REVIEW

Efficacy and tolerability of intralesional bleomycin in dermatology: A systematic review

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Bleomycin is widely used as an off-label treatment for various dermatologic indications. However, a much-needed critical appraisal of the currently available evidence is lacking. We therefore evaluated the quality of clinical evidence for the efficacy and safety of intralesional bleomycin treatment for dermatologic indications with the aim to provide evidence-based recommendations for clinical practice. The PubMed, Embase, Medline Ovid, Web of Science, Cochrane Central, and Google Scholar databases were systematically searched. Two authors independently selected relevant studies according to predefined inclusion and exclusion criteria. We assessed the methodologic quality with the Cochrane Collaboration risk-of-bias assessment tool and selected 10 randomized clinical trials and 15 clinical controlled trials. Treatment indications included common warts, nonmelanoma skin cancer, cutaneous metastases, keloid and hypertrophic scars, and hemangioma. Intralesional bleomycin treatment showed significantly higher cure rates for warts compared with other treatments. Local adverse events included erythema, blackening, eschar formation, and superficial ulceration. None of the studies reported systemic adverse events. Methodologic quality of the studies was generally low. Consequently, no firm recommendations can be made for intralesional bleomycin treatment in clinical practice. However, this review suggests that intralesional bleomycin is a successful and well-tolerated treatment for recalcitrant warts. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2020.02.018.)

Key words: bleomycin; cutaneous metastases; dermatology; drug response; efficacy; electrochemotherapy; hemangioma; hypertrophic scars; intralesional; keloid; nonmelanoma skin cancer; safety; systematic review.

Bleomycin has been approved as cytostatic drug for the treatment of squamous cell carcinoma of head, neck, and external genitalia in dermatology.[1,2] In clinical practice, however, bleomycin is also used off-label for various other dermatologic indications.

Bleomycin is an antineoplastic antibiotic derived from *Streptomyces verticillus*.[3] Multiple subtypes (A1-6 and B1-5) are available, of which bleomycin A2 and B2 are most commonly used in clinical practice. The latter subtypes are hydrophilic and have a metal binding core that is the key factor in the mechanism of action. Bleomycin is primarily eliminated by renal excretion and to a lesser extent by the bleomycin hydrolase (BMH) enzyme.[4] BMH shows the highest activity in bone marrow and is least active in the lungs and skin, with consequently more bleomycin-related toxicity in the latter tissues.[5]

Bleomycin's main mechanism of action is DNA-strand scissoring. Specifically, in the presence of molecular oxygen, it can oxidize metal ions such as Fe^{2+} to Fe^{3+}, creating free radicals. Bleomycin binds to DNA by an electrostatic attraction and breaks the DNA backbone, which ultimately ends in cell cycle arrest.[5-7] Bleomycin administered to the skin results in apoptosis of keratinocytes, sclerosing of endothelium cells, and inhibition of collagen synthesis.[8]

Severe adverse reactions have been reported after intravenous chemotherapy with bleomycin. Pulmonary fibrosis has been the most serious

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reported adverse reaction after a total dose exceeding >400 U.[9,10] Severe cutaneous toxicity has been reported after cumulative dosages of 200 to 300 U, including scleroderma, neutrophilic eccrine hidradenitis, and acute generalized exanthematous pustulosis.[10-13]

In dermatology, bleomycin is mainly used as an intralesional treatment, and the dosage usually does not exceed 2 to 6 U per session.[14] Sporadic reported adverse reactions after intralesional administration include gangrene, onychodystrophy, Raynaud phenomenon, scleroderma, and flagellate erythema.[11,15-18] Local skin reactions after bleomycin injections include transient symptoms of erythema, edema, blackening, eschar formation, pain, and pigmentary changes.[19,20]

Contraindications for bleomycin include pregnancy, Raynaud phenomenon, peripheral vascular diseases, and bleomycin intolerance.[21]

The efficacy and safety of intralesional bleomycin treatment for dermatologic indications has been investigated in various clinical trials. To date, however, a much-needed critical appraisal of the currently available evidence has been lacking. The objective of this study was to systematically review and evaluate the quality of clinical evidence for the efficacy and safety of intralesional bleomycin treatment for dermatologic indications and to provide evidence-based recommendations for clinical practice.

CAPSULE SUMMARY

- This systematic review entails an overview and methodologic quality assessment of the currently available evidence for efficacy and safety of bleomycin treatment for dermatologic indications.
- Insufficient evidence was available to provide firm recommendations for bleomycin treatment in dermatology. However, intralesional bleomycin should be considered as a treatment option for recalcitrant warts.

METHODS

In January 2019, we conducted a systematic literature search for intralesional bleomycin treatment for dermatologic indications. Relevant keywords were used to search in PubMed, Embase, Medline Ovid, Web of Science, Cochrane Central, and Google Scholar. The systematic review was registered in PROSPERO (CRD42019131934) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews.

The inclusion criteria for selection of the articles were English language, published from inception to January 2019, randomized controlled trials (RCTs), nonrandomized clinical controlled trials (CCTs), intralesional bleomycin treatments for dermatologic indications, and reporting clinical outcomes from intervention. Exclusion criteria were preclinical studies, monotherapy with intravenous or topical bleomycin, and case series with fewer than 10 patients. The primary outcome measure was efficacy, and the secondary outcome measure was safety.

Selection of the articles was performed independently by 2 authors (L.B. and T.S.). Articles were preselected based on the title and abstract. The final selection was based on full-text assessment. Reference lists of selected articles were screened for additional relevant studies. Standardized data extraction of the included studies was performed independently by 2 authors (L.B. and T.S.). The dosage of bleomycin was converted to United States Pharmacopeia units (U): 1 U represents 1 mg (by potency) or 1000 international units (IU).[22]

Methodologic quality was independently evaluated according to the Cochrane Collaborations risk-of-bias assessment tool. Disagreement between the 2 authors was resolved by discussion and involved a third author when necessary.

