily affects the skin and mucous membranes. However, the lymphatic system and internal organs may also be affected. Kaposi sarcoma appears as purplish, reddish-blue or dark brown/black patches, plaques or nodules on the skin, typically on the lower extremities [8, 9]. Ninety-five per cent of all Kaposi sarcoma are caused by human herpes virus-8 (HHV-8). Risk factors are male sex, Eastern-European or Mediterranean heritage, older age, immunosuppression and HIV. Possible symptoms include oedema, bleeding and functional impairment. The prognosis of Kaposi sarcoma depends on the subtype. Usually, Kaposi sarcoma grows slowly and remains confined to the skin. Aggressive, rapidly progressive forms that may lead to death occur mainly in immunosuppressed or HIV-infected patients [10]. The suspected clinical diagnosis of Kaposi sarcoma should always be confirmed histologically. If visceral involvement is suspected, computer tomography, esophagogastroduodenoscopy, colonoscopy, and bronchoscopy may be necessary. Regarding German S1-guidelines, immediate, specific Kaposi sarcoma treatment is not always necessary if the prognosis is good and the patient is asymptomatic. Treatment of Kaposi sarcoma is either systemic for aggressive or disseminated forms or local for single lesions causing cosmetic or functional problems. In 2015, a

systematic review comparing the different treatment options for Kaposi sarcoma found that the existing evidence is of very low quality. Therefore no particular intervention can be recommended [11]. Local treatment options include intralesional chemotherapy, electrochemotherapy, local immunotherapy, cryotherapy and radiotherapy [8, 10].

- **Angiosarcoma:** angiosarcoma is an uncommon, aggressive tumour in either blood or lymphatic vessels. It is one of the most common tumours caused by therapeutic radiation, often after breast cancer or Hodgkin lymphoma treatment. In Germany, the estimated incidence is 40-50 cases per year [12]. Higher age and male sex are risk factors for angiosarcoma. The prognosis is poor, with five-year survival less than 40%. The evidence for the treatment of angiosarcoma is generally poor. However, there are treatment recommendations in a German S1-Guideline [12]. Complete surgical resection with wide margins is preferred in local or locoregional diseases when possible. Pre- or postoperative radiotherapy is often recommended because angiosarcomas frequently recur locally or metastasize distantly. The role of (neo-)adjuvant chemotherapy is unclear. Patients with unresectable or metastatic angiosarcoma are treated with chemotherapy and/or RT [13]. Electrochemotherapy is listed as a treatment option in the palliative setting [12].

Angiosarkom: aggressiver Tumor in Blut- oder Lymphgefäßen

Vascular malformations

Vascular malformations result from disorders of vascular development. They are always present at birth and never regress spontaneously. However, they may be asymptomatic at birth and over a long time before they start growing due to mechanical or hormonal influences. Depending on histology, size, and localization, they can cause pain, functional impairment, ulceration, infection, bleeding, peripheral malperfusion or cosmetic issues, among others [2, 14]. Vascular malformations are classified as capillary, venous, lymphatic, or arterio-venous, depending on their dominant involved vasculature. Furthermore, they can be either simple lesions with only one vessel type involved or combined lesions with a combination of vascular anomalies.

Symptome: asymptomatisch bis funktionell einschränkend

Vascular malformations are sub-classified as slow-flow (venous, capillary and lymphatic vessels) or fast-flow (direct fistulous arteriovenous connections) lesions [4, 15]. To date, there is no standardised diagnostic or therapeutic approach in most vascular anomalies. Treatment is primarily based on expert opinions rather than on evidence [2]. In our search, we found three relevant treatment guidelines: a Japanese guideline on vascular anomalies from 2017 [16], a US guideline on Port-Wine Birthmarks in Sturge-Weber-Syndrome [17] and a Guideline on venous malformations by the International Union of Phlebology [18]. These guidelines are consensus documents lacking evidence base regarding vascular anomalies. A German S3 guideline for vascular malformations is currently registered with estimated finalisation in 2024 [19].

vaskuläre Malformationen mit schnellem und langsamen Durchfluss

The following are exemplary descriptions of some of the more common vascular malformations:

- **Venous malformations:** Venous malformations are slow-flow lesions and the most common vascular malformation. Most of the patients experience swelling and pain [20]. Superficial and localised lesions may be diagnosed clinically. Doppler ultrasonography or MRI can be useful in extensive or deeply localised lesions in initial staging, and post-treatment follow-up. Sometimes a biopsy for a histopathological diag-

venöse Malformationen: am häufigsten vorkommene Malformationen

nosis may be required. The International Union of Phlebology guideline provides treatment recommendations for venous malformations [20]. For some venous malformations, observation may be sufficient. If treatment is necessary for symptoms or complications, first-line therapy is sclerotherapy. Sclerotherapy is the intralesional injection of a sclerosing agent (e.g., bleomycin, ethanol, hypertonic saline) [2, 21]. Multiple treatment cycles are often required. Surgical extirpation can be favourable in some lesions, especially small, well-localized lesions or venous malformations localized next to an important anatomical structure [4, 22].

kapilläre Malformationen = "Feuermal"

- **Capillary malformations:** Capillary malformations, also known as port wine stains or naevus flammeus, are slow-flow lesions [4]. They are usually diagnosed clinically. Capillary malformations primarily cause cosmetic problems and can therefore burden patients psychologically [23]. According to US- and Japanese guidelines, the first-line treatment is pulsed dye laser therapy, which lightens the port wine stains without scarring [16, 17].

Lymphangiom: Malformationen mit schnellem Durchfluss

- **Lymphatic malformations:** Lymphatic malformations are slow-flow lesions [4] and do not need to be treated unless they become very large or cause symptoms such as pain, bleeding or obstruction and distortion of surrounding structures [3, 15]. According to a Japanese guideline, first-line therapy is sclerotherapy or surgical removal, depending on the size and location of the lesion [16].

arteriovenöse Malformationen: schwierigste zu behandelnde Fehlbildungen

- **Arterio-venous malformations:** Arterio-venous malformations are fast-flow lesions and the most challenging malformations to treat. They expand over time and can cause serious clinical problems, including pain, ulceration, bleeding, destruction of vital structures, heart insufficiency, or cardiac failure in decompensated arterio-venous malformations [4]. According to Japanese guidelines, they are usually treated by embolization followed by resection[16]. However, a cure is rare because arterio-venous malformations often involve important anatomical structures. The treatment goal is usually a control of the lesion [3].

1.2 Features of the intervention[10]

1.2.1 Electrochemotherapy and Bleomycin Electrosclerotherapy[11,12,13,14,15]

durch reversible Elektroporation sind Zellmembranen vorübergehend durchlässiger

Electrochemotherapy is a treatment based on reversible electroporation, which utilises electric pulses to augment the effects of chemotherapy. Electroporation is based on permeabilizing cells in the tissue exposed to electric pulses to facilitate enhanced cellular uptake of hydrophilic chemotherapeutic agents [24]. This alteration of the cell membrane augments its permeability, thereby enabling molecules that are usually unable to traverse the cell membrane to be transported to the intracellular environment [24, 25].

verstärkte Wirkung von Chemotherapeutika (Bleomycin)

Bleomycin, a cytotoxic drug used as a sclerosing agent in treating vascular malformations, is the most commonly administered drug in electrochemotherapy [26]. Bleomycin can be injected either intravenously or intratumorally during the procedure of electrosclerotherapy.

chirurgisches Setting: lokale Anästhesie oder Vollnarkose

patient*innenindividuelle Applikation (Elektroden, Dosis, Dauer, Zyklen)

Electrochemotherapy is a local treatment performed in surgical settings with the patient under general or local anaesthesia with or without sedation. After drug administration, the treatment area must be evenly covered by a sufficient electric field, where the bleomycin dose is individualised and based on tumour size. Shortly after administering the drug, brief and intense electric pulses are delivered around or directly into the tumour using either surface plates or needle electrodes. This makes the cell membranes temporarily more permeable to the chemotherapeutic drugs, increasing their cytotoxic effect. Therefore a reduced dose of bleomycin can be administred.[16] Manufacturers offer differently shaped plates or electrodes depending on the tumour's size, extent, shape, and location. The duration of the treatment may vary according to the number and size of the tumours. For larger tumours, multiple applications may be required to cover the entire surface. Repeated treatments can be carried out if necessary and if the lifetime dose limits of the chemotherapy drugs are not exceeded [27, 28].

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10 This section addresses the EUnetHTA Core Model® domain TEC.

11 **B0004** – Who administers bleomycin electrosclerotherapy and the comparators and in what context and level of care are they provided?

12 **A0001** – For which health conditions, and for what purposes is bleomycin electrosclerotherapy used?

13 **A0002** – What is the disease or health condition in the scope of this assessment?

14 **B0008** – What kind of special premises are needed to use the technology and the comparator(s)?

15 **B0009** – What supplies are needed to use the technology and the comparator(s)?

16 **B0002** – What is the claimed benefit of bleomycin electrosclerotherapy in relation to the comparators?

Elektrochemotherapie: kutane Metastasen jeglicher Histologie sowie kutane Metastasen & primärer Hautkrebs

Elektrochemotherapie bei Vaskulären Anomalien = Elektrosklerotherapie

Electrochemotherapy has been used to treat cutaneous metastases of any histology and for cutaneous metastases and primary skin cancer [27, 28]. It is mainly used by dermatologists, plastic surgeons, head and neck surgeons, general surgeons, and oncologists, and for different degrees and manifestations of metastases to skin and primary skin tumours not amenable to surgery [24]. Electrochemotherapy of vascular malformations is called electrosclerotherapy [26]. The use of this procedure for treating vascular anomalies is relatively new, and this systematic review aims to explore if bleomycin electrosclerotherapy for vascular malformations and vascular tumours in comparison to standard of care is effective and safe. A proposed benefit of bleomycin electrosclerotherapy is the lower dose of bleomycin in comparison to sclerotherapy.

in Ö: Elektrosklerotherapie derzeit nicht im LKF Katalog abgebildet;

CE Kennzeichen für die gängigen Elektrosklerotherapie Geräte vorhanden

Bleomycin electrosclerotherapy is currently not included in the Austrian catalogue of benefits for the indication of vascular anomalies. Related codes (EC040, EF020) do not reflect procedure, personnel, and material costs according to the submission documents received.[17]

According to the submission materials, the expected annual utilisation of bleomycin electrosclerotherapy based on the previous years' experience is 80 interventions per year in Austria.[18] Features of the intervention and marketed products are displayed in Table 1-2.

Table 1-2: Features of the intervention and marketed products

	Electrosclerotherapy/electrochemotherapy	
Name/Proprietary name	CLINIPORATOR® [29]	CLINIPORATOR® VITAE [30]
Manufacturer	IGEA S.p.A. clinical biophysics	IGEA S.p.A. clinical biophysics
Names in other countries	N/A	N/A
Reference codes	Italian Medical Device Repertory: Registration Number: 295232/R	Italian Medical Device Repertory: Number: 425494/R
Class/GMDN code	EN 60601-1: Class I, BF MDD 93/42 CEE: IIa	EN 60601-1: Class I, BF MDD 93/42 CEE: IIb
CE-Certification	CE0051 (European directives for medical devices 93/42/CEE and 2007/47/CEE)	CE0051 (European directives for medical devices 93/42/CEE and 2007/47/CEE)
CND Classification:	K0299: Electrosurgery devices – others	K0299: Electrosurgery devices – others
Indications	Tumour nodules located to the skin, subcutaneous tissue, mucosa and parenchyma	Tumour nodules located to the skin, subcutaneous tissue, parenchyma and bone

[17] **A0021** – What is the reimbursement status of bleomycin electrosclerotherapy?

[18] **A0011** – How much is bleomycin electrosclerotherapy utilised?

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

Is bleomycin electrosclerotherapy, in comparison to standard of care in patients with vascular malformations and vascular tumours, more effective and equally safe or equally effective and safer concerning disease progression, recurrence rate, survival/progression-free survival, symptom control and improvements in health-related quality of life (HRQoL) as well as post-interventional side effects and serious adverse events (SAEs)?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

The inclusion criteria for relevant studies are summarised in Table 2-1.

