Needle-free jet injector treatment with bleomycin is efficacious in patients with severe keloids: a randomized, double-blind, placebo-controlled trial

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Needle-free jet injector treatment with bleomycin is efficacious in patients with severe keloids: a randomized, double-blind, placebo-controlled trial

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Abstract

Background Severe keloids are difficult to treat. Corticosteroid injections with needles are painful and associated with frequent recurrences. Therefore, more effective, safe and patient-friendly alternative treatments are urgently needed.

Objectives To assess the efficacy, tolerability and patient satisfaction of intralesional bleomycin treatment using a needle-free electronic pneumatic jet injector (EPI) in severe keloids.

Methods Patients with severe keloids were included in this double-blind, randomized, placebo-controlled trial with split-lesion design. Three EPI treatments with bleomycin or saline were administered every 4 weeks in the intervention and control sides. Outcome measures were change in scar volume assessed by three-dimensional imaging, Patient and Observer Scar Assessment Scale (POSAS), skin perfusion with laser speckle contrast imaging (LSCI), spilled volume, procedure-related pain, adverse events and patient satisfaction.

Results Fourteen patients (nine female, five male) were included. The estimated mean keloid volume was significantly reduced by 20% after EPI-assisted bleomycin, compared with a slight increase of 3% in the control side ($P<0.01$). The estimated mean POSAS patient and observer scores decreased by respectively 28% and 20% ($P=0.03$ and $P=0.001$). LSCI showed no significant change in perfusion. EPI treatment was preferred over previous needle injections in 85% of patients. The estimated mean spilled volume after EPI was around 50%, and numerical rating scale pain scores were moderate. Adverse events included bruising, hyperpigmentation and transient superficial necrosis.

Conclusions A course of three EPI-assisted bleomycin injections is efficacious and well tolerated in severe keloids. Moreover, EPI was preferred by most patients and may serve as a patient-friendly alternative treatment.

What is already known about this topic?

- Severe keloids can be extremely painful upon injection and can be very difficult to treat.

What does this study add?

- Needle-free jet injections with bleomycin, a chemotherapeutic agent, are efficacious and well tolerated in patients with severe keloids.

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Keloids are abnormally healing scars that are associated with a substantially reduced quality of life due to pain, itching and restriction of movement.[1,2] Keloids are most common in Fitzpatrick skin types IV–VI and are more prevalent in African and Asian populations (prevalence of 5–10%), while Fitzpatrick skin types I–III are less frequently affected (prevalence of < 0.1%).[3] Recent studies suggest that a dysregulated transforming growth factor (TGF)-β1 pathway contributes to keloid formation by inducing neovascularization and the formation of abnormal fibrosis.[4] Neoangiogenesis and increased activation and proliferation of fibroblasts lead to increased collagen deposits, which play an important role in keloid formation.[5]

Severely affected patients with keloid are defined as having a single keloid exceeding a surface area of 10 cm^2 and/or multiple keloids.[6] Various factors, including Fitzpatrick skin type, anatomical location and lesion duration, may play a role in the development of severe keloids.[7–9] Also, external factors such as low income and severe manipulation of keloids have been associated with the development of more severe keloids.[10]

The first-line treatment for keloids consists of conventional intralesional needle injections with corticosteroids.[11] Other treatment options include cryotherapy, intralesional 5-fluorouracil injections and (non)ablative laser treatments.[12,13] However, drug delivery techniques such as conventional needle injections and laser treatment can be painful. Moreover, corticosteroids and 5-fluorouracil often lead to adverse effects and treatment failure.[14] Therefore, alternative treatment options are urgently needed.

Bleomycin, an antineoplastic agent, is a second-line option for intralesional keloid treatment. Its mechanism of action comprises delaying the cell cycle in the G_2 phase, inhibition of DNA and RNA synthesis, apoptosis of fibroblasts, and suppression of collagen production.[15–17] Moreover, bleomycin induces endothelial cell damage by inhibiting cytokines, including TGF-β1, resulting in a reduction of the perfusion of keloids.[18]

Intralesional administration of bleomycin with conventional needles has several disadvantages: it is not a patient-friendly treatment in those with severe keloids because multiple painful injections are usually needed to achieve significant clinical improvement, and it cannot be used in patients with needle phobia.[19] As an alternative to needle injections, less painful intralesional delivery methods, such as needle-free electronic pneumatic-assisted injection (EPI), have been developed.[20]

A few retrospective studies have shown that intralesional EPI-assisted triamcinolone acetonide (TCA) was effective and minimally painful and resulted in high treatment satisfaction in patients with keloids and hypertrophic scars.[21,22] However, as intralesional TCA is associated with frequent recurrences, it is often less effective in severe keloids.[22] Therefore, in this double-blind, randomized, vehicle-controlled, split-lesion trial, we investigated whether intralesional bleomycin delivered with an EPI is a patient-friendly delivery method with better treatment responses than placebo in severe keloids.