RESULTS

Study characteristics

The data search returned 2672 references. Duplicates were removed. The remaining 1647 references were screened based on title and abstract, whereupon 1531 references were excluded. Full texts of 116 references were obtained, and the inclusion and exclusion criteria were used to select 25 studies for this review (Fig 1).

The included studies are 10 RCTs and 15 CCTs published between 1979 and 2018, comprising a total of 1130 patients. The studies investigated intralesional bleomycin treatments for the following dermatologic indications: common warts, nonmelanoma skin cancer, cutaneous metastases, keloid, hypertrophic scars, hemangioma, and other indications. Described routes of administration included needle injections, jet injector, microneedling pen, multipuncture technique, and a bleomycin-covered microneedle patch.

Common warts

Fourteen studies with a total of 584 patients investigated intralesional bleomycin in 2657

Abbreviations used:

RCT:	randomized controlled trial
CCT:	clinical controlled trial
PROSPERO:	International prospective register of systematic reviews
PRISMA:	transparent reporting of systematic reviews and meta-analyses
5-FU:	5-fluorouracil
TCA:	Triamcinolone acetonide

common warts. Study characteristics and results are summarized in Table I.[19,23-35]

Intralesional bleomycin injections resulted in significantly higher complete cure rates than saline injection or cryotherapy ($P < .05$).[19,23-30] Administration of intralesional bleomycin via a microneedling pen showed comparable cure rates as intralesional bleomycin injections ($P = .474$), but fewer patients reported pain (20% vs 100%; $P = .001$).[31] A bleomycin-covered microneedle patch resulted in comparable complete cure rates compared with cryotherapy but with significantly lower pain scores on a visual analog scale (0.48 ± 0.5 vs 7.29 ± 0.13; $P < .0001$).[32]

Use of a local electroporation procedure after bleomycin injections resulted in significantly higher complete cure rates than bleomycin alone ($P = .0015$).[33] During electroporation, electric pulses were generated with electrodes at the lesion site to increase cellular drug uptake.

One study showed significantly higher response rates in the placebo groups than in the group receiving bleomycin injections administered with a jet injector ($P = .018$).[34] The authors did not provide a specific explanation.

Patients who had received a transplant and were taking immunosuppressant drugs and patients without a transplant showed significantly higher complete cure rates for intralesional bleomycin injections than for placebo ($P < .0001$). However, transplant recipients showed lower complete cure rates than patients without a transplant.[27] No difference in complete cure rates was observed between different dosages of bleomycin injections (0.25, 0.50, or 1 U/mL) (no P value reported).[35] Overall, plantar warts were more resistant to bleomycin treatment than warts on other anatomic locations.[19,25,26,35]

Nonmelanoma skin cancer

One study including 113 patients investigated intralesional bleomycin with local electroporation in 113 nonmelanoma skin cancer tumors (Table II).[14,20,36-44] This study showed a higher sustained complete response rate for electroporation with biphasic pulses of 50 + 50 μs than for electroporation with biphasic pulses of 25 + 25 μs after intralesional bleomycin administration (no statistical test reported).[36]

Cutaneous metastases

Three studies including a total of 93 patients investigated intralesional bleomycin with local electroporation in 390 cutaneous metastases (Table II). Intralesional bleomycin, followed by local electroporation, showed significantly higher response rates in metastases of melanoma ($P = .017$) compared with intralesional bleomycin alone ($P = .002$).[37,38] For cutaneous metastases of melanoma and nonmelanoma cancers, similar response rates have been reported for intralesional bleomycin, intravenous bleomycin, and intralesional cisplatin, all followed by local electroporation at the tumor site ($P = .09$).[39]

Keloid and hypertrophic scars

Three studies with a total of 191 patients investigated intralesional bleomycin treatment in 191 keloids and hypertrophic scars (Table II). A significantly greater improvement on the Vancouver Scar Scale was reported with intralesional bleomycin compared with intralesional 5-fluorouracil (5-FU) or 5-FU combined with triamcinolone acetonide (TCA; $P < .005$).[14] Intralesional bleomycin showed improvement on the Patient and Observer Scar Assessment Scale comparable to TCA injections in patients with dark skin color (Fitzpatrick skin types III to V; no P value reported).[20] Bleomycin multipuncture technique showed better resolution scores compared with cryotherapy combined with TCA injections ($P = .001$).[40] No recurrences were described after intralesional bleomycin treatment.[14,40]

Hemangioma

Two studies with a total of 87 patients investigated intralesional bleomycin in 87 hemangiomas (Table II). Intralesional bleomycin showed significantly better response rates than intralesional TCA injections, but only in nonresponders to oral propranolol ($P = .037$).[41] No difference in hemangioma volume reduction was seen between intralesional bleomycin injections and oral propranolol in children (no statistical test reported).[42]

Other indications

Two studies with a total of 62 patients investigated 76 lesions of other indications for intralesional bleomycin treatment in dermatology (Table II). In