Table 2-1: Inclusion criteria

Population	Adults and children with ■ Vascular Malformations (e.g., Capillary malformation, Lymphatic malformation, Venous malformation) ■ Vascular Tumours (e.g., Hemangioma, Kaposi sarcoma, Angiosarcoma)
Intervention	Bleomycin electrosclerotherapy *Medical devices: CLINIPORATOR® and CLINIPORATOR® VITAE by IGEA SpA*
Control	Standard of care (Surgery, Sclerotherapy)
Outcomes	
Efficacy	■ Complete response/partial response/Stable disease/progressive disease ■ Recurrence rate/progression-free survival ■ Survival ■ Other disease-related symptoms (pain, swelling, impaired physical functioning, wounds, skin discoloration) ■ Quality of life
Safety	■ Pain ■ Skin toxicity ■ Any procedure-related (serious) adverse events ■ Any device-related (serious) adverse events ■ Any adverse events/serious adverse events
Study design	
Efficacy	■ Randomised controlled trials ■ Prospective non-randomised controlled trials
Safety	■ Randomised controlled trials ■ Prospective non-randomised controlled trials ■ Prospective case series, prospective registry-based trials ■ Other observational studies (e.g. retrospective case series)

3 Methods

3.1 Research questions

Forschungsfragen nach EUnetHTA

Assessment elements from the EUnetHTA Core Model® for the production of rapid relative effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment [31]. The assessment elements are referred in the footnotes in each chapter.

3.2 Clinical efficacy and safety

3.2.1 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 16th of December 2022 in the following databases:

- The Cochrane Library
- Embase
- Medline via Ovid
- International Network of Agencies for Health Technology Assessment (INAHTA)

deutsche & englische Literatur

The systematic search was not date limited but was restricted to articles published in English or German. After deduplication, overall, 793 citations were screened by title and abstract. The specific search strategy employed can be found in the Appendix.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials (EUdraCT) Register) was conducted on the 9th of March 2023 resulting in 63 potential relevant hits.

A manufacturer (IGEA S.p.A. clinical biophysics) of currently available devices for bleomycin electrosclerotherapy/bleomycin-based electrochemotherapy (CLINIPORATOR® and CLINIPORATOR® VITAE) was contacted. The manufacturer did not respond.

nach Handsuche insgesamt 794 Publikationen identifiziert

One additional study was found by hand-search (screening reference lists of included studies and identified background literature, e.g. systematic reviews), resulting in overall 794 hits.

3.2.2 Flow chart of study selection

Literaturauswahl: 8 Fallserien

Overall, 794 hits were identified. Two independent researchers screened the references, and a third researcher was involved in resolving the differences in case of disagreement.

Randomised controlled trials and prospective non-randomised controlled trials were included for evaluating the efficacy of bleomycin electrosclerotherapy.

For safety issues, prospective single-arm studies (case series), prospective registry-based trials, and other observational studies (e.g. retrospective case series) were included in the present report. The selection process is displayed in Figure 3-1.

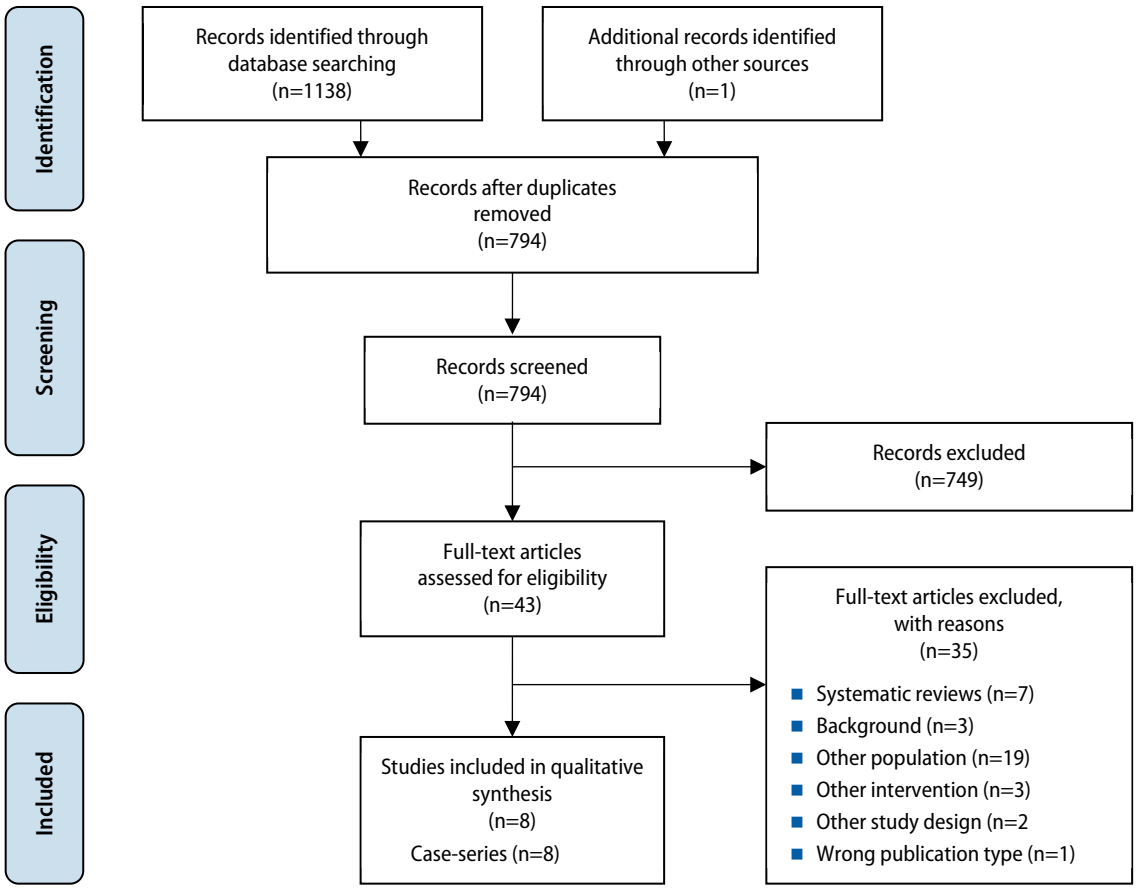

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

Datenextraktion

Bewertung des Verzerrungsrisikos (RoB) mit IHE-Checkliste

The data retrieved from the selected studies were systematically extracted into a data-extraction-table by one author (TJ) and controlled by the respective co-authors (NF, CS) (see Table A-1). No further data processing (e.g., indirect comparison) was applied. Subsequently, one researcher (TJ) systematically assessed the risk of bias (RoB) of the included studies using the International Health Economics (IHE) [32, 33] checklist with 20 assessment elements for case series and single-arm studies (see Table A-2). The risk of bias assessment was independently controlled by the respective co-author (CS).

Overall RoB for single-arm studies was calculated using a predefined point score (range: 0-20; Table 3-1): a high score indicates a low RoB and a low score indicates a higher RoB. Detailed thresholds are presented in Table 3-2.

Table 3-1: Overall risk of bias (RoB) point scores for RoB assessment of case series and single-arm studies

Answers to specific questions of the IHE-20 checklist	Points
No	0
Partial	0.5
Unclear	0.5
Yes	1

Table 3-2: Cut-off criteria for the risk of bias (RoB) assessment of overall RoB of case series and single-arm studies

Criteria	Points
Low risk	>18
Moderate risk	15.5 to 18
High risk	≤15

3.2.4 Synthesis

Verwendung von GRADE zur Synthese der Evidenz (sofern anwendbar)

Based on the data extraction tables (see Appendix Table A-1), data on each selected outcome category were, if applicable, synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [34]. The research questions were answered in plain text format with reference to GRADE evidence tables (see Table A-3).

4 Results: Clinical Efficacy and Safety

4.1 Outcomes

4.1.1 Outcomes efficacy

Entscheidungs-relevante Endpunkte für die Wirksamkeit:

The following outcomes were defined as critical to deriving a recommendation:

- **Response rate/change in size**
- **Recurrence rate/progression-free survival**
- **Survival**
- **Pain**
- **Other disease-related symptoms (swelling, impaired physical functioning, wounds, skin discolouration)**
- **Quality of life**

The outcomes defined as critical to deriving a recommendation are considered the most relevant to patients with vascular anomalies.

Ansprechrate

Response to therapy in terms of lesion shrinkage is a critical outcome to patients with malignant diseases (malignant vascular tumours) as well as for patients with locally destructive or symptomatic benign diseases (benign/ borderline vascular tumours, vascular malformations)[35]. Four studies used the Response Evaluation Criteria in Solid Tumours (RECIST) [36] to assess the response rate [37-40].

RECIST defines the response as [36]

- *Complete Response (CR):* the disappearance of all target lesions
- *Partial Response (PR):* At least a 30% decrease in the sum of diameters of target lesions
- *Progressive Disease (PD):* At least a 20% increase in the sum of diameters of target lesions
- *Stable Disease (SD):* Neither sufficient shrinkage to qualify for a partial response nor sufficient increase to qualify for progressive disease

Other studies used other clinical [41-43] or volumetric analysis [44] for the determination of response.

Rezidivrate

Recurrence rate as the duration of overall response, measured from the time measurement criteria first met for CR/PR until the first date of recurrent or progressive disease [36], is another critical outcome for malignant vascular tumours. The recurrence rate is reported in both included studies regarding angiosarcoma [37, 38] and in one study out of three regarding Kaposi sarcoma [40]. The importance of the recurrence rate for patients with vascular malformations is still under discussion [35]. The ongoing discussion is reflected by the included studies on vascular malformations, in which the recurrence rate was not reported [42-44]. Three studies [37, 38, 40] reported the recurrence rate also as **local progression-free survival** (LPFS, time from Electrochemotherapy to local recurrence or progression within ECTfield) or **progression-free survival** (PFS, date of Electrochemotherapy to disease progression at any site).

Überleben

Overall survival (OS) is a gold standard end point in evaluating a procedure in oncologic clinical trials [45]. It is reported in both included studies regarding angiosarcoma [37, 38] and in one study out of three regarding Kaposi sarcoma [40]. OS was not reported in the trials regarding vascular malformations. Since vascular malformations are rarely life-threatening, OS is not a critical outcome in these studies [35].

Schmerz

Pain is one of the main symptoms and, therefore, a critical outcome for patients with vascular anomalies [35]. Patient-reported pain intensity changes were reported in all included studies. In four studies, four different instruments were used. One study [37] used a 10-point Verbal Numerical Rating Scale [46] and another study used a 0-10 visual analogue scale [38]. In one study, pain assessment was part of the Patient and Observer Scar Assessment Scale (POSAS Score) [47]. The fourth study used a Likert type-7 point scale [42]. No specific instrument for pain assessment was used in the other four studies [39-41, 44]. Since pain is a symptom of the disease and a side effect of the treatment with bleomycin electrosclerotherapy, it is an outcome for efficacy and safety in this report.

andere krankheitsbedingte Symptome wie Schwellungen, eingeschränkte körperliche Leistungsfähigkeit, Wunden, Hautverfärbungen

Other disease-related symptoms such as swelling, impaired physical functioning, wounds or skin discolouration are other critical outcomes, especially for patients with vascular malformations [35] caused primarily by local destructive processes of the disease. Currently, there is no standardised instrument for reporting symptoms for patients with vascular malformations. Two out of three studies regarding vascular malformations reported other symptoms: one study [43] used the Patient and Observer Scar Assessment Scale (POSAS) for evaluating changes in symptoms [47], another study used a non-standardized clinical assessment (categorization as asymptomatic, improved, unchanged or worsened)[44].

Lebensqualität

Quality of life (QoL) is another important aspect in treating patients with vascular anomalies [35]. EQ 5D-3L score [48] was used in one study [38] and a non-validated instrument in another study [40]. The other included studies did not report QoL.

4.1.2 Outcomes safety

entscheidende Endpunkte für Sicherheit:

The following outcomes were defined as critical to deriving a recommendation:

- **Pain**
- **Skin toxicity**
- **Any procedure-related (serious) adverse events**
- **Any device-related (serious) adverse events**
- **Any adverse events/serious adverse events**

Pain and many symptoms of skin toxicity (e.g. necrosis, hyperpigmentation, and infection) can be caused by the disease and bleomycin electrosclerotherapy. Therefore, the safety outcomes must be cautiously interpreted.

Schmerz

Pain is a known side effect of electrosclerotherapy and a main symptom of patients with vascular anomalies. Therefore, pain is a critical outcome [35, 49]. Patient-reported pain intensity changes were reported in all included studies (see 4.1.1 on pain).

Skin toxicity is an important safety aspect when using electrosclerotherapy. The known adverse effects of the skin are inflammatory reaction, superficial necrosis, injection site rash, erythema, oedema, scarring, hyperpigmentation and infection [28, 50].

Hauttoxizität

Four of the eight included studies used standardized reporting criteria for adverse events or toxicity [37, 38, 40, 44]. Common Toxicity Criteria for Adverse Events (CTCAE v4.0 or v5.0) was used in two studies [37, 38]. One study used the Health Organization toxicity grading scale [40]. Another study [44] used the classification system of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) [51]. One study reported on adverse events during follow-up in a non-standardized way [43] and three studies did not provide any information on how they evaluated adverse events.