Patients and methods

Study design

BLEOJET (NCT04582305) is a double-blind, randomized, placebo-controlled trial with split-lesion design to evaluate the efficacy and tolerability of bleomycin compared with placebo in keloids using an EPI. The study was conducted between March 2022 and December 2022 at the dermatology department of Erasmus University Medical Center, Rotterdam, the Netherlands.

Patients

Inclusion criteria were (i) age ≥ 18 years, (ii) at least one keloid ≥ 4 cm in length, or two separate keloids of ≥ 2 cm a minimum 1 cm apart in the same anatomical region, and (iii) willingness to fill in questionnaires and take photos using an e-diary application. A maximum of two large (≥ 4 cm) keloids were included to be treated in the trial.

Exclusion criteria were hypersensitivity to any component of the test materials, pregnancy or breastfeeding, previous bleomycin treatment of the keloid within the last 12 weeks prior to screening, nonresponse to previous bleomycin treatments of the keloid, and any medical or psychiatric condition that would preclude the participant from adhering to the protocol or completing the study per protocol.

Randomization

The participants, treating physicians and other investigators, were blinded for the allocation of treatment. One larger keloid (≥ 4 cm) that was divided into two comparable halves, or two comparable smaller keloids (< 4 cm) were included. Each lesion half was randomly assigned to three consecutive treatments with bleomycin or three consecutive placebo (physiological saline) treatments. Allocation and sequence were randomized by a validated computer system (SAS version 9.4M6; SAS Institute Inc., Cary, NC, USA) in blocks of four by a study-independent statistician. The randomization list was administrated and stored in a locked office at our hospital pharmacy. Blinding was concealed by an unblinded pharmacist who prepared identical syringes, with either bleomycin or physiological saline. Blinding was ensured until data were locked.

Intervention

For each lesion, a transparent sheet was consistently used, indicating 'lesion 1' and 'lesion 2'. To prevent a carry-over effect, an exclusion zone of 1 cm was respected between the lesions (Figure S1; see Supporting Information). A physician blinded to treatment administered three treatments, one every 28 days. Each treatment consisted of intralesional bleomycin in one lesion and physiological saline in the other lesion, using an EPI (Enerjet 2.0; Sinclair Pharma, Rehovot, Israel). This device comprises a 10-mL syringe and a 200-μm nozzle. Approximately 1 cm^2 of the included keloid lesion received one intralesional injection.

Each injection had a volume of 100 μL, delivered with a starting pressure of 3 bar (device range 50–150 μL, 2–6 bar). The pressure ranged from 3 to 5 bar depending on the scar characteristics and was increased by 10% if the clinical endpoint (papule or blanching) was not observed after injection. In each keloid lesion 1 USP mL^{-1} of bleomycin (Bleomedac; Pharmanovia Benelux, Breda, the Netherlands) was delivered, while in the control lesion NaCl 0.9% was delivered. The syringes with bleomycin could not be distinguished from the syringes with NaCl. A maximum dose of 2 USP bleomycin was administered per treatment.

Primary and secondary outcomes

The primary outcome was change in keloid volume. Secondary outcomes included change in keloid height, Patient and Observer Scar Assessment Scale (POSAS), change in perfusion, spilled volume during treatment, procedure-related pain scores, adverse events and patient satisfaction. All outcome measures were assessed at all three treatment visits and at follow-up (week 12, 4 weeks after the third treatment).