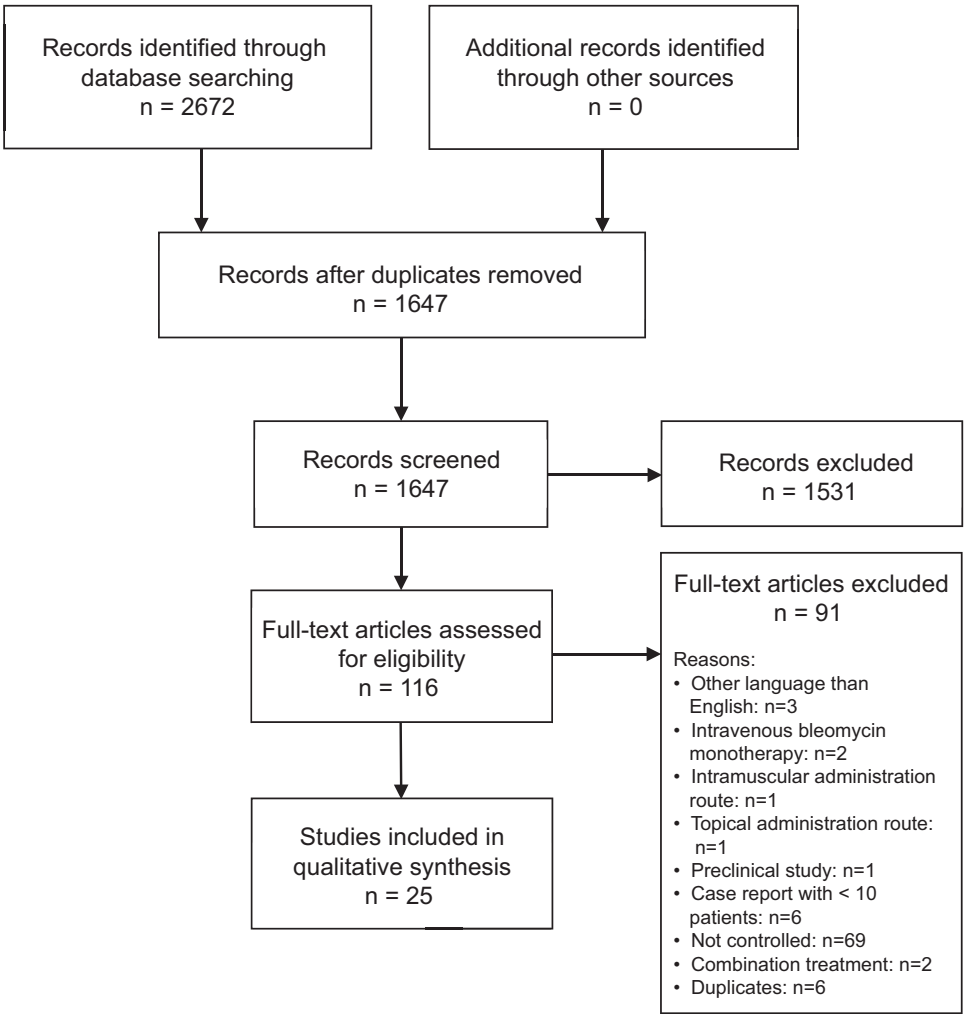

Fig 1. Flowchart of the exclusion process ending with 25 included studies.

corns, intralesional bleomycin injections after callus paring resulted in higher complete cure rates and pain reduction than callus paring alone (no *P* value reported).[43] In vulvar intraepithelial neoplasia, intralesional bleomycin injections and topical bleomycin application showed poor remission rates and high rates of disease progression (no statistical tests reported).[44]

Reports of adverse events

One study reported 3 cases of significant adverse events due to intralesional bleomycin treatment, but no details were described.[29] Local skin reactions, including erythema, blackening, and eschar formation were described as part of the therapeutic effect of bleomycin.* Superficial ulceration was frequently reported but generally healed with no or minimal scarring.[14,41,42,44] Hyperpigmentation after treatment was mainly observed in patients with dark skin types.[14,20,40] Pain during or after the procedure, or both, was reported in 22 of 25 included studies.[14,19,20,23-39,43,44] None of the included studies reported systemic adverse events.

*References 19, 24, 26-28, 35, 37, 38, 43.

Methodologic quality of the included studies

Most of the included studies had an unclear risk of bias for most of the methodologic criteria of the Cochrane Collaborations risk-of-bias assessment tool (Fig 2). Only 3 of the 25 included studies used high-quality randomization sequences,[23,30,41] and all studies lacked concealment of allocation. Poor methodologic quality was found for blinding, incomplete outcome data, selective reporting, and other bias.

DISCUSSION

This systematic review provides an overview of the clinical studies investigating the efficacy and safety of intralesional bleomycin for dermatologic

Table I. Characteristics and summary of results of included studies on intralesional bleomycin in common warts

First author, year	Type of lesion	Study design	No. of patients (lesions)	Intervention	Anesthetics	Frequency	Concentration & dosage	Comparative intervention	Results per patient	Results per lesion	Follow-up time	Adverse events	Conflicts of interest/ funding
Amer,[19] 1988	Resistant warts	CCT	38 (143)	Intralesional bleomycin injection	Not reported	1-2×, interval of 2 weeks	1 U/mL, ≤2 mL per treatment	Placebo: intralesional saline injection (in same patient)	Not reported	CR 67.8% vs 2.9% and PR 17.5% vs 5.7% resp. bleomycin or saline injection. CR after bleomycin per location: 77% for hands and feet, 71.4% for periungual warts, 47.6% for plantar warts (no statistical tests)	Not reported	No systemic adverse events. Local: pain during injection, erythema, blackening and eschar formation	Not reported
Barkat,[23] 2018	Plantar warts	RCT	46 (46)	Intralesional bleomycin injection	Bleomycin diluted in lidocaine 2%	1-4×, interval of 2 weeks	1 U/mL, ≤2 mL per treatment and ≤1 mL per wart	Placebo: intralesional saline injection	CR clinical and dermoscopic view, 69.3% vs 0%; clinical clearance but dermoscopic remnants of wart, 19.2% vs 0%; partial clinical improvement, 7.7% vs 5%; no response, 3.8% vs 95% resp. bleomycin or saline. ($P < .0001$). Recurrence rate 0%	Not reported	3 months	No systemic adverse events. Local: pain on first or second day after injection	None declared
Shumack,[24] 1979	Common warts	CCT	? (1052)	Intralesional bleomycin injection	Local anesthetic injection (Xylocaine 1%)*	1-3×, interval of 4 weeks	1 U/mL, ≤2 U per patient in total	Placebo: intralesional saline injection	Not reported	OR 99.23% vs 0% resp. bleomycin or saline injection (no statistical tests)	Not reported	No systemic adverse events. Local: pain, blackening thrombosis, desiccating. and pigmentary changes	Not reported
Bunney,[25] 1984	Resistant warts	RCT	24 (118)	Intralesional bleomycin injection	Not reported	1-3×, interval of 3-6 weeks	1 U/mL, ≤0.2 mL per treatment and ≤4 U bleomycin in total	Placebo: intralesional saline injection	87.5% showed favorable reaction to bleomycin than to saline. CR in 75% of	CR 76% vs 10% resp. bleomycin or saline	>6 months	No systemic adverse event. Local: pain	Not reported