Serious adverse events (SAEs) comprise any adverse event with serious medical consequences, including post-interventional mortality, complications that result in substantial morbidity or disability, admission to the hospital or prolonged hospitalization [52]. Six out of eight included studies reported on serious adverse events [37-40, 42, 44].

schwerwiegende unerwünschte Ereignisse (UE)

Procedure-related adverse events (AEs) are complications associated with the intervention. Possible procedure-related complications are events related to anaesthesia or chemotherapeutic drug use [28]. Six out of eight included studies reported on procedure-related adverse events [37-41, 44].

verfahrensbedingte UE wie bspw. Infektionen

4.2 Included studies

4.2.1 Included studies for efficacy and safety

We considered RCTs and non-randomised controlled trials comparing bleomycin electrosclerotherapy with conservative interventions/standard of care (e.g. surgery or intralesional bleomycin alone – sclerotherapy), as well as retrospective and prospective single-arm studies reporting on before versus after intervention outcomes to evaluate the efficacy and safety of bleomycin electrosclerotherapy in patients with vascular malformations and vascular tumours.

Study characteristics

No comparative studies were identified. One study was a small pilot trial with five patients where three comparable regions (lesions) of interest within-patients were randomised [43]. In addition, no critical efficacy outcome was reported. In this report, we categorised this trial as a prospective single-arm case series. Therefore, the overall evidence covering safety issues is based on two retrospective [37, 44] and six prospective [38-43] single-arm studies (case-series). All studies were conducted in Europe (Germany, Italy, Netherlands, United Kingdom) and published between 2012 and 2021. Five studies were single-centred [39, 41-44] and three multi-centred [37, 38, 40]. In one study [43], electroporation equipment was provided by the manufacturer of the product, four studies did not report on a sponsor [37, 40-42] and three studies had no sponsor [38, 39, 44].

2 retrospektive & 6 prospektive unkontrollierte vorher/nachher Studien eingeschlossen

151 pts, 48 % Frauen, Alter: Ø 20-68 Jahre

A total of 151 patients were assessed pre-operatively in the eight included studies. Of the total included patients, 48.3% were female. The mean age ranged from 20.8 to 68.4 years, and the median age ranged from 69 to 77 years.

Follow-Up-Zeiten: Median 3,7 Monate bis 1,5 Jahre

The median follow-up of the studies ranged from 3.7 months to 1.5 years (overall range from two months to 4.2 years). The length of the follow-up period was not appropriately reported (mean, SD/median, range) in four trials [38, 41-43]. Loss to follow-up was only reported in one trial (response evaluation 10% and patient-reported outcome measures 27%) [42].

Patient characteristics

Indikationen & Einschlusskriterien heterogen: 3 Studien Kaposi-Sarkom, 2 Studien Angiosarkom, jeweils 1 Studie vaskuläre Malformationen, venösen Malformationen & hypertrophe kapilläre Malformationen.

The included studies are heterogeneous regarding the population (indication and inclusion criteria). Three studies evaluated bleomycin electrosclerotherapy in patients with Kaposi sarcoma [39-41] and two studies in patients with angiosarcoma (cutaneous angiosarcoma) [38] (locally advanced or metastatic angiosarcomas) [37]. Three single studies explored the effect of bleomycin electrosclerotherapy in congenital vascular malformations [42], venous malformations [44] and hypertrophic capillary malformations [43]. Therefore, the inclusion and exclusion criteria differed significantly between studies. For detailed information, see Appendix (Table A-1).

Intervention gut beschrieben

The delivery and procedure of bleomycin electrosclerotherapy were overall well described, including information on the use of the medical device. Only one study provided no information on the procedure [42]. Five studies [37-41] used the European Standard Operating Procedures on Electrochemotherpy (ESOPE) either from 2006 [53] or 2018 [24]. Depending on tumour size and location, either plate electrodes (960V) or needle electrodes (400 V) were used. Pulse application lasted between eight to 28 minutes. With every application, eight pulses were delivered in a standardized frequency of 100 Hz to 5000 Hz.

überwiegend Bleomycin intraläsional

1 Studie 90 % intravenös (kutanes Angiosarkom)

am häufigsten Vollnarkose gefolgt von Lokalanästhesie

Mehrfachzyklen: 1-3

In the studies evaluating bleomycin electrosclerotherapy in patients with Kaposi sarcoma [39-41] or locally advanced or metastatic angiosarcomas [37], all study participants received bleomycin intravenously. In studies evaluating the effect of bleomycin electrosclerotherapy in venous malformations [44], congenital vascular malformations [42], and hypertrophic capillary malformations [43], all study participants received bleomycin intralesionally. In one study treating patients with cutaneous angiosarcoma, participants received bleomycin either intravenously (90%) or intralesionally (10%) [38]. During treatment, general anaesthesia was the most common form of anaesthesia, followed by local anaesthesia. Depending on the response to therapy and tumour size, patients were treated in multiple cycles, ranging from one to three cycles per patient. Study characteristics and results of included studies are displayed in Table A-1, and the evidence profile in Table A-3.

4.3 Results

kein Vergleich mit Standardtherapie oder konservativer Therapie möglich

Without data from controlled trials, no comparisons can be made between the intervention bleomycin electrosclerotherapy and any conservative therapy/standard of care (e.g. surgery or intralesional bleomycin alone – sclerotherapy) for the treatment of patients with vascular malformations and vascular tumours.[19] No evidence was found to answer the research question on the efficacy of bleomycin electrosclerotherapy.

4.3.1 Results clinical efficacy[20,21,22,23,24]

keine vergleichenden Wirksamkeitsdaten verfügbar

For bleomycin electrosclerotherapy no efficacy outcomes were available.

4.3.2 Results safety[25,26,27,28]

nur Beobachtungsstudien für die Bewertung der Sicherheit

No comparative study was identified. One study was a small pilot trial with five patients where three comparable regions (lesions) of interest within-patients were randomised and not patients [43]. In this report, we categorised this trial as a prospective single-arm case series. Therefore, the overall evidence covering safety issues is based on two retrospective [37, 44] and six prospective [38-43] single-arm studies (case-series).

Due to the absence of controlled trial data, no comparisons can be made between bleomycin electrosclerotherapy and standard of care (e.g. surgery or intralesional bleomycin alone – sclerotherapy).

Concerning the safety of bleomycin electrosclerotherapy in treating patients with vascular malformations and vascular tumours, any AEs, SAEs, pain and skin toxicity (procedure-related) were considered critical/important outcomes.

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19 **B0010** – What kind of data/records and/or registry is needed to monitor the use of bleomycin electrosclerotherapy and the comparator?

20 **D0005** – What is the expected beneficial effect of bleomycin electrosclerotherapy on complete response/partial response/stable disease/progressive disease?

21 **D0006**– What is the expected beneficial effect of bleomycin electrosclerotherapy on recurrence rate/progression-free survival?

22 **D0001** – What is the expected beneficial effect of bleomycin electrosclerotherapy on mortality?

23 **D0012** – What is the expected beneficial effect of bleomycin electrosclerotherapy on generic quality of life?

24 **D0013** – What is the effect of bleomycin electrosclerotherapy on disease-specific quality of life?

25 **C0008** – How safe is bleomycin electrosclerotherapy in comparison to conservative therapy?

26 **C0002** – Are the harms related to dosage or frequency of applying the technology?

27 **C0005** – What are the susceptible patient groups that are more likely to be harmed through the use of bleomycin electrosclerotherapy?

28 **C0007** – Are the technology and comparator(s) associated with user-dependent harms?

Serious adverse events

keine SAEs

Six included studies reported narratively on serious adverse events. No serious adverse event occurred across the studies involving 128 patients undergoing bleomycin electrosclerotherapy [37-40, 42, 44].

verfahrensbedingte UE selten: Fieber und Übelkeit (keine Zahlen)

Procedure-related adverse events were reported in one study. However, the authors did not state how many patients had post-treatment fever and nausea [41].

keine gerätespezifischen UE

In five studies, no device-related adverse events were reported [37-39, 44] [40]. Three studies did not report device-related adverse events [41-43].

keine postoperativen UE

Six of the eight studies reported on post-operative adverse events. Not a single case was reported [37-42, 44]. Overall, adverse events/serious adverse events are rare.

Any adverse events[29,30,31]

Overall, reporting of adverse events and complications was inconsistent across included studies, and formal statistical analyses rarely were performed. Therefore, results on pain and skin toxicity are reported narratively.

Pain

Erhebungsinstrumente (4 Studien)

Patient-reported pain was reported in all included studies. However, not all studies provided information on pain assessment instruments or the actual number of patients with pain (descriptive data). The following instruments were used in four studies: a 10-point Verbal Numerical Rating Scale (VNRS) [37], a 0-10 visual analogue scale (VAS) [38], and pain assessment [43] as part of the POSAS Score [47] or a Likert type-7 point scale (during treatment) [42].

keine Erhebungsinstrumente (4 Studien)

In four studies, no specific instrument for pain assessment was used [39-41, 44].

postoperativer Schmerz 15 von 90 pts (4 Studien)

Four studies provided information on the number of patients having pain after treatment [38, 40, 42, 44]. Post-operative patient-reported pain was reported in 15 of 90 patients (16.6%, range 6.6-30%). Three studies did not report on the number of patients [39, 41, 43].

Schmerz als Symptom postoperativ berichtet (3 Studien)

Three studies reported pain as a symptom before the treatment (at baseline) and after the follow-up [37, 38, 44]. In one study, ten patients (52.6%) reported that the treated tumours were moderately (3-6 points, on the VNRS pain scale) to highly painful (7-10 points, on the VNRS pain scale) at baseline. Two months after bleomycin electrosclerotherapy, the pain level was significantly reduced and was indicated as “moderate” by only four patients (p-value = 0.01)[37]. In the second study, all patients (n=17) had pain preoperatively. After treatment, only five patients (29.4%) reported having mild pain (no statistical tests were performed)[44]. In the third study, there were no significant correlations between post-treatment pain and patient/tumour characteristics or electrochemotherapy parameters (quantitative data were not provided) using a visual analogue pain scale (0-10) [38].

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[29] C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of bleomycin electrosclerotherapy?

[30] C0002 – Are the harms related to dosage or frequency of applying the technology?

[31] C0007 – Are the technology and comparator(s) associated with user-dependent harms?

Another study used a pain item (POSAS Score), but no specific results on pain were provided [43]. One study evaluated pain during treatment using a Likert type-7 point scale. The patients rated the pain during treatment with 4.7 points on average (mild to moderate pain, SD not reported)[42].

Skin toxicity[32]

Hauttoxizität
40 von 107 Pts (5 Studien);
Hautulzerationen
17 von 97 Pts (5 Studien);
Erythemen/Schwellungen
16 von 127 Pts (6 Studien)

Skin toxicity was descriptively reported in seven studies [37, 38, 40-44]. Overall 40 of 107 (37.3%, range 5.6-60%) patients in five studies [37, 40-42, 44] suffered from some skin toxicity. One study reported skin toxicity but did not provide any results based on patients [39]. The most common adverse event was skin ulceration, reported in 17 of 97 patients (17.5%, range 0-47.3%) in five studies [37, 38, 40, 41, 44], followed by erythema/swelling in 16 of total 127 (12.5%, range 0-31.5%) patients in six studies [37, 38, 40-42, 44].

Hyperpigmentierung
7 von 127 Pts;
Infektion 8 von 127 Pts
(6 Studien)

Hyperpigmentation was reported in seven of 127 (5.5%, range 0-20%) patients in six studies [37, 38, 40-42, 44], and infection was reported in eight of 127 (6.2%, range 0-15%) patients in six studies [37, 38, 40-42, 44].

Postoperative Blutungen
2 von 88 Pts (4 Studien)

Four studies reported on bleeding [40-42, 44]. Post-treatment bleeding was reported in two of 88 (2.2%, range, 0-6.6%) patients. The two cases occurred in one study, followed by a full recovery [42]. In three studies, no cases of bleeding were reported [40, 41, 44].

In two studies [37, 38], the number of patients bleeding decreased after the intervention. These studies were not included in the GRADE table, as the bleeding was not reported as an adverse event. In the first study, lesions were bleeding pre-operatively in six patients, of whom bleeding persisted in one patient after treatment [37]. In the second study, pre-operative bleeding was reported in 14 patients (70%). At one month follow-up, one patient reported bleeding (5%)[38].

Hautnekrosen
2 von 127 Pts (6 Studien)

Skin necrosis was reported in six studies [37, 38, 40-42, 44] in two of 127 patients (1.5%, range 0-10%). The two cases occurred in one study [38]. In the other studies, no necrosis cases were reported [37, 40-42, 44]. No statistical analysis on skin toxicity, including bleeding were performed, and overall, skin toxicity was mostly mild with spontaneous healing.