Outcome assessments

The outcome assessments used are as follows. (i) Change in volume (in mm^3) and height (in mm) of keloid tissue measured by a three-dimensional (3D) camera (LifeViz Micro; Quantificare, Sophia Antipolis, France) at baseline compared with follow-up. (ii) Change in POSAS at baseline compared with follow-up. (iii) Change in skin perfusion measured by laser speckle contrast imaging (LSCI; Perimed PeriCam LSCI; Perimed AB, Järfälla, Sweden) at baseline compared with follow-up. (iv) Average spilled volume assessed by weighing a filtration paper before and after each EPI-assisted injection. Postinjection weight was determined by weighing the filtration paper after dabbing it at the injection site. (v) Procedure-related pain score measured with an 11-point numerical rating scale (NRS pain) directly after every EPI-assisted treatment. (vi) Incidence and type of adverse events, assessed every 4 weeks by the treating physician, and by the patient, who was instructed to take photographs daily and report adverse events with an e-diary app. (vii) Treatment satisfaction measured with the five-point Likert scale, evaluated by the patient at follow-up.

Statistical analysis

The sample-size calculation was based on prior studies that investigated bleomycin treatment in keloids. We employed a two-sided paired *t*-test with $\alpha = 0.05$ to detect a significant difference of ≥35% in volume reduction between treatments. To reach a statistical power of 90% and account for a corresponding coefficient variance of the difference of 40%, a sample size of 11 patients was determined to be necessary. Anticipating a dropout rate of 25%, 14 patients were needed to demonstrate a treatment effect.

The descriptive statistics and data in the tables are presented as the least-squares mean (LSM) with a 95% confidence interval (CI). A mixed-effects model with a random-subject factor and prevalue as covariate was used to compare bleomycin and placebo treatment. Statistical analysis was performed using SAS for Windows v9.4 (SAS Institute Inc.).

Results

Demographics

Fourteen patients with at least one keloid were included (age range 18–48 years; nine female, five male; Fitzpatrick skin types I–VI) (Table 1; and Figure S2; see Supporting Information). In four patients, two smaller, separated keloid lesions were assigned to treatment with bleomycin or placebo. In the remaining 10 patients, one large (> 4 cm diameter) keloid was regarded as two smaller lesions, which were assigned to treatment with bleomycin or placebo. Anatomical locations included the abdomen ($n = 1$), neck ($n = 1$), upper extremity ($n = 2$), chest ($n = 4$) and shoulder ($n = 6$). All patients completed the three consecutive treatments. However, one patient was lost to follow-up and missed the follow-up visit.

Scar volume by three-dimensional imaging

Three-dimensional imaging showed a statistically significant reduction in volume ($P < 0.01$) in bleomycin-treated

Table 1 Baseline characteristics of the 14 patients

Characteristic	*N* = 14
Sex, female	5 (36)
Age (years), median (IQR)	27.5 (23.5–35.3)
Fitzpatrick skin types	
I–II	2 (14)
III–IV	10 (71)
V–VI	2 (14)
Anatomical location	
Chest	4 (29)
Shoulder(s) or back	6 (43)
Abdomen	1 (7)
Neck	1 (7)
Upper extremities	2 (14)
Aetiology	
Acne	5 (36)
Spontaneous or unknown	5 (36)
Trauma or surgery	2 (14)
Chickenpox	1 (7)
Folliculitis	1 (7)
Previous treatments	
Intralesional TCA	11 (79)
Intralesional bleomycin/Kenacort	4 (29)
Cryotherapy	4 (29)
(Shave) excision	4 (29)
Clobetasol cream	3 (21)
Vascular or ablative laser	2 (14)
Excision + brachytherapy	2 (14)
Ciclosporin tablets	1 (7)
Surface area of included keloid lesions, cm^2	
0–10	8 (57)
10–30	3 (21)
> 30	3 (21)
Total number of previous treatments, mean (SD)	9.8 (7.7)
Total POSAS observer score at baseline, mean (SD)	41.1 (8.1)
Total POSAS patient score at baseline, mean (SD)	47.4 (5.9)
Total number of keloids	
1	1 (7)
2–10	7 (50)
10–20	3 (21)
20–30	2 (14)
> 30	1 (7)

The data are presented as *n* (%) unless stated otherwise. IQR, interquartile range; POSAS, Patient and Observer Scar Assessment Scale; TCA, triamcinolone acetonide.

lesions compared with placebo-treated lesions (Figures 1 and 2a, Table 2). The baseline volume of the included lesions was 465 mm^3, which was reduced by 20% in the bleomycin-treated lesions at follow-up (LSM −91.9 mm^3, 95% CI −122 to −61.5 mm^3). In contrast, a slight increase in volume of +3% was observed in the placebo-treated lesions at follow-up (LSM +13.4 mm^3, 95% CI −17.0 to 43.9). Consistently with the volume results, statistically significant changes were observed in lesion height (Table 2).