Continued

Table I. Cont'd

First author, year	Type of lesion	Study design	No. of patients (lesions)	Intervention	Anesthetics	Frequency	Concentration & dosage	Comparative intervention	Results per patient	Results per lesion	Follow-up time	Adverse events	Conflicts of interest/ funding
									resistant hand warts and 66% in mosaic plantar warts				
Shumer,[26] 1983	Resistant warts	Cross-over CCT	40 (151)	Intralesional bleomycin injection	Not reported	1-2×, interval of 2 weeks	1 U/mL, ≤2 mL per treatment	Placebo: intralesional saline injection (switch to other intervention after 2 failure injections)	Not reported	CR 81% vs 0% resp. bleomycin or saline injection. Specified CR: plantar warts, 60%; periungual warts, 94%; warts elsewhere on extremities, 95%. Recurrence rate 0%	6-12 months	No systemic adverse events. Local: hemorrhagic eschar, pain, erythema, and swelling for 24-72 hours	Not reported
Sobh,[27] 1991	Resistant warts	CCT	36 (193)	Intralesional bleomycin injection	Not reported	1-3×, interval of 3 weeks	1 U/mL, ≤2 mL per treatment	Placebo: intralesional saline injection	Not reported	Renal transplant patients: CR 37% vs 0%, PR 3% vs 4% resp. bleomycin or saline. ($P < .0001$). Nontransplant patients: CR 60% vs 2.5%, PR 24% vs 2.5% resp. bleomycin or saline. ($P < .001$). Difference between patient groups not statistically tested	Not reported	No systemic adverse events. Local: pain, redness, blackening and eschar formation	Not reported
Soni,[28] 2011	Palmo-plantar and periungual warts	CCT	50 (157)	Intralesional bleomycin injection	Bleomycin diluted with 2% lignocaine	1-2×, interval of 2 weeks	1 U/mL, ≤2 mL per treatment	Placebo: intralesional saline injection	Not reported	CR 96.47% vs 11.11% resp. bleomycin or saline ($P = .001$). Recurrence rate 0%	1 year	No systemic adverse events. Local: pain and eschar formation	None declared
Adalatkhah,[29] 2007	Common warts of hand and feet	RCT	52 (479)	Intralesional bleomycin injection	Bleomycin diluted with 2% lidocaine	1-3×, interval of 15 days	0.5 U/mL, dosage not reported	Cryotherapy (number of freeze-thaw cycles not reported)	CR 86.4% vs 68.2% resp. bleomycin or cryotherapy ($P < .05$).	CR 87.6% vs 72.3% resp. bleomycin or cryotherapy ($P < .001$). RR	Not reported	No systemic adverse events, but 3 unspecified	Not reported

									RR = 1.27 (1-1.6)	bleomycin = 1.23 (1.22-1.33)		cases of significant adverse complications due to bleomycin treatment. Local: pain	
Dhar,[30] 2009	Common warts	RCT	80 (155)	Intralesional bleomycin injection	Bleomycin diluted with 2% lidocaine	1-4×, interval of 3 weeks	1 U/mL, ≤2 mL per treatment	Cryotherapy, double freeze-thaw cycle	CR 94.9% vs 76.5% resp. bleomycin or cryotherapy ($P < .05$ and RR = 7.67). Treatment visits needed 1.38 vs 3.09 resp. bleomycin or cryotherapy ($P < .05$).	CR 97% vs 82% resp. bleomycin or cryotherapy ($P < .05$). Recurrence rate 13% vs 23% resp. bleomycin or cryotherapy (not statistically significant)	8 weeks	No systemic adverse events. Local: pain and pigmentation changes	None declared
Al-Nagar,[31] 2018	Plantar warts	CCT	60 (60)	Intralesional bleomycin injection	Bleomycin diluted with 2% lidocaine	1-4×, interval of 2 weeks	1 U/mL, ≤1 U per treatment	Microneedling pen with 2-mm depth applied for 2-3 minutes, followed by bleomycin under occlusion for 2 hours	CR 70% vs 83.3% and PR 30% vs 16.7% resp. bleomycin injections or microneedling followed by topical bleomycin ($P = .474$). Recurrence rate 0% for both groups. Pain described 100% vs 20% resp. bleomycin injection or microneedling and bleomycin ($P = .001$)	Not reported	6 months	No systemic adverse events. Local: pain, erythema, edema and transient induration	None declared
Ryu,[32] 2018	Common warts	RCT	42 (42)	Intralesional bleomycin via bleomycin-coated microneedle patch	None	1×/d, interval of 2 weeks until complete clearance	518.12 μg of bleomycin on the surface of microneedling patch	Cryotherapy, double freeze-thaw cycle	VAS score mean ± SD: 0.48 ± 0.5 vs 7.29 ± 0.13 resp. bleomycin or cryotherapy ($P < .0001$)	CR 61.90% vs 76.19% resp. bleomycin or cryotherapy. (statistical tests not reported). Treatment duration until clearance 14.0 ± 6.6 vs 12.5 ± 5.7 resp. bleomycin or	Not reported	No systemic adverse events. Local: pain, erythema. Scarring and pigmentary changes in cryotherapy	None declared