Sicherheitsprofil
in der Pilot-Studie

In the small pilot study [43], including five patients with hypertrophic capillary malformations, lesions within patients were randomised to treatment arms (three comparable regions of interest). Each of the three regions were treated with either bleomycin electrosclerotherapy, bleomycin alone, or no treatment. After electrosclerotherapy, mild hyper-pigmentation was reported in two patients (40%) and superficial skin necrosis in one patient (20%). In regions treated with bleomycin alone, single patients reported on mild erythema (20%), hematoma (20%), and hyperpigmentation (20%). No adverse events were reported for the regions of interest receiving no treatment.

[32] All studies reported on skin toxicity, but the reporting was inconsistant. If an outcome was not specifically reported, but other symptoms were reported in detail and including numbers, the outcome of interest was rated as 0 and the study was included in the calculation (denominator).

5 Quality of evidence

Risk of Bias (RoB) mit IHE Checkliste bewertet; hohes RoB in den eingeschlossenen Studien

The risk of bias (RoB) for individual studies was assessed with the IHE checklist for single-arm studies [33] and is presented in Table A-2 in the Appendix. The overall RoB of each study was high.

The main reasons for downgrading were the single-centred set-up of the studies, lack of information about patients recruited consecutively, lack of blinding of the investigators, and patients entering the studies during different stages of the disease. Moreover, reasons were uncertainties in using appropriate statistical tests. In some studies, baseline patient characteristics and data distribution were not fully reported, and estimates of random variability in the data analysis of relevant outcomes were partially not reported. Furthermore, the length of follow-up periods (mean/median) and losses to follow-up were not always appropriately reported.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [34] (for each endpoint individually). Each study outcome was independently rated by two researchers (TJ, CS). In case of disagreement, a third researcher was involved in solving the difference (NF). A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [34].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking, according to the GRADE scheme, can be found in the summary of findings table below (Table 5-1) and in the evidence profile in Table A-3 in the Appendix.

Qualität der Evidenz der klinischen Wirksamkeit konnte aufgrund fehlender kontrollierter Studien nicht untersucht werden

The strength of evidence on clinical efficacy of bleomycin electrosclerotherapy in comparison to standard of care (e.g. surgery or sclerotherapy) could not be assessed due to the lack of trials with a comparative treatment arm (single-arm study design).

Overall, the strength of evidence for the safety of bleomycin electrosclerotherapy in vascular malformations and vascular tumours compared to conservative treatment is very low.

Table 5-1: Summary of findings table for bleomycin electrosclerotherapy

Outcomes	Impact	№ of studies (Pts I vs C)	Certainty of the evidence (Importance)	Comments
Efficacy				
Due to the lack of a control group, no data on efficacy can be reported				
Safety				
Any procedure-related (serious) adverse events	Post treatment fever and nausea in one study, no. of pts not reported.	1 (pts not reported) [41]	⨁◯◯◯ VERY LOW [1,2] (critical)	-
Any device-related (serious) adverse events	No device-related adverse events were reported.	5 observational studies (98) [37-40, 44].	⨁◯◯◯ VERY LOW [1,2] (critical)	-
Serious adverse events	No SAE was reported across all studies.	6 observational studies (128) [37-40, 42, 44]	⨁◯◯◯ Very LOW [1,2] (critical)	-
Pain	■ Patient-reported pain across the studies: in 15/90 pts (16.6%, range 6.6-30%) ■ Patient-reported pain was reported in all included studies. However, three studies provided no information actual number of pts with pain [39, 41, 43]. ■ One study [37] reported on pain reduction as effect after BEST. Pain was not reported as adverse event and therefore not included in this table.	4 observational studies (90) [38, 40, 42, 44]	⨁◯◯◯ VERY LOW[1,2] (critical)	-
Skin toxicity[3]	■ Overall skin toxicity across all studies[4]: in 40/107 pts (37.3%, range, 5.6-60%) [37, 40-42, 44] ■ Skin ulceration: 17/97 pts (17.5 %, range, 0-47.3%) [37, 38, 40, 41, 44] ■ Necrosis: 2/127 pts (1,5%, range 0-10%) [37, 38, 40-42, 44] ■ Erythema/swelling: 16/127 pts (12.5%, range 0-31.5%) [37, 38, 40-42, 44] ■ Bleeding[5]: 2/88 pts (2.2 %, range, 0-6.6%) [40-42, 44] ■ Infection[6]: 8/127 pts (6.2%, range, 0-15%) [37, 38, 40-42, 44] ■ Hyperpigmentation[6]: 7/127 pts (5.5%, range, 0-20%) [37, 38, 40-42, 44]	7 observational studies (146)[4]	⨁◯◯◯ VERY LOW[1,2] (critical)	-

Skin toxicity[7]	■ Bleomycin electrosclerotherapy (5 pts):
	  ■ Superficial skin necrosis: 1 pt (20%)
	  ■ Mild hyper-pigmentation: 2 pts (40%)
	■ Bleomycin alone (5pts):
	  ■ Mild erythema: 1 pt (20%)
	  ■ Hematoma: 1 pt (20%)
	  ■ Hyperpigmentation: 1 pt (20%)
	■ Control group (no treatment) (5pts):
	  ■ No adverse events were reported (5pts)
		1 (5) [43]	⨁◯◯◯ VERY LOW[1,2] (critical)	-

Any other adverse events	■ Any other AEs across all studies 0/116 pts.	5 observational studies (116) [37-40, 44]	⨁◯◯◯ VERY LOW[1,2] (critical)	-

Abbreviations: AE – Adverse event, BEST – Bleomycin electrosclerotherapy, IHE – Institute of Health Economics, NA – Not applicable, pts – patients, RoB – Risk of bias, SAE – Serious adverse event.

Comments:

[1] *Using the IHE RoB checklist, the overall RoB was rated as high risk (≤15 points) in all studies. Very serious limitations are given due to the lack of a controlled study design*

[2] *Only descriptive data are available. The sample size is small, and no formal statistical analyses were performed.*

[3] *All studies reported on skin toxicity, but the reporting was inconsistent. If an outcome was not specifically reported, but other symptoms were reported in detail, including numbers, the outcome of interest was rated as 0, and the study was included in the calculation (denominator). If the outcomes were reported without numbers or in a general way, the study was not included.*

[4] *In one study [38], data were presented in a way that did not allow the identification of the total number of patients with skin toxicity. Therefore, this study was not included in the calculation of overall skin toxicity.*

[5] *In two studies [37, 38], the number of patients bleeding decreased after the intervention. These studies were not included in this calculation, as bleeding was not reported as adverse event.*

[6] *In one study [38], two pts (10%) experienced hyperpigmentation, and one patient (5%) had an infection already at baseline.*

[7] *This outcome pertains to a small (n=5) pilot trial with random assignment of the lesions in three comparable regions of interest to the treatment arms (within-patient randomisation) and not random assignment of patients. Each of the three regions was treated with either bleomycin electrosclerotherapy, bleomycin alone, or no treatment. In this report, we categorized this trial as a prospective single-arm case series.*

6 Discussion

Vascular anomalies encompass a wide range of disorders of the endothelium affecting capillaries, arteries, veins, or the lymphatic system. These anomalies are categorised as vascular tumours with increased cell proliferation and vascular malformations with mesenchymal and angiogenetic disorders resulting from developmental defects [1]. The prevalence of these anomalies is estimated to be around 4.5%, with 121 different syndromes encompassed by this term, some of which are very rare [2, 3]. Vascular tumours are further divided into benign, locally aggressive/borderline, and malignant tumours [4]. Each type has its own set of histological and clinical manifestations, and the necessary diagnostics and treatment will vary depending on the type, location, and symptoms.

verschiedene Formen von vaskulären Anomalien

Prävalenz: ~4.5 %

Behandlung abhängig von Typ, Lokalisation und Symptomen

This report aimed to assess the clinical efficacy and safety of bleomycin electrosclerotherapy in patients with vascular anomalies in comparison to standard of care (e.g. surgery or intralesional bleomycin alone – sclerotherapy). However, it should be noted that the standard of care is usually not based on evidence but on expert opinion.

Ziel: Evidenzsynthese der klinischen Wirksamkeit & Sicherheit von Bleomycin-Elektrosklerotherapie

To explore the effect, we focused on patient-relevant outcomes, such as disease progression, recurrence rate, survival/progression-free survival, symptom control and improvements in health-related quality of life (HRQoL) as well as post-interventional side effects and serious adverse events (SAEs).

Summary of evidence

Included studies

A total of eight observational studies involving 151 patients treated with bleomycin electrosclerotherapy were included [38-43]. The included studies are heterogeneous regarding the population (indication and inclusion criteria). Three prospective case series evaluated bleomycin electrosclerotherapy in patients with Kaposi sarcoma [39-41], two case series (one prospective and the other one retrospective) in patients with angiosarcoma (cutaneous angiosarcoma) [38] (locally advanced or metastatic angiosarcomas) [37]. Single case series explored the effect of bleomycin electrosclerotherapy in congenital vascular malformations (prospective) [42] and venous malformations (retrospective) [44]. One small (n=5) pilot study involved patients with hypertrophic capillary malformations [43]. In this study, lesions within patients were randomised to treatment arms and not patients. No critical efficacy outcomes were reported in this study [43] and we categorised this trial as a prospective single-arm case series.

Evidenz aus 8 Fallserien

insgesamt 151 Patient*innen

keine kontrollierten Studien verfügbar

Efficacy

No controlled evidence, such as studies comparing bleomycin electrosclerotherapy to conservative/standard of care interventions (e.g. surgery or sclerotherapy) was found to answer the research question on the efficacy of the treatment.

kein Vergleich mit Standardtherapie oder konservativer Therapie möglich

Safety

Sicherheit: keine Vergleiche der Endpunkte möglich

Eight observational studies were considered to evaluate the safety of bleomycin electrosclerotherapy in patients with vascular malformations and vascular tumours. The current evidence indicates that bleomycin electrosclerotherapy is safe.

keine SAEs

No SAEs across the studies were reported. Procedure-related adverse events were reported in one study. However, the authors did not state how many patients experienced post-treatment fever and nausea [41]. In five studies, no device-related adverse events were reported [37-40, 44] and three studies did not report device-related adverse events [41-43]. Six of the eight studies reported on post-operative adverse events. No case was reported [37-42, 44]. No case of lung fibrosis, which is a known dose-dependent adverse event of Bleomycin,[49] was reported in the included studies.

Hauttoxizität & postoperativer Schmerz am häufigsten

Other adverse events included patient-reported pain and skin toxicity. These events were mostly reported as mild with spontaneous healing. Of the 90 patients eligible for post-operative patient-reported pain assessment, 15 (16.6%) reported on pain [38, 40, 42, 44]. In 40 of 107 (37.3%) patients, a skin toxicity event was reported [37, 40-42, 44]. The most common events were skin ulceration (n=17) and erythema/swelling (n=16). Overall, serious adverse events and other adverse events are rare.

Internal and external validity

Evidenz: kleine Fallserien

Bias-Risiko: hoch

eingeschränkte interne und externe Validität

In summary, the overall certainty of the evidence was very low for bleomycin electrosclerotherapy considering the safety outcomes. The results of this review should be interpreted cautiously due to concerns with both the internal and external validity of the included studies. Current evidence on bleomycin electrosclerotherapy is mainly based on prospective and retrospective single-arm case series with small sample sizes. These study designs have a number of serious limitations. The absence of a comparison group makes it impossible to know what would have happened without the intervention. Some of the particular problems with interpreting data from uncontrolled studies include vulnerability to problems with confounding and regression to the mean [54]. Across studies, reporting adverse events and complications was inconsistent, and formal statistical analyses were rarely performed. The primary factors for downgrading the evidence rating were the single-centred set-up, absence of data about consecutively recruited patients, failure to blind the investigators, and enrolment of patients at different stages of the disease.

Berichterstattung zu UE nicht konsistent

Furthermore, based on limitations in reporting (baseline characteristic incl. symptoms) and study design (lack of RCT), a clear differentiation of symptoms caused by (a progression of) disease and symptoms caused by treatment was not always possible. Overall, reporting of adverse events and complications was inconsistent across included studies.

externe Validität mit Unsicherheit verbunden

For external validity, there are applicability concerns for the included populations (indication and disease stage) and the setting of the studies. In some studies, patient baseline characteristics and data distribution were not fully reported.

keine Studienprotokolle

Overall, the small underpowered studies (range, 5-30 patients) lacked a study protocol (a priori) including pre-defined outcomes/reporting criteria on adverse events (e.g. procedure-related or device-related adverse events).