Patient and Observer Scar Assessment Scale

POSAS scores were filled in by the patients and physicians during all visits from baseline up to follow-up. Data on the changes over time are displayed for bleomycin vs. placebo treatment in Table 2, Figure 2(c, d) and Table S1 (see Supporting Information). The total POSAS patient score was 47.3 at baseline. At follow-up this was reduced by 28% (LSM −13.3, 95% CI −17.3 to −9.4) for the bleomycin-treated lesions vs. a reduction of 16% (LSM −7.8,

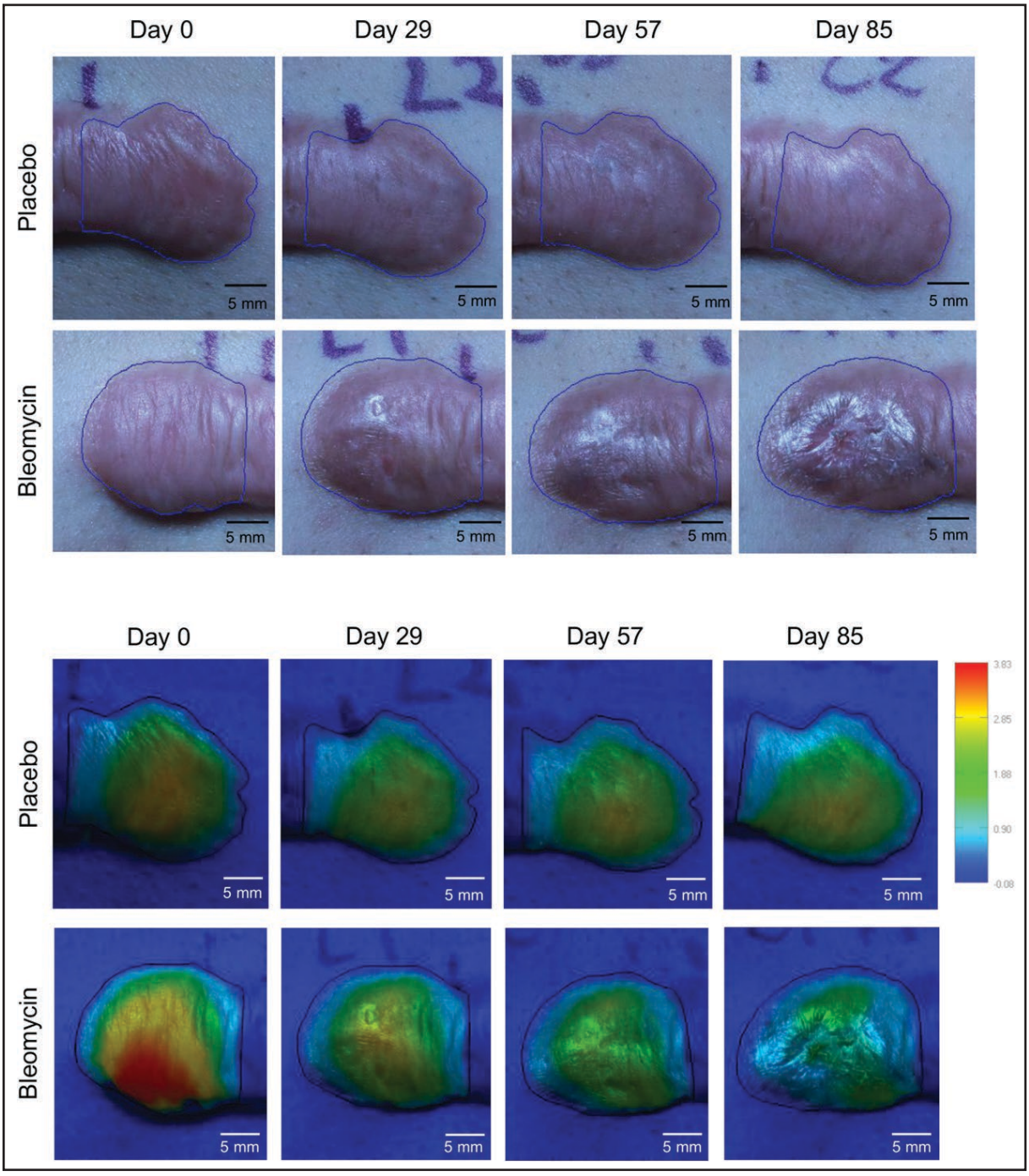

Figure 1 Clinical pictures (top) and three-dimensional images (bottom) of two keloid lesions that were treated with respectively placebo and bleomycin. A reduction of 46% in volume was detected in the intervention site at follow-up compared with baseline, while the lesion that received placebo did not change.