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Table I. Cont'd

First author, year	Type of lesion	Study design	No. of patients (lesions)	Intervention	Anesthetics	Frequency	Concentration & dosage	Comparative intervention	Results per patient	Results per lesion	Follow-up time	Adverse events	Conflicts of interest/ funding
										cryotherapy (P = .2771)			
Pasquali,[33] 2017	Plantar warts	CCT	22 (22)	Intralesional bleomycin followed by electroporation	Local anesthetic injection (lidocaine)	1 treatment	1 U/cm^3; ≤0.1 mL per injection	Intralesional bleomycin injection alone	CR 78% vs 16% and PR 22% vs 76% resp. bleomycin + electroporation or bleomycin alone after 3 months (P = .0015)	CR 78% vs 16% and PR 22% vs 76% resp. bleomycin + electroporation or bleomycin alone after 3 months (P = .0015)	3 months	No systemic adverse event. Local: pain, redness, tenderness, skin discoloration	E.P. Spugnini and A. Baldi are stockholders in Biopulse s.r.l.
Munkvad,[34] 1983	Common warts	RCT	68 (108)	Intralesional bleomycin injection administered with a jet injector	Not reported	1-4×, interval of 2 weeks	1 U/mL, ≤0.9 U in total	Group II: Intralesional saline. Group III: intralesional bleomycin in oil. Group IV: intralesional sesame oil alone	Not reported	CR 18%, 42%, 23% and 46% resp. bleomycin in saline, saline alone, bleomycin in oil or sesame-oil alone. Placebo treatments have significant better response rates than active treatments with bleomycin (P = .018)	3 months	No systemic adverse events. Local: dullness, pain, swelling or bleeding	Not reported
Hayes,[35] 1986	Resistant warts	RCT	26 (79)	Intralesional bleomycin injection	Not reported	1-3×, interval of 3 weeks	0.25 or 0.5 U/mL, ≤3 mL per treatment	Bleomycin injection of 1 U/mL	Not reported	CR 73.5%, 86.7%, 73.3% resp. 1, 0.5, and 0.25 U/mL No statistical difference. Plantar warts remained the refractory. Owing to small number in 0.25 U/mL group, no assumptions can be made about the effectivity. Recurrence rate 0%	3 months	No systemic adverse events. Local: pain, tenderness, swelling, erythema, blackening, eschar formation, and horizontal ridging of nail plate after periungual warts injection	Not reported

CCT, Clinical controlled trial; *CR*, complete response rate; *No.*, number; *OR*, overall response rate (CR + PR); *PR*, partial response rate; *RCT*, randomized controlled trial; *resp.*, respectively; *RR*, relative risk; *U*, United States Pharmacopeia unit; *VAS*, visual analog scale.
*Fresenius Kabi USA, Lake Zurich, Illinois.

Table II. Characteristics and summary of results of included studies on intralesional bleomycin in nonmelanoma skin cancer, cutaneous metastases, keloids and hypertrophic scars, hemangioma, and other indications

First author, year	Type of lesion	Study design	No. of patients (lesions)	Intervention	Anesthetics	Frequency	Concentration & dosage	Comparative intervention	Result per patient	Result per lesion	Follow-up time	Adverse events	Conflicts of interest/ funding
Nonmelanoma skin cancer													
Peycheva,[36] 2004	BCC and SCC	CCT	113 (113)	Intralesional bleomycin injection followed by electroporation sequence with short pulses*	Local anesthetic injection (lidocaine 1%)	1 treatment	Concentration not reported, 0.5-0.8 U depending on tumor size	Intralesional bleomycin injections, followed by electroporation sequence with long pulses†	Initial CR of 100% for both groups. Sustained CR for BCC 80% vs 100%, and SCC 71.4% vs 78.6% resp. electroporation with short pulses or long pulses (no statistical tests)	Not reported	12 months	No systemic of serious adverse events. Local: reduced pain described in electroporation group with short pulses.	Not reported
Cutaneous metastases													
Gaudy,[37] 2006	Metastases of melanoma	RCT	12 (54)	Intralesional bleomycin injection, followed by electroporation	Local anesthetic injection (lidocaine 1% + epinephrine)	1 treatment	4 U/mL, ≤40 U of bleomycin in total.	Intralesional bleomycin alone	Intention-to-treat population (n = 12): OR 46% vs 25% resp. ECT or bleomycin alone (P = .10). CR per patient 36% vs 8% resp. bleomycin + electroporation or bleomycin alone (P = .016)	CR per lesion 64% vs 18% and OR 82% vs 54% resp. bleomycin + electroporation or bleomycin alone (P = .017) (P = .12)	24 weeks	No systemic adverse event. Local: pain, muscle spasm with myoclonia, erythema, edema and necrosis	Not reported
Byrne,[38] 2005	Metastases of melanoma	CCT	19 (46)	Intralesional bleomycin injection, followed by electroporation	Local anesthetic injection (1% lignocaine + 1:100,000 adrenaline), mild oral sedative or oral analgesic	1-3×, interval not reported	1 U/mL, dosage not reported	Intralesional bleomycin injection alone	Not reported	CR per lesion 72% vs 26%, PR 5% vs 5%, no response 18% vs 15%, and disease progression 5% vs 53% resp. bleomycin + electroporation or bleomycin alone (P = .002)	36.5 months	No systemic adverse events. Local: electric shock sensation, muscle spasm, pain, necrosis, and eschar	Funded in part by Genetronic Inc, San Diego, CA, USA