Electrochemotherapy in dermatology and other areas of use

Elektrochemotherapie kommt in der Dermatoonkologie zum Einsatz

In dermatology, electrochemotherapy is used for different common malignant tumours such as basal and squamous cell carcinoma. It can be used for local control of cancers unsuitable for surgery and resistant to radiotherapy or chemotherapy [27].

NICE-Leitlinie: Einsatz nur, wenn Maßnahmen getroffen werden

primäres Ziel: palliative Behandlung

A NICE guidance recommends that electrochemotherapy for primary basal and squamous cell carcinoma should only be used in appropriate clinical settings. Currently, there are no major safety concerns. However, due to the limited amount of studies and quality of evidence on its efficacy, this procedure should only be employed with appropriate clinical governance, consent, and local audit measures in place [27]. Electrochemotherapy is also used in treating cutaneous and subcutaneous metastases of non-skin origin and melanoma that often occur in the setting of disseminated disease and cause significant clinical problems, including bleeding, pain and ulceration. The primary aim of electrochemotherapy in these patients is, therefore, palliative. According to NICE (2014) there is enough evidence of the efficacy of electrochemotherapy for treating metastases in the skin from tumours of non-skin origin and melanoma to support its use as a palliative treatment. Furthermore, there are no major safety concerns [27].

AWMF-Empfehlung: mögliche Anwendung bei nicht-operablen Satelliten- & Transitmetastasen

According to the current German AWMF S3 guideline on melanoma, electrochemotherapy with bleomycin can be used for patients with non-operable satellite and in-transit metastases. The highest response rates were described for intratumoural injection of interleukin 2 and intratumoural electrochemotherapy with bleomycin or cisplatin (open recommendation, level of evidence 2a[33]). Talimogene laherparepvec (T-VEC) can be used as another treatment option for locoregional metastases [55].

Evidenz zur Elektrochemotherapie meist Kohorten- & registerbasierte Studien & kleine Fallserien

In addition to current guidelines, we identified six systematic reviews of mainly observational studies on electrochemotherapy with bleomycin within the field of dermatology [49, 50, 56-59] (primary basal cell carcinoma, cutaneous malignancies metastatic, cutaneous melanoma, malignant melanoma). Overall, the evidence on electrochemotherapy is mainly based on cohort studies, small case series and register-based studies.

nur eine vergleichende Nicht-unterlegenheits-Studie

To our knowledge, only one non-inferiority RCT trial (n=100) has compared electrochemotherapy with surgery in patients with primary basal cell carcinoma [60]. After a five-year follow-up, the complete response rate in the electrochemotherapy group was 71.1% (32/45 pts.) compared to 83.3% (35/42 pts.) in the surgery group. Reported complication rates (mainly infections, erythema and swelling) between the groups were comparable [60].

InspECT-Register: 27 Zentren in Europa erheben Daten zur Elektrochemotherapie

The International Network for Sharing Practices on Electrochemotherapy (InspECT) register was formed in 2008 and is an essential source of evidence for electrosclerotherapy and electrochemotherapy [61]. The InspECT register is a European register dedicated to electrochemotherapy. To date, 27 European centres are submitting data on patients undergoing electrochemotherapy, including details of case selection, methods of follow-up and outcomes. InspECT is supported by IGEA (Carpi, Italy) in terms of the upkeep of the database and support for meetings, but the forum is formed and maintained by active clinicians.

[33] Oxford level of evidence 2009, SR (with homogeneity*) of cohort studies

Publikationen zu den Daten meist einarmige Studien

kein Appraisal dieser Studien, da Fokus des vorliegenden HTA-Bericht auf Elektrosklerotherapie bei vaskulären Anomalien

Based on the InspECT register, the involved centres have published numerous articles evaluating the effect of electrochemotherapy in different patients (indications). In our literature search, we could identify eight large register-based trials (over 300 participants per study) [62-68]. All studies are single-arm registry-based trials with some general concerns about this study design. It is not clear if the authors use a prospective or retrospective design. No results from these studies are presented in this report as the scope of this HTA was not to explore the efficacy and safety of electrochemotherapy in dermatology. Electrochemotherapy is also under investigation in clinical trials in other areas of use, such as internal tumours, liver, pancreas and lung [24].

Evidence gaps and ongoing studies

To our knowledge, this is the first systematic review on bleomycin electrosclerotherapy in vascular tumours or vascular malformations.

2 laufende einarmige Studien

Through the clinical trial search, no ongoing registered or planned controlled trials for bleomycin electrosclerotherapy could be identified. Two single-arm studies (one feasibility study and one retrospective observational study) for bleomycin electrosclerotherapy in the treatment of vascular malformations was identified (NCT05494710 and DRKS00031072). However, as these trials are uncontrolled studies, it will most likely not add to the current evidence on efficacy or safety.

hoher Bedarf nach kontrollierten Studien

Currently, there is neither a standardised diagnostic nor a uniform therapeutic approach for most types of vascular anomalies. Their treatment is primarily based on expert opinion and experience rather than on evidence from studies. Due to the rarity of each syndrome, it is very challenging to gather experience or to conduct scientific studies with an adequate sample size [2]. However, there is a high need for adequately powered controlled trials. Validated instruments for outcome assessment should be developed and used. Reporting on adverse and skin toxicity events should be standardised.

fehlende hochwertige Leitlinien

In addition, there is a need for high-quality guidelines. The few existing international guidelines for specific syndromes are usually consensus statements [10, 12, 17, 20] or reports of weak or very weak evidence (except for hemangioma) [16]. A German S3 guideline for vascular malformations is currently registered with estimated finalisation in 2024 [19].

kaum hochwertige Evidenz für Therapien

In the field of rare vascular diseases, where therapy is mostly not evidence-based due to a lack of well-powered clinical studies, an additional treatment alternative is sometimes necessary. The need for other treatment options is especially true for patients for whom established therapies are ineffective or not applicable due to their physical or anatomical condition. Bleomycin electrosclerotherapy might provide a potentially safe treatment alternative.

Strengths and limitations of this report

Mangel an prospektiven kontrollierten Studien

Due to a lack of prospective controlled evidence, we included retrospective studies for the evaluation of safety. Normally, large randomised controlled trials, prospective non-randomised controlled trials, cohort studies and prospective case series are the best way to explore the safety of an intervention. Including only small retrospective studies may have resulted in (rare) safety events not being captured.

Most studies reported narratively on adverse events, and it was not always clear if the symptoms were present before treatment or as a consequence of bleomycin electrosclerotherapy. Future studies should include details on study participants, including symptoms at baseline.

nur narrative Analyse der sicherheitsrelevanten Endpunkte möglich

Furthermore, we could not assess the comparative quality of evidence of clinical efficacy outcomes because we only identified studies with a single-arm design. Therefore, only a narrative analysis of safety outcomes within GRADE was possible due to the limitations in study designs and data reporting. All studies reported on skin toxicity, but the reporting was inconsistent. If a skin toxicity event was not specifically reported, but other symptoms/adverse events were reported in detail, including numbers, the outcome of interest was rated as zero (0), and the study was included in the calculation (denominator). This reporting might overestimate the good safety profile of bleomycin electrosclerotherapy. However, the skin toxicity events were mostly mild followed by spontaneous healing.

The pre-specified critical outcomes for decision-making represent measures of the most important clinical therapeutic goals. However, this assessment did not evaluate other patient-relevant outcomes, such as aesthetics.

Conclusion

Bewertung der relativen Benefit-Harm-Ratio war nicht möglich

In the absence of comparative data, it is difficult to ascertain the relative risk and benefit of bleomycin electrosclerotherapy for treating patients with vascular tumours or vascular malformations in comparison to standard of care (e.g. surgery or sclerotherapy). Therefore, without any control, we cannot conclude that bleomycin electrosclerotherapy might be more effective, equally safe or safer than its comparators.

weitere Forschung und Leitlinien wesentlich

In this field of rare vascular diseases, where therapy is mostly not evidence-based due to a lack of well-powered clinical studies, an additional treatment alternative is sometimes necessary. Based on the limited evidence of the included uncontrolled studies (prospective and retrospective single-arm case series), bleomycin electrosclerotherapy might provide a potentially safe treatment alternative if other treatment options are not efficient or not possible.

keine hochwertigen laufenden Studien

Unfortunately, no ongoing controlled trial was identified to support existing evidence (single-arm studies) that bleomycin electrosclerotherapy might be more effective or safer than its comparators.

Concerning safety, serious and procedure-related adverse events are rare, but a comparison to the safety profile of a conservative therapy was not possible.

7 Recommendation

Empfehlung

In Table 7-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 7-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is **currently not recommended**.
	The **inclusion in** the catalogue of benefits is **not recommended**.

Reasoning:

Evidenz unzureichend: eine Aufnahme von Bleomycin-Sklerotherapie in den LKF-Katalog wird derzeit nicht empfohlen

The current evidence and lack of prospectively controlled trials are not sufficient to prove that the assessed intervention bleomycin electrosclerotherapy in vascular anomalies is more effective than a comparator (e.g. surgery or sclerotherapy). No major safety concerns were reported in the retrospective and prospective observational studies (single-arm case series).

Due to the methodological shortcomings of the available evidence and the lack of controlled evidence, no solid conclusions can be drawn for efficacy or the safety of the device at stake.

hochwertige (vergleichende) Evidenz nicht in Aussicht

Two ongoing single-arm studies of bleomycin electrosclerotherapy treating vascular malformations were identified. As these trials are uncontrolled studies (one feasibility study and one retrospective observational study), it will most likely not add to the current evidence on efficacy or safety.

hochwertige (vergleichende) Studien notwendig für eine Re-evaluation

There is a high need for adequately powered controlled trials. Validated instruments for outcome assessment should be developed and used. Reporting of adverse and skin toxicity events should be standardised. In addition, there is a need for high-quality guidelines. Based on the report's findings, the re-evaluation of bleomycin electrosclerotherapy for treating vascular tumours and vascular malformations is recommended in 2028.

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Appendix

Evidence tables of individual studies included for clinical efficacy and safety

Table A-1: Results from observational studies (case series, single-arm studies) (safety), part 1

Author, year	Guida, 2016 [37]	Campana, 2019 [38]	Horbach, 2019 [43]	Kostusiak, 2021 [42]
Disease	Locally advanced or metastatic angiosarcomas	Cutaneous angiosarcoma (cAS)	Hypertrophic capillary malformations (CMs)	Congenital vascular malformations
Country/Setting	Italy, multi-institutional (8 hospitals)	Eight european sarcoma referral Centres (InspECT Registry)	Netherlands, single centre plastic surgery department	United Kingdom, single centre, plastic surgery department, day cases
Recruitment period	July 2007 to May 2014	October 2013 to May 2019	December 2017 to February 2018	NR
Sponsor	NR	None	Equipment: IGEA medical	NR
Study design	retrospective case series	Prospective case series (Register based single-arm study)	Controlled pilot study, lesions randomised within-patients	prospective case series
Comparator	NA	NA	Bleomycin Sclerotherapy, or no treatment (regions of interest randomised)	NA
Intervention/Product	BEST/Cliniporator® (IGEA)	BEST/Cliniporator® (IGEA)	BEST/Cliniporator® (IGEA)	BEST/Cliniporator® (IGEA)
Procedure/Technique (electric pulses, sequences)/Electrode	European Standard Operating Procedures of ECT (ESOPE) [53] After an interval of 8 min, short (8 pulses of 100 µs duration, at a repetition frequency of 5,000 Hz), high-voltage (400-960 V) electric pulses were delivered to the tumour by means of a needle electrode. Pulse application lasted between 8 and 28 min after infusion of chemotherapy.	European Standard Operating Procedures of ECT (ESOPE) from 2006 [53] and 2018 [24] After one (IT) or 8 min (IV) patients received 8 square wave pulses of 400-960V, 100 ms duration and 5000 Hz repetition frequency	Directly after the bleomycin injection, 8 pulses were delivered to ROI in a standardized frequency of 100 Hz. Either plate electrodes (960V) or needle electrodes (400 V) were used	NR
Bleomycin administration (Route/Dose/Frequency)	Bleomycin was administered intravenously as a bolus, at the dose of 15,000 IU/m^2.	Bleomycin administered intratumourally (250-1000 IU/cm3 depending on tumour volume) or intravenously (15,000 IU/m^2)	1 unit/mL in a dosage of 0.25 units/cm^3, was injected in the ROIs allocated to bleomycin injection or EST. As the ROIs were 1.5x1.5 cm with a maximum depth of 1 cm, a fixed volume of 0.56-mL bleomycin was injected.	Intralesional bleomycin injection: calculated based on the size of the lesion and mixed with 1 mL of plain 1% lidocaine local anesthetic. Foaming of the solution by mixing it with air and albumin was performed in low-flow malformations.
Anesthesia (Local, general sedation, general anesthesia)	General anaesthesia (n=7 pts) or mild general sedation (n=12 pts)	General anaesthesia (n=19 pts) Local anesthesia (n=1 pts)	Local anesthesia	General anesthetic (9/30 pts), regional block (8/30 pts), Penthrox methoxyfluorane patient-controlled sedation (8/30 pts), remifentanil sedation (5/30 pts)

Author, year	Guida, 2016 [37]	Campana, 2019 [38]	Horbach, 2019 [43]	Kostusiak, 2021 [42]
Inclusion criteria	Patients with locally advanced or metastatic angiosarcomas, if surgical resection was excluded and patients where not suitable for, or refractory to, radiotherapy or systemic treatment. In patients with concomitant visceral disease: symptomatic superficial tumours, at least 3-month life expectancy was estimated.	Patients with locally advanced or metastatic cutaneous angiosarcomas not amenable to surgical treatment	Adult patients with CMs showing signs of hypertrophy, diffuse thickening, or nodularity No restrictions regarding previous treatment	Patients with vascular malformations who had limited or no response to standard bleomycin sclerotherapy
Exclusion criteria	Standard ECT selection criteria (European Standard Operating Procedures of ECT, ESOPE) [53]	Inclusion/exclusion criteria indicated in the European Standard Operating Procedures of ECT (ESOPE) [53]	Patients with CMs in the face, mucosa, or in the skin overlying joints. Patients with contraindications to receiving electrical therapy or bleomycin	NR
Patient characteristics				
Number of pts/lesions	19/54	20/51	5/15	30/48
Bleomycin application, intravenous (i.v.) intratumoural (i.t.)	All intravenously	i.v.: 18 (90%) i.t.: 2 (10%)	All Intralesionally	All Intralesionally
No of BEST cycles	1 cycle 15 pts (79%) 2 cycles 2 pts (10%) 3 cycles 2 pts (10%)	24 (median, 1/pt, range, 1-2)	NR	NR
Age of patients (yrs, ±SD/median, range)	Median 69 (range 66-76)	Median 76 (range 61-84)	Mean 56.6 (±15.5)	Mean 42±21 (range 6-75).
Sex, female (n, %)	15 (79%)	13 (65%)	2 (40%)	17 (56.7%)
Tumour histology/Site of lesions	Anatomical location primary disease: Scalp: 5 pts (26%) Breast: 8 pts (42%) Skin, other sites: 3 pts (16%) Soft tissue: 3 pts (16%) Anatomical location (tumour): Scalp 5 (9%) Upper limb 7 (13%) Chest wall 38 (70%) Abdominal wall 4 (8%)	Anatomical location: Scalp/face: 7 pts (35%) Breast/chest wall: 10 pts (50%) Limbs: 3 pts (15%)	Anatomical location Abdomen: 1 pt Upper arm: 1 pt Right lateral side of neck: 1 pt Coeur: 1 pt Scapula area: 1 pt	Histology: VM: 17 pts (56%) CVM: 6 pts (20%) Arterio-VM: 3 pts (10%) LM: 2 pts (7%) Mixed malformations: 2 pts (7%) Anatomical location: Head and neck: 18 pts (60%) (mostly lip) Upper limb: 4 pts (10%) Lower limb: 7 pts (13%) Others: 1 pt (3%)
Lesion size (cm^2, range)	1.5 to 3.5 cm (median, 2 cm)	Tumour size (cm) 2.3 (1-20)	NR	NR
Disease stage	AJCC stage at diagnosis: IB 1 pt (5%) IIA 5 pts (26%) IIB 3 pts (16%) III 9 pts (48%) IV 1 pt (5%)	AJCC TNM staging: IIA 1 pt (5%) IIB 8 pts (40%) III 8 pts (40%) IV 3 pts (15%)	NA	NA

Author, year	Guida, 2016 [37]	Campana, 2019 [38]	Horbach, 2019 [43]	Kostusiak, 2021 [42]
Symptoms before Treatment n pts (%)	Pain mild 7 pts (36.8%), moderate 9 pts (47.3%), severe 1pt (5.3%) Bleeding 7 pts (13%)	Bleeding 14 pts (70%)	NR	Swelling (88%), pain (42%), speech impediment, dribbling, bleeding, cosmetic issues
Previous therapies/ Concurent therapies	Previous treatments: Surgery 11 pts (58%) Surgery + Systemic treatment 3 pts (16%) Surgery + RT 2 pts (11%) Surgery + RT + Systemic treatment 1 pt (5%) RT pts (10%) 1 pt concomitant paclitaxel chemotherapy at the time of ECT	Previous treatments: Surgery 3 pts (15%) Surgery + RT 4 pts (20%) Surgery + Systemic treatment 8 pts (40%) Systemic treatment 1 pt (5%) Systemic treatment + RT 4 pts (20%) Surgery + RT + Systemic treatment 1 pt (5%) Concurrent treatment: Combination of ECT with surgery 5 pts (25%) Concomitant systemic treatment 3 pts (15%)	None: 2 Pts Pulsed dye laser, neodymium-doped yttrium aluminum garnet (ROIs not treated): 1 pt Pulsed dye laser, Bleomycin sclerotherapy (ROIs not treated): 1pt Pulsed dye laser (ROIs not treated): 1 pt	22 pts (73%) received standard bleomycin sclerotherapy before receiving EST 17 pts (57%) received previous treatment in the past other than sclerotherapy (e.g., surgery or cryotherapy)
Follow-up (months) (mean/median)	Median follow-up of 12 months (range, 3-48)	Median follow-up 15 months (range NR)	NR (data collected at baseline and after 7 ± 1 weeks)	NR
Loss to follow-up, n (%)	NR	NA (Register based single arm study)	NR	Response evaluation: follow-up in 3 pts (10%) not completed Patient-reported outcome measures: received from 22 pts (response rate 73%)
Reponse evaluation	Modified Response Evaluation Criteria in Solid Tumours (RECIST v1.1) [36] No confirmatory biopsies were performed Pain level was assessed by a 10-point Verbal Numerical Rating Scale (VNRS; 0 = no pain; 1-2 = mild pain; 3-6 = moderate pain; 7-10 = severe pain).	Adapted Response Evaluation Criteria in Solid Tumours (RECIST v1.1) [36] Pain evaluation: 0-10 visual analogue scale (VAS)	The Patient and Observer Scar Assessment Scale (POSAS) [47] Global assesment of change (GAC) score completed by patient and physician Pain assessment as part of the POSAS Score Color Photographs Colorimetry Laser Speckle Contrast Imaging (to visualize skin perfusion)	Assessment scores (surgeon): (1) no response (0% regression) (2) minor response (MR) (0%–30% regression) (3) moderate im provement (MI) (30%–60%) regression), (4) Significant improvement (SI) (60%–90% regression) (5) near complete or complete response (CR) (90%–100% regression) Pain evaluation Likert type-7 point scale
Adverse events evaluation (toxicity)	Common Terminology Criteria for Adverse Events (CTCAE, v4.0).	Common Toxicity Criteria for Adverse Events (CTCAE v5.0)	NR (AE reported during follow-up)	NR
Outcomes				
Efficacy				
Complete response (CR)/partial response(PR)/ Stable disease/progressive disease	At 2 months: CR 8 pts (42%) PR 4 pts (21%) SD 6 pts (32%) PD 1 pt (5%)	Per-tumour local response: CR, 61%; PR, 22%; SD, 18%; PD, 2%. Per-patient local response: CR, 40%; PR, 40%; SD, 15%; PD, 5%	Difference in POSAS (decrease indicating improvement) BEST: patient -11 (range 0-22), observer -13 (range 1-19) Bleomycin alone and control group: patient and observer 0	CR: 17 pts SI: 7 pts MI, MR, no response: 3 pts

Author, year	Guida, 2016 [37]	Campana, 2019 [38]	Horbach, 2019 [43]	Kostusiak, 2021 [42]
Recurrence rate	Recurrence or progression within ECT field: 6 pts (31.6%) After median interval 4.5 months. Out of field progression: 5 pts (26.3%)	7 pts (35%) local recurrence, after a median interval of 3.4 months (range, 0.9-28). 13 pts (65%) developed new skin lesions after a median of 1.8 months (range, 0.7-10) 7 pts (35%) systemic recurrence/ progression after a median of 6.4 months (range, 1.8-31).	NR	NR
Survival/progression-free survival	One-year LPFS was 68% (95%CI 41-94%) One-year PFS in the whole cohort was 45% (95%CI 12-69%) Disease-free 4/19 (21.1%) Alive with local disease: 5/19 (26.3%) Dead of disease: 10/19 (52.6%) Median OS after ECT of the entire cohort was 12 months (range, 4-44)	One-year local progression-free survival (LPFS) was 68% (95% CI 47%-90%) Median OS was 12.5 months (range, 6.1-53.5)	NA	NA
Other disease-related symptoms (pain, swelling, impaired physical functioning, wounds, skin discoloration)[34]	See below (safety)	See below (safety)	See below (safety)	See below (safety)
Quality of life	NR	The median EQ-VAS score was 44 (range, 0-83) at baseline and 50 (range, 0-80) at 2 months. EQ-5D: no sign. Diff. In either the five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression)	NR	NR
Safety				
Pain, n (%)	At baseline: No pain n=2 pts (10%), mild n=7 pts (37%), moderate n=9 pts (47%), severe n=1 pt (5%) First follow-up (median 29 days, range 23-46): No pain n=10 pts (53%), mild n=5 pts (26%), moderate n=4 pts (21%), severe n=0 pt Two months after ECT pain level was significantly reduced and was indicated as "moderate" by only four patients (P= 0.01)	6 pts. (30%) various grades of treatment-induced pain, severe in 2 pts (10%) There were no significant correlations between post-treatment pain and patient/tumour characteristics or ECT parameters.	Pain item (POSAS Score) deteriorated in the first weeks after treatment	Pain during treatment (Likert type-7 point scale, n=22): mean 4.7 (moderate to mild pain) Pain 2 pts (6.6%)

[34] Lack of controlled trials and since a clear differentiation of symptoms caused by (a progression of) disease and symptoms caused by treatment is not possible, these outcomes are summarized under 'safety'

Author, year	Guida, 2016 [37]	Campana, 2019 [38]	Horbach, 2019 [43]	Kostusiak, 2021 [42]
Skin toxicity, n (%)	*Skin toxicity:* G1: 6 pts (32%, erythema, tissue oedema and skin ulceration); G2: 1 pts (5%, skin ulceration); G3: 2 pts (11%, skin ulceration) All the toxicities resolved within 6 months. *Bleeding:* 7 lesions (13%, 6 pts) bleeding at baseline; 2 lesions (1 pt) bleeding at last follow-up	*Skin ulceration:* 5 pts (25%) various grades of skin ulceration reversible and manageable on an outpatient basis in all cases *Bleeding* baseline 14 pts (70%), 1 month 1 pt (5%) *Hyperpigmentation:* Baseline 2 pts (10%), 1 month 6 pts (30%) *Skin infection:* Baseline 1 pt (5%), 1 month 3 pts (15%) *Necrosis:* baseline 0, 1 month 2 pts 10%)	*EST bleomycin:* Superficial skin Necrosis: 1 pts (20%) (persisted for 8w) Mild hyper-pigmentation: 2 pts (40%) *Bleomycin alone:* Mild erythema: 1 pts (20%) Hematoma: 1pts (20%) Hyperpigmentation: 1pts (20%) *Control group:* No adverse events were reported	Minor side effects: 18 pts (60%) Swelling 6 (20%) Infection 3 (10%) Bleeding 2 (6.6%) Patients also complained of weeping, drooling, crusting, and ulceration (n=NR) All reported side effects were self-limiting, followed by a full recovery.
Any procedure-related (serious) adverse events	None	None	NR	NR
Any device-related (serious) adverse events	None	None	NR	NR
Any adverse events/ serious adverse events	None	None	NR	None

Abbreviations: NR – Not Reported, NA – Not Applicable

Table A-1: Results from observational studies (case series, single-arm studies) (safety), part 2

Author, year	Wohlgemuth, 2021 [44]	Di Monta, 2014 [39]	Curatolo, 2012 [40]	Latini, 2012 [41]
Disease	Venous malformations (VM)	Kaposi sarcoma	Kaposi sarcoma	Kaposi sarcoma
Country/Setting	Germany, single-center	Italy, single-center	Italy, two dermatologic centers	Italy, single-center
Recruitment period	January 2019 to January 2020	January 2010 to June 2012	October 2005 and September 2010	March 2007 to March 2011
Sponsor	None	None	NR	NR
Study design	Retrospective case series	Prospective case series	Prospective case series	Prospective case series
Comparator	NA	NA	NA	NA
Intervention/Product	BEST/Cliniporator VITAE® (IGEA)	BEST/Cliniporator VITAE® (IGEA)	BEST/Cliniporator VITAE® (IGEA)	BEST/Cliniporator VITAE® (IGEA)
Procedure/Technique (electric pulses, sequences)/Electrode	Voltage applied between each needle electrode: 1000 V/cm and applied for 10 min. after bleomycin injection Different types of electrodes were chosen in accordance with the anatomic location and lesion size Updated European Standard Operating Procedures of ECT (ESOPE) from 2018 [24]	European Standard Operating Procedures of ECT (ESOPE) from 2006 [53] and 2018 [24] Electrics pulses administered in a time interval of 8-28 min after injection of Bleomycin	European Standard Operating Procedures of ECT (ESOPE) Electric pulses were delivered from 8 to 28 min after bleomycin infusion	Therapeutic window of about 20-25 min.