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Table II. Cont'd

First author, year	Type of lesion	Study design	No. of patients (lesions)	Intervention	Anesthetics	Frequency	Concentration & dosage	Comparative intervention	Result per patient	Result per lesion	Follow-up time	Adverse events	Conflicts of interest/ funding
Marty,[39] 2006	Cutaneous metastases of melanoma and nonmelanoma cancer	CCT	62 (290)	Intralesional bleomycin injection, followed by electroporation	Local anesthetic injection (lidocaine 2% + epinephrine) or general anesthesia (propofol + remifentanil)	1 treatment	1 U/mL, 0.25-1 U/cm^3 depending on tumor size.	Intralesional cisplatin (2 mg/mL, 0.5- 2 mg/cm^3) or intravenous bleomycin (15 U/m^2), all followed by electroporation	OR for all nodules per patient 63.4% (intralesional and intravenous bleomycin and intralesional cisplatin)	CR per nodule 88.2%, 73.1%, and 75.4% resp. bleomycin intravenous, bleomycin intralesional or cisplatin intralesional, all followed by electroporation (P = .09)	60-380 days	No systemic adverse events. Local: pain and muscle contraction	Not reported
Keloids and hypertrophic scars													
Kabel, 2016[14]	Keloids and hypertrophic scars	CCT	120 (120)	Intralesional bleomycin injection	Local anesthetic injection (mepivacaine HCl 3%)	2-6×, interval of 2 weeks	1.5 U/mL, 0.5-1 mL/cm^2, ≤4 mL per treatment	II: Intralesional 5-FU 50 mg/mL. III: intralesional 5-FU 0.9 mL of 50 mg/mL + TCA 0.1 mL of 40 mg/mL	VSS mean improvement of 73% vs 54% vs 55%, resp. bleomycin or 5-FU or 5-FU + TCA. (P < .05) No. of treatments required 2-6 vs 4-6 vs 5-6 resp. bleomycin vs 5-FU or 5-FU + TCA (P < .05). Recurrence rate 0% vs 40% vs 46.67%	Not reported	12 months	No systemic adverse events. Local: hyperpigmentation, pain, and ulceration	None declared
Payapvipapong,[20] 2015	Keloids and hypertrophic scars (Fitzpatrick skin types III to V)	RCT	26 (26)	Intralesional bleomycin injection	None	3×, interval of 4 weeks	1 U/mL, ≤6 mL per treatment	Intralesional TCA injection, 10 mg/mL	(1) POSAS improvement 38.1% vs 27.5%, and reported very good improvement 50% vs 50% resp. bleomycin or TCA. (No statistical difference.) (2) Improvement evaluated by ultrasonography 30% vs 46% resp. bleomycin or	Not reported	Not reported	No systemic adverse events. Local for bleomycin injection: Hyperpigmentation, pruritus, pain, burning sensation and vesicle-bullae formation. Local for TAC injection: pruritus, pain, and skin atrophy	None declared

									TCA. (No statistical difference.) (3) Photograph evaluation by 3 dermatologists: no difference				
Naeini,[40] 2006	Keloids and hypertrophic scars	CCT	45 (45)	Intralesional bleomycin injection administered with multipuncture technique	Local anesthetic injection (2% lidocaine)	4×, interval of 1 month	1.5 U/mL, ≤2 mL/cm^2 and ≤10 U of bleomycin per treatment session	Cryotherapy (1 freeze-thaw cycle) + intralesional TCA injections 40 mg/mL, 0.1-1 mL.	Mean resolution score 88.3% vs 67.3% resp. bleomycin or cryotherapy + TCA (P = .001). >100 mm^2 lesions had significant better therapeutic response with bleomycin (P = .03). Disappearance of pain, tenderness, or pruritus 69% vs 49% resp. bleomycin or cryotherapy + TCA. Recurrence rate 0% for both groups	Not reported	3 months	No systemic adverse events. Local reaction after bleomycin: hyperpigmentation. Local reaction after cryotherapy + TCA: hypopigmentation and telangiectasia. Treatment related pain not reported.	None declared
Hemangioma Pandey,[41] 2018	Infantile hemangioma (not responding to propranolol)	RCT	67 (67)	Intralesional bleomycin injection	Not reported	4-6×, interval of 4 weeks	Concentration not reported, 0.5 U/kg per treatment, ≤15 U per single dose	Intralesional TCA 2 mg/kg	Excellent response rate per patient 47.2% vs 25.8%, PR 44.4% vs 48.4%, no response 8.3% vs 25.8% resp. bleomycin or TCA (P = .074). Bleomycin has better response rates than TCA in nonresponders to propranolol (50% vs 7.7%, P = .037)	Not reported	7.42-9.38 months	No systemic adverse events. Local: superficial ulcer. Pain not reported	None declared

Continued

Table II. Cont'd

First author, year	Type of lesion	Study design	No. of patients (lesions)	Intervention	Anesthetics	Frequency	Concentration & dosage	Comparative intervention	Result per patient	Result per lesion	Follow-up time	Adverse events	Conflicts of interest/ funding
Thayal,[42] 2012	Infantile hemangiomas	CCT	20 (20)	Intralesional bleomycin injection	General anesthesia	1-3×, interval of 6 weeks	Concentration not reported, 0.5 U/kg body weight per treatment, ≤12 U per treatment	Propranolol (oral) 0.16-2 mg/kg body weight per day for 6 weeks	Volume reduction of 75%-90% after 5 months: 62.5% vs 60%, overall size reduction 80% vs 85% resp. bleomycin or oral propranolol	Not reported	5 months	No systemic adverse events. Local: febrile episode, superficial ulceration and raised alkaline phosphatase. Pain not reported	Not reported
Other indications													
Lee,[43] 2014	Corns	CCT	50 (64)	Intralesional bleomycin injection	Bleomycin diluted with 2% lidocaine	3-10×, interval of 3 weeks	1 U/mL, ≤2 U per treatment	Only callus paring	CR per patient 37% vs 7%, excellent/good response in pain reduction 86% vs 47% resp. bleomycin or callus paring (statistically significant)	>50% decrease in size in 80% vs 38% resp. bleomycin or callus paring. Recurrence rate per lesion 38% vs 67% resp. bleomycin or paring	3 months	No systemic adverse events. Local: blackening, eschar formation and pain	None declared
Roberts,[44] 1980	VIN	CCT	12 (12)	Intralesional bleomycin injection	None	Once weekly until pain or ulceration required treatment termination	1 U/mL, 0.3-0.5 U per treatment, ≤19.9 U total dose	Topical bleomycin 5% solution applied twice daily for max. 21 days	Remission rate 20% vs 0%, disease progression 50% vs 57% resp. bleomycin injection or topical bleomycin	Not reported	Not reported	No systemic adverse events. Local: vulvar erythema, vulvitis, pain, ulceration, dark discoloration	Not reported