Author, year	Wohlgemuth, 2021 [44]	Di Monta, 2014 [39]	Curatolo, 2012 [40]	Latini, 2012 [41]
Bleomycin administration (Route/Dose/Frequency)	Percutaneous intralesional injection into the vascular malformation under ultrasound and fluoroscopic guidance. Bleomycin concentration: max. 0.25 mg/mL or max. volume of 1 mL/1 cm^3 of the vascular malformation.	Intravenous injection of bleomycin at the dose of 15,000 IU/m2, in bolus	Intravenous bleomycin at a dose of 15 mg/m2 for 30 s to 1 min.	Bleomycin was administered intravenously (15 U.I.) 8 minutes before ECT.
Anesthesia (Local, general sedation, general anesthesia)	All general anesthesia	Loco-regional or under general anesthesia	Mild general anesthesia or spinal anesthesia	All general anesthesia
Inclusion criteria	Patients with symptomatic VMs, Previously undergone at least two interventional or open surgical treatments of venous malformation that had not led to sufficient symptom improvement	Patients with classic KS lesions stage I-II	histologically confirmed KS with cutaneous lesions not treatable by surgery, radiotherapy, or intralesional vincristine; absence of extracutaneous involvement radiologically confirmed; age>18 years, Karnofsky performance status of >70; washout period of at least 4 weeks after previous treatments.	Patients with clinical and histological diagnosis of kaposi sarcoma, skin limited disease, with failed previous cryo-therapy. The ECOG status had to be ≤2. Inclusion criteria and technical procedures were in adherence with the European Standard Operating Procedures of Electrochemotherapy study [69].
Exclusion criteria	Children <5yrs, pregnant and breastfeeding women, patients with childbearing potential not using contraception, chronic pulmonary dysfunction, intolerance to bleomycin or previous bleomycin-related toxicity, cumulative dose of bleomycin of ≥100 mg, previous chest radiotherapy, history of seizures or epilepsy.	Kidney failure (creatinine level <150 mmol/L); known allergy to the drug; interstitial lung fibrosis (bleomycin); cumulative bleomycin dose more than 400,000 UI/m^2	Inclusion/exclusion criteria indicated in the European Standard Operating Procedures of ECT (ESOPE) [53]	Patients with visceral extension of the disease diagnosed by a total body computer thomography scan, esophageal-gastro-duodenoscopy and colonoscopy.
Patient characteristics				
Number of pts/lesions	17/20	19/NR	23/532	18 Lesions: 57 Nodular plaque: 15
Bleomycin application, intravenous (i.v.) intratumoural (i.t.)	All Intralesionally	All intravenously	All intravenously	All intravenously
No of BEST cycles	1 cycle 15 pts (88%) 2 cycles 2 pts (12%) (22 sessions were performed on 20 lesions)	1 cycle 14 pts (73.6%) 2 cycles 3 pts (15.7%) 3 cycles 2 pts (10.5%)	1 cycle 18 pts (78%) 2 cycles 3 pts (13%) 3 cycles 2 pts (9%)	1 cycle: 9 pts 2 cycles: 7 pts 3 cycles: 2 pts
Age of patients (yrs, ±SD/median, range)	Mean 20.8 ± 8.2	Median 70 (range 44-85)	Median 77 (range 43-86)	Mean 68.4±11.1
Sex, female (n, %)	9 (52.9%)	3 (15.8%)	10 (43.5%)	4 (22.2%)
Tumour histology/Site of lesions	Anatomical location (no. leisons): Thigh (8), knee (2), foot (3), calf (2), flank (1), lower arm (1), trunk (1), finger (1), gluteal area (1)	Anatomical location: Foot 9 pts lower limbs 9 pts genitalia 1 pt	Anatomical location: Lower limbs 19 pts Genitalia 1 pt Disseminated 3 pts	Anatomical location (no. leisons): Face: 1 Foot: 4 Lower limb: 19 Upper limb: 5

Author, year	Wohlgemuth, 2021 [44]	Di Monta, 2014 [39]	Curatolo, 2012 [40]	Latini, 2012 [41]
Lesion size (cm^2, range)	median 24.89 cm^3 (range, 3.99-690.65 cm^3)	NR	NR	NR
Disease stage	NA	Stage I: 12 pts Stage II: 7 pts	NR	cKS stage I: 5 pts II: 8 pts III: 5 pts
Symptoms before Treatment n pts (%)	Most common: Pain 17 pts (100%) Swelling 13 pts (76.5%) (Partial-)immobilization 13 pts (76.5%) Contracture 3 pts (17.6%)	Local pain, functional limitation	NR	local pain or functional limitation
Previous therapies/ Concurent therapies	Sclerotherapy (eg, alcohol, sodium tetradecyl sulfate, polidocanol) n=18 pts, surgery n=12 pts, embolization	NR	None 9 pts systemic chemotherapy 6 pts interferon therapy 3 pts radiotherapy 5 pts intralesional vincristine 1 pt	Failed cryotherapy (see inclusion/exclusion criteria)
Follow-up (months) (mean/median)	3.7 months (range, 3-8.2 months).	Median 13 months (range 3-28)	1.5 years (range 2 months to 4.2 years)	Range 6-48 months
Loss to follow-up, n (%)	NA	NR	NR	NA
Reponse evaluation	MRI volumetric analysis Clinical response was then categorized as asymptomatic, improved, unchanged, or worsened. Pain evaluation: no specific instrument	Response Evaluation Criteria in Solid Tumors (RECIST- Guidelines) [36] Pain evaluation: no specific instrument	Response Evaluation Criteria in Solid Tumors (RECIST). [36] progressive disease for an increase in sum of diameters of >20%; partial response (PR) for a decrease of 30% for at least 4 weeks; no change for an increase Of <20% or a decrease of <50%; and CR for total clinical disappearance of the lesion. Pain evaluation: no specific instrument	Complete response, when nodules were no longer palpable, or partial response, when the lesion area (d_1 ¥ d_2) was reduced more than 50%. Pain evaluation: no specific instrument
Adverse events evaluation (toxicity)	Classification system of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) [51]	NR	The systemic toxicity of the treatment was graded according to World Health Organization criteria. Quality of life was assessed by means of the Patient Global Assessment (PGA)	NR
Outcomes				
Efficacy				
Complete response (CR)/partial response(PR)/ Stable disease/progressive disease	Complete response (100% volume reduction, MRI): 3/17 pts (17.6%) Lesion response rate: 19/20 lesions (95%) 8 pts (47%) asymptomatic 9 pts (53%) improvement in clinical symptoms Lesion volume after treatment 3.48 cm^3 (range, 0-454.64 cm^3) median volume reduction of 86%	Complete response (CR) was observed in 14 (73.6%) out of 19 pts after first ECT session, while 3 (15.7%) and 2 (10.5%) pts received respectively a second and a third ECT treatment. All patients showed no residual disease after the last ECT session.	CR 14 (60.9%) PR 9 (39.1%) (4 weeks after first ECT) 2nd ECT session: 3 pts retreated for new lesions in previously untreated areas achieved 1 CR and 2 PR. 2 pts retreated for the nodules that remained after the first course; 1 CR, 2 PR. 3rd ECT session: 2 pts maintained a PR	CR 16 pts (89%) PR: 2 pts (11%)

Author, year	Wohlgemuth, 2021 [44]	Di Monta, 2014 [39]	Curatolo, 2012 [40]	Latini, 2012 [41]
Recurrence rate	NR	NR	5 pts (21.7%) developed a cutaneous disease progression (2 in previously untreated areas and 3 in treated body sites) that was no longer manageable with ECT	NR
Survival/progression-free survival	NA	NR	The local tumour control rate at 2 years was 76.2% Sustained local control of treated lesions was achieved in 20 of 23 patients. overall survival rate was 74.4% at 2 years	NR
Other disease-related symptoms (pain, swelling, impaired physical functioning, wounds, skin discoloration)[34]	See below (safety)	See below (safety)	See below (safety)	See below (safety)
Quality of life	NR	NR	In 22 patients (95%), an improvement in the quality of life was scored (PGA) this improvement was not necessarily related to complete remission.	NR
Safety				
Pain, n (%)	At baseline: 17 pts (100%) After treatment: Mild pain 5 pts (29.4%). Post interventional local inflammatory response with pain that required medication only: 6 treatments	Pain and erythema to the treated and surrounding area were among the most commonly reported side effects. They were considered tolerable by most patients.	Local pain in 2 pts (9%)	Posttreatment pain All responsive patients showed a progressive improvement of pretreatment symptoms as local pain or functional limitation.
Skin toxicity, n (%)	Adverse events reported in 10 pts (59%) Skin discoloration at needle puncture site: 4 pts (23.5%) Temporary skin hyperpigmentation 1 pt (5.9%) Swelling: 4 pts (23.5%) Skin lesion: 2 pts (11.8%)	Pain and erythema to the treated and surrounding area were among the most commonly reported side effects. They were considered tolerable by most patients.	Cutaneous infection in 2 pts (9%)	Local ulceration: 1 pts (5%)
Any procedure-related (serious) adverse events	None	None	None	Yes (Posttreatment fever, nausea)
Any device-related (serious) adverse events	None	None	None	NR
Any adverse events/ serious adverse events	None	None	None	NR

Abbreviations: NR – Not Reported, NA – Not Applicable

Risk of bias tables and GRADE evidence profile

Table A-2: Risk of bias – study level (case series) IHE checklist

Study reference/ID	Guida, 2006 [43]	Campana, 2019 [38]	Horbach, 2019 [37]	Kostusiak, 2021 [42]	Wohlgemuth, 2021 [44]	Di Monta, 2014 [39]	Curatolo, 2012 [40]	Latini, 2012 [41]
Study objective								
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study design								
2. Was the study conducted prospectively?	No	Unclear	Yes	Yes	No	Yes	Yes	Unclear
3. Were the cases collected in more than one centre?	Yes	Yes	No	No	No	No	No	No
4. Were patients recruited consecutively?	No	Unclear	Unclear	Unclear	No	Yes	Unclear	Unclear
Study population								
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Partial	Partial	Partial	Partial	Partial	Partial
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Partial	Partial	Yes	No	Yes	Partial	Partial	Partial
7. Did patients enter the study at a similar point in the disease?	No	No	No	No	No	Unclear	Unclear	Unclear
Intervention and co-intervention								
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Partial	Partial	Partial	No	Yes	No
Outcome measures								
10. Were relevant outcome measures established a priori?	Yes	No	Yes	Yes	No	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Partial	Partial	Partial	Yes	Yes	Partial
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Statistical Analysis								
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	No	No	No	Unclear	Unclear	Unclear
Results and Conclusions								
15. Was follow-up long enough for important events and outcomes to occur?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
16. Were losses to follow-up reported?	NA (retrospective case series)	NA (registry-based study)	Unclear	Yes	NA (retrospective case series)	No	Yes	No

Study reference/ID	Guida, 2006 [43]	Campana, 2019 [38]	Horbach, 2019 [37]	Kostusiak, 2021 [42]	Wohlgemuth , 2021 [44]	Di Monta, 2014 [39]	Curatolo, 2012 [40]	Latini, 2012 [41]
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	No	No	No	No	Yes	No
18. Were the adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Unclear	Unclear	No	Unclear	Unclear	Unclear
Competing interests and sources of support								
20. Were both competing interests and sources of support for the study reported?	Partial	Yes	Partial	Partial	Yes	Yes	No	No
Overall Risk of bias	**High risk**	**High risk**	**High risk**	**High risk**	**High risk**	**High risk**	**High risk**	**High risk**

Table A-3 Evidence profile: efficacy and safety of bleomycin electrosclerotherapy

Certainty assessment							Impact	Certainty of the evidence (importance)
№ of studies (patients)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Efficacy								
Due to the lack of a controlled group, no data on efficacy outcomes can be compared and synthesised								
Safety								
Serious adverse events								
6 (128)	Case series (Single-arm before after BEST)	Very serious[1]	Not serious	Not serious	Very serious[2]	None	No. of SAEs across all studies reporting on SAEs: 0/128 pts [37-40, 42, 44]	⨁◯◯◯ VERY LOW (critical)
Pain								
7 (146)	Case series (Single-arm before after BEST)	Very serious[1]	Not serious	Not serious	Very serious[2]	None	Patient-reported pain across all studies: in 15/90 pts (16.6%, range 6.6-30%) [38, 40, 42, 44][3]	⨁◯◯◯ VERY LOW (critical)
Skin toxicity								
7 (146)[4]	Case series (Single-arm before after BEST)	Very serious[1]	Not serious	Not serious	Very serious[2]	None	■ Overall skin toxicity across all studies[5]: in 40/107 pts (37.3%, range, 5.6-60%) [37, 40-42, 44] ■ Skin ulceration: 17/97 pts (17.5 %, range, 0-47.3%) [37, 38, 40, 41, 44] ■ Necrosis: 2/127 pts (1,5%, range 0-10%) [37, 38, 40-42, 44] ■ Erythema/swelling: 16/127 pts (12.5%, range 0-31.5%) [37, 38, 40-42, 44] ■ Bleeding6: 2/88 pts (2.2 %, range, 0-6.6%) [40-42, 44] ■ Infection7: 8/127 pts (6.2%, range, 0-15%) [37, 38, 40-42, 44] ■ Hyperpigmentation[7]: 7/127 pts (5.5%, range, 0-20%) [37, 38, 40-42, 44]	⨁◯◯◯ VERY LOW (critical)

Certainty assessment							Impact	Certainty of the evidence (importance)
№ of studies (patients)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Skin toxicity8								
1 (5) [43]	Prospective case series (Single-arm before after BEST) [9]	Very serious[1]	Not serious	Not serious	Very serious[2]		■ Bleomycin electrosclerotherapy (5 pts): ■ Superficial skin necrosis: 1 pt (20%) ■ Mild hyper-pigmentation: 2 pts (40%) ■ Bleomycin alone (5pts): ■ Mild erythema: 1 pt (20%) ■ Hematoma: 1 pt (20%) ■ Hyperpigmentation: 1 pt (20%) ■ Control group (no treatment) (5pts): ■ No adverse events were reported (5pts)	⨁◯◯◯ VERY LOW (critical)
Any other adverse events								
6 (116)	Case series (Single-arm before after BEST)	Very serious[1]	Not serious	Not serious	Very serious[2]	None	■ Posttreatment fever and nausea in one study, no. of pts not reported [41] ■ Any other AEs across all studies 0/116 pts [37-40, 44]	⨁◯◯◯ VERY LOW (critical)

Abbreviations: AE – adverse event, BEST – Bleomycin Electrosclerotherapy, IHE – Institute of Health Economics, NRS – non-randomised studies, pts – patients, RoB – risk of bias, SAE – serious adverse event

Comments:

[1] *Using the IHE RoB checklist. Very serious limitations are given, due to the lack of a controlled study design.*

[2] *Only descriptive data available. Sample size is small and no formal statistical analyses where performed.*

[3] *One study [37] reported on pain reduction as effect after BEST. Pain was not reported as adverse event and therefore not included in this table. In another study [44] all patients had pain already at baseline, but mild pain was reported as an adverse event in five patients and were therefore included in the calculation.*

[4] *All studies reported on skin toxicity, but the reporting was inconsistent. If an outcome was not specifically reported, but other symptoms were reported in detail and including numbers, the outcome of interest was rated as 0 and the study was included in the calculation (denominator). If the outcomes were reported without numbers or in a general way, the study was not included.*

[5] *In one study [38] data were presented in a way that did not allow identification of the total number of patients with skin toxicity. This study was not included in the calculation of overall skin toxicity.*

[6] *In two studies [37, 38] the number of patients bleeding decreased after the intervention. These studies were not included in this calculation, as bleeding was not reported as adverse event.*

[7] *In one study [38] there were 2 pts (10%) with hyperpigmentation and one patient (5%) with infection already at baseline.*

[8] *A small (n=5) pilot trial where lesions within-patients were randomized and not patients (three comparable regions of interest). Each of the three regions were treated with either bleomycin electrosclerotherapy, bleomycin alone, or no treatment. In this report we categorized this trial as a prospective single-arm case series.*

Applicability table

Table A-4: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The studies included a total of 151 patients for the safety profil of bleomycin electrosclerotherapy. Mean age ranged from 20.8 to 68.4 years and 48.3% of the study participants were female. Three studies evaluated bleomycin electrosclerotherapy in patients with Kaposi sarcoma [39-41], two studies in patients with angiosarcoma (cutaneous angiosarcoma) [38] (locally advanced or metastatic angiosarcomas) [37]. Single studies explored the effect of bleomycin electrosclerotherapy in congenital vascular malformations [42], venous malformations [44] and hypertrophic capillary malformations [43]. The inclusion and exclusion criteria differed significantly between studies.
Intervention	Two different divices, both on the market were used across the trials to treat vascular anomalies: BEST/Cliniporator® (IGEA) BEST/Cliniporator VITAE® (IGEA)
Comparators	No controlled trials identified.
Outcomes	The most frequently reported important/critical outcomes were serious adverse events, patient-reported post-operative pain and skin toxicity.
Setting	Overall, all studies were carried out across four European countries (Germany, Italy, Netherlands, United Kingdom). The studies were published between 2012 and 2021. The intervention was performed in University or public hospitals (e.g. sarcoma, plastic surgery or dermatologic departments). The settings of the studies reflect the clinical setting in which the technology is intended to be used appropriately. No applicability issues are expected from the geographical setting.

List of ongoing studies

Table A-5: List of ongoing trials of bleomycin electrosclerotherapy

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
Randomized controlled trials						
NA						
Prospective single arm studies						
NCT05494710	Vascular malformation (20 Patients)	Bleomycin electrosclerotherapy treatment	-	Change in Quality of life questionnaire scores Clinician assessment tool of treatment response	December 1, 2022	South Tees Hospitals NHS Foundation Trust
Retrospective observational study (single arm study)						
DRKS00031072	Vascular anomalies or vascular tumors (300)	Bleomycin electrosclerotherapy treatment	-	Analysis of complication rates after interventional treatment using image-guided bleomycin electro-sclerotherapy (BEST) of simple or mixed peripheral slow-flow malformations (periinterventional and postinterventional complications <30 day).	-	LMU München Marchioninistr. 15, 81377 München Deutschland

Literature search strategies

Search strategy for Cochrane

Search Name: Electrosclerotherapy/Electrochemotherapy with Bleomycin	
Search date: 16.12.2022	
ID	Search
#1	(electrosclerotherap*) (Word variations have been searched)
#2	(electr* NEAR (sclerotherap OR chemotherap* OR chemo-therap* OR porat* OR permeabili?at*)) (Word variations have been searched)
#3	MeSH descriptor: [Electrochemotherapy] explode all trees
#4	(electrochemotherap*) (Word variations have been searched)
#5	(electro-chemotherap*) (Word variations have been searched)
#6	(electrochemo-therap*) (Word variations have been searched)
#7	MeSH descriptor: [Electroporation] explode all trees
#8	(electroporation*) (Word variations have been searched)
#9	(electro-poration*) (Word variations have been searched)
#10	(electropermeabili?ation*) (Word variations have been searched)
#11	(electro-permeabili?ation*) (Word variations have been searched)
#12	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 (Word variations have been searched)
#13	MeSH descriptor: [Bleomycin] explode all trees
#14	(bleomycin*) (Word variations have been searched)
#15	(bleomicina*) (Word variations have been searched)
#16	(bleolem*) (Word variations have been searched)
#17	(bl?noxan*) (Word variations have been searched)
#18	(bleocell*) (Word variations have been searched)
#19	(blenamax*) (Word variations have been searched)
#20	(bleo)
#21	(bleocin*) (Word variations have been searched)
#22	(bleocris*) (Word variations have been searched)
#23	(blexit*) (Word variations have been searched)
#24	(blocamicina*) (Word variations have been searched)
#25	(bloicin-s) (Word variations have been searched)
#26	("nsc 125066") (Word variations have been searched)
#27	(nsc125066) (Word variations have been searched)
#28	("11056-06-7") (Word variations have been searched)
#29	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
#30	#12 AND #29
#31	#1 OR #30
#32	(conference proceeding):pt
#33	(abstract):so
#34	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#35	#32 OR #33 OR #34
#36	#31 NOT #34
Total hits: 25	

Search strategy for Embase

Search Name: Electrosclerotherapy/Electrochemotherapy with Bleomycin		
Search date: 16.12.2022		
No.	Query Results	Results
#39.	#37 NOT #38	711
#38.	#37 AND 'Conference Abstract'/it	148
#37.	#32 NOT #35 AND ([english]/lim OR [german]/lim)	859
#36.	#32 NOT #35	882
#35.	#33 OR #34	2,553,215
#34.	'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)	2,489,680
#33.	(rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de	1,186,064
#32.	#1 OR #31	1,028
#31.	#13 AND #30	1,025
#30.	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	57,731
#29.	nsc125066	11
#28.	'nsc 125066'	63
#27.	'bloicin-s'	
#26.	blocamicina*	4
#25.	blexit*	
#24.	bleocris*	
#23.	bleocin*	91
#22.	bleo	468
#21.	blenamax*	4
#20.	'bleo-cell*'	
#19.	bleocell*	3
#18.	bl*noxan*	730
#17.	bleolem*	1
#16.	bleomicina*	171
#15.	bleomycin*	56,761
#14.	'bleomycin'/exp	54,112
#13.	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	28,581
#12	'electro-permeabili*at*'	13
#11.	electropermeabili*at*	579
#10.	'electro porat*'	40
#9.	electroporat*	26,603
#8.	'electroporation'/exp	23,152
#7.	'electro-chemo-therap*'	5
#6.	'electrochemo-therap*'	4
#5.	'electro-chemotherap*'	27
#4.	electrochemotherap*	1,825
#3.	'electrochemotherapy'/exp	1,631
#2.	electr* NEAR/3 (sclerotherapy OR sclerotherap* OR chemotherap* OR 'chemo-therap*' OR porat* OR permeabili*at*)	983
#1.	electros*lerotherap*	8
Total hits: 711		

Search strategy for Medline via Ovid

Search Name: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 15, 2022>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2018 to December 15, 2022>	
Search date: 16.12.2022	
ID	Search
1	electros#lerotherap*.mp. (12)
2	electr*.mp. adj3 (exp Sclerotherapy/ or sclerotherap*.mp. or chemotherap*.mp. or chemo-therap*.mp.) (1687)
3	exp Electrochemotherapy/ (1057)
4	electrochemotherap*.mp. (1773)
5	electro-chemotherap*.mp. (13)
6	electrochemo-therap*.mp. (7)
7	electro-chemo-therap*.mp. (4)
8	exp Electroporation/ (11008)
9	electroporat*.mp. (20374)
10	electro-porat*.mp. (14)
11	electropermeabili#ation*.mp. (543)
12	electro-permeabili#ation*.mp. (16)
13	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (22772)
14	exp Bleomycin/ (18511)
15	bleomycin*.mp. (25716)
16	bleomicina*.mp. (94)
17	bleolem*.mp. (0)
18	bl#noxan*.mp. (23)
19	bleocell*.mp. (0)
20	bleo-cell*.mp. (0)
21	11056-06-7.mp. (3)
22	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (25956)
23	13 and 22 (783)
24	1 or 23 (787)
25	exp animals/ not humans.sh. (5663916)
26	24 not 25 (606)
27	limit 26 to (english or german) (594)
28	remove duplicates from 27 (402)
Total hits: 402	

Search strategy for HTA-INATHTA

Search Name: Electrosclerotherapy/Electrochemotherapy with Bleomycin	
Search date: 19.12.2022	
ID	Search
9	(bleo-cell*) OR (bleocell*) OR (blanoxan*) OR (blenoxan*) OR (bleolem*) OR (bleomicina*) OR (bleomycin*) OR ("Bleomycin"[mhe]),"0","2022-12-19T10:53:05.000000Z"
8	bleo-cell*,"0","2022-12-19T10:52:52.000000Z"
7	bleocell*,"0","2022-12-19T10:52:47.000000Z"
6	blanoxan*,"0","2022-12-19T10:52:31.000000Z"
5	blenoxan*,"0","2022-12-19T10:52:21.000000Z"
4	bleolem*,"0","2022-12-19T10:52:02.000000Z"
3	bleomicina*,"0","2022-12-19T10:51:46.000000Z"
2	bleomycin*,"0","2022-12-19T10:51:23.000000Z"
1	"Bleomycin"[mhe],"0","2022-12-19T10:50:53.000000Z"
Total hits: 0	

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