5-FU, 5-fluorouracil; *BCC*, basal cell carcinoma; *CCT*, clinical controlled trial; *CR*, complete response; *ECT*, electrochemotherapy; *OR*, overall response (CR + PR); *POSAS*, Patient and Observer Scar Assessment Scale; *PR*, partial response; *RCT*, randomized controlled trial; *RR*, relative risk; *SCC*, squamous cell carcinoma; *TCA*, Triamcinolone acetonide; *U*, United States Pharmacopeia unit; *VAS*, visual analog scale; *VIN*, vulvar intraepithelial neoplasia; VSS, Vancouver Scar Scale.

*16 biphasic pulses of 25- + 25-μs duration, spaced at 0.6 cm with a duration-number product of 0.8 milliseconds and a total sequence duration of 9.6 milliseconds.

†16 biphasic pulses of 50- + 50-μs duration, spaced at 1.0 milliseconds with a duration-number product of 0.8 milliseconds and a total sequence duration of 7.1 milliseconds.

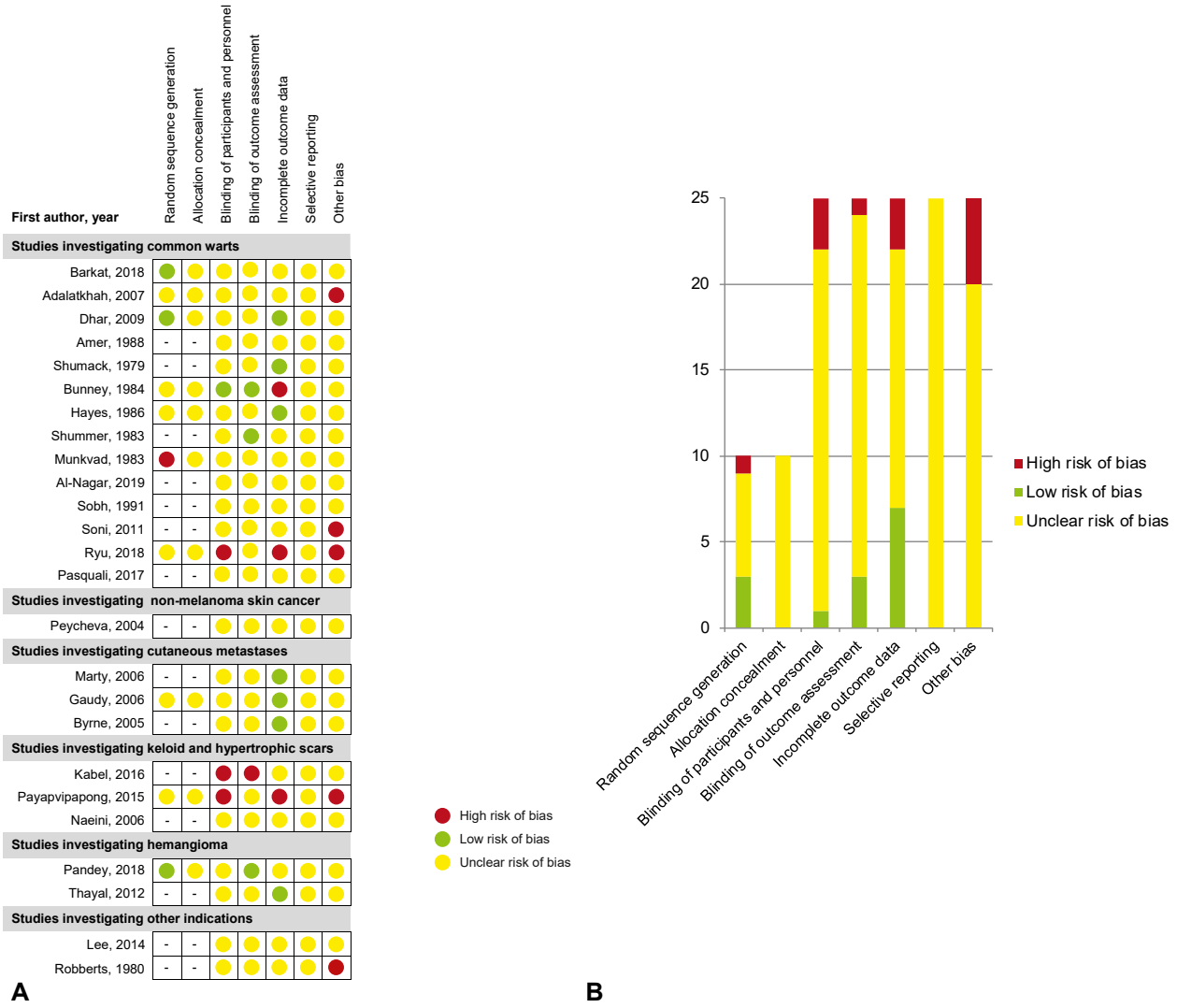

Fig 2. Methodologic quality of the included studies according to the Cochrane risk-of-bias assessment tool. (**A**) Methodologic quality of the included studies was categorized as high, low, or unclear risk of bias according to the Cochrane risk-of-bias assessment tool. Overall, methodologic quality was poor because of an unclear risk of bias for most of the assessed criteria. (**B**) Graph summarizing risk of bias of all 25 included studies.

indications. All included studies had a controlled study design, of which 10 were RCTs. Favorable efficacy outcomes were reported in 14 of 18 studies of intralesional bleomycin compared with placebo or other interventions. Methodologic quality was generally poor, with only 3 of 25 studies using appropriate randomization sequences and all studies lacking concealment of allocation. Furthermore, most studies had an unclear risk of bias for blinding and incomplete outcome data.

For all included studies, heterogeneity was found in treatment indication, use of anesthetics, treatment frequency and dosage, comparative intervention, outcome measures, and follow-up time. This heterogeneity precluded performing a meta-analysis.

Intralesional bleomycin treatment generally showed good results for common warts, keloids, hypertrophic scars, propranolol-resistant hemangioma, and corns. However, most studies focused on bleomycin treatment of common warts.

Recommendations for daily clinical practice are preferably based on adequately powered head-to-head clinical trials in which the new intervention is compared against another (gold standard) intervention. In common warts, intralesional bleomycin showed higher cure rates than cryotherapy.[29,30,32] Plantar warts were more recalcitrant, possibly because of the endophytic character of the lesions leading to suboptimal drug delivery.[19] In keloid and hypertrophic scars, intralesional

bleomycin treatment resulted in better improvements than cryotherapy, followed by intralesional TCA, intralesional 5-FU/TCA injection, or intralesional 5-FU alone.[14,40] In hemangioma, intralesional bleomycin was comparable to oral propranolol treatment but favorable to TCA injections in propranolol nonresponders.[41,42] No head-to-head clinical trials are available for nonmelanoma skin cancer, cutaneous metastases, and vulvar intraepithelial neoplasia.

Topical treatment is a key element in dermatologic practice. Topical bleomycin administration showed poor results, however, because of the limited penetration of the lipophilic stratum corneum by this hydrophilic drug.[44] Intralesional administration methods provided greater bleomycin bioavailability in the skin. Needle injections were most often used, but the microneedle patch and microneedling pen device may be the least painful techniques.[32] One study using a mechanical jet injector reported poor response rates in common warts. This could be explained by spill of bleomycin solution due to suboptimal positioning of the device leading to insufficient dermal drug delivery.[34]

Five included studies reported outcomes of intralesional bleomycin, followed by electroporation (electrochemotherapy).[33,36-39] Electroporation provides permeabilization of the lipophilic cell membrane, which enhances penetration of bleomycin into the cytosol and leads to increased cytotoxicity.[45] Electrochemotherapy was primarily investigated in uncontrolled trials focusing on cutaneous malignancies.[46] In all included studies, electrochemotherapy showed significant higher success rates than intralesional bleomycin alone for metastases of melanoma and common warts.[33,37,38]

Besides electroporation, local anesthetics have shown to change the cell permeabilization and increase cellular uptake of bleomycin *in vitro*.[47] In clinical studies, adding anesthetics to the bleomycin solution led to higher complete cure rates in common warts than with bleomycin alone.[23,28-31]

Strengths and limitations

Strengths of this systematic review include the use of a comprehensive data search, inclusion of only controlled studies with appropriate sample sizes, reporting of outcome measures as effect size and adverse events, assessment of methodologic quality, and inclusion of off-label dermatologic indications.

Limitations of this review are that one-third of the studies were published before 2000 (1979-1994) with a lack of statistical analyses, all studies had an unclear risk of bias for most of the methodologic criteria, and several studies did not report the number of patients or lesions and follow-up time.

Intralesional bleomycin treatment in clinical practice

Treatment characteristics, such as efficacy, safety, tolerability, usability, and also patient preference are important factors considered in making a treatment choice. No systemic adverse events were reported after bleomycin treatment for any of the dermatologic indications, making this a relatively well-tolerated treatment. Local pain was reported during and after the procedure but was evidently well-tolerated, and cotreatment with local anesthetics was usually sufficient. With regard to usability, bleomycin is relatively easy to administer, requires minimal resources, is inexpensive, and is widely available, making it a treatment that can be easily incorporated into daily clinical practice.

Recalcitrant common warts and keloids are daily treated in our clinic with intralesional bleomycin. A reproducible success is seen using a mixture of bleomycin (1 U/mL) with lidocaine hydrochloride (5 mg/mL) in saline (unpublished data). In most cases, a conventional 30- or 33-gauge needle injection is used, with a maximum of 2 mL per treatment. The bleomycin solution should be deposited in the mid-dermal part of keloids to prevent necrosis or ulcerations. In warts, however, bleomycin should be injected in the superficial dermis to induce necrosis. Intralesional bleomycin treatment is well tolerated, but patients experience pain for an average of 2.5 days after the injection. A mechanical jet injector (eg, DermoJet; Akra, Pau, France) is also practical but has several disadvantages such as risk of aerosol formation and drug spill. To reduce the risk of bleomycin inhalation, a pair of wet gauzes is wrapped around the tip of the device, the operator and patient wear surgical respirator (3M, St Paul, MN) and safety glasses, and a laser smoke evacuator is used to capture any aerosols.

CONCLUSIONS

This review provides a systematically conducted overview and methodologic quality assessment of the efficacy and safety of intralesional bleomycin treatment for dermatologic indications. For all reviewed indications, there was insufficient evidence to provide firm recommendations for intralesional bleomycin treatment in clinical practice. However, this review suggests that intralesional bleomycin is a successful and well-tolerated treatment option for recalcitrant warts.

Clearly, more head-to-head trials with high methodologic quality are needed to provide future evidence-based recommendations for daily clinical practice. New and less painful administration methods, such as laser-assisted drug delivery and needle-free pneumatic injection, should be investigated besides conventional injections for common warts, keloid, hypertrophic scars, and nonmelanoma skin cancer.

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