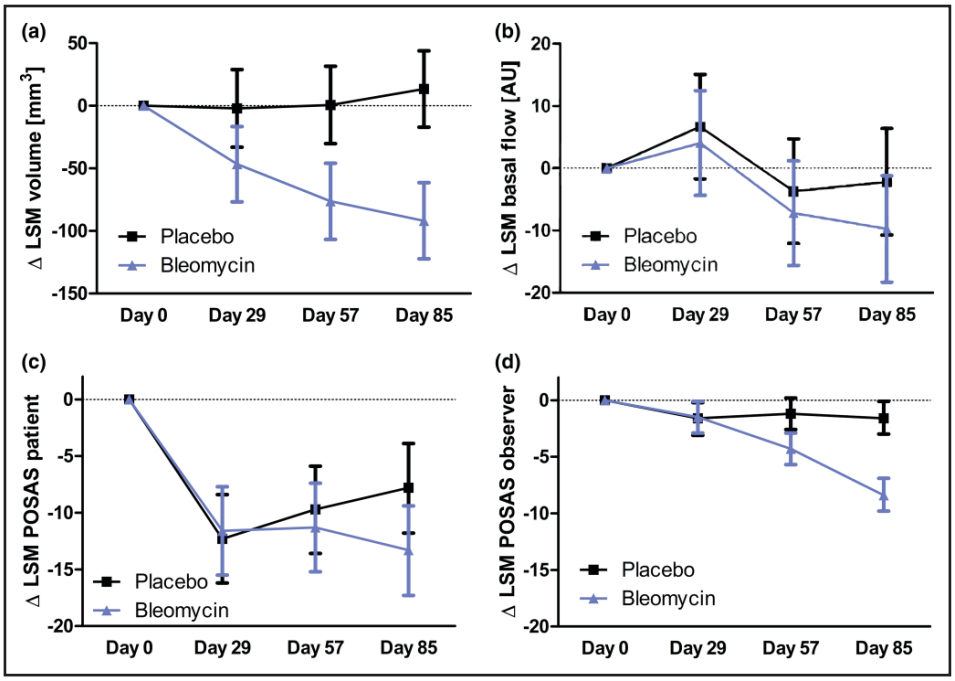

Figure 2 Results of three-dimensional (3D) imaging, perfusion and Patient and Observer Scar Assessment Scale (POSAS) measurements. Errors bars show the least-squares mean (LSM) with upper and lower limits. (a) LSM change from baseline in volume (mm^3) by 3D imaging. (b) LSM change from baseline in basal flow (AU) by laser speckle contract imaging. (c) LSM change from baseline in total POSAS patient score. (d) LSM change from baseline in total POSAS observer score.

95% CI −11.8 to −3.9) for the lesions treated with placebo ($P=0.03$).

For the patient POSAS, the parameters itch (−62.2%; LSM −2.8, 95% CI −3.9 to −1.7; $P=0.04$), thickness (−39.7%; LSM −2.7, 95% CI −3.8 to −1.7; $P=0.02$) and overall opinion (−28%; LSM −2.3, 95% CI −3.2 to −1.4; $P=0.002$) showed statistically significant improvements in the bleomycin-treated lesions.

Similarly, the total POSAS observer score was 41.0 points at baseline, which was reduced by 20% (LSM −8.4, 95% CI −9.8 to −6.9) at follow-up, vs. a reduction of 4% (LSM −1.6, 95% CI −3.0 to −0.1) for those lesions treated with placebo ($P=0.001$).

For the observer POSAS, the parameters thickness (−32%; LSM −2.3, 95% CI −2.8 to −1.7; $P=0.01$), relief (−23%; LSM −1.7, 95% CI −2.2 to −1.2; $P=0.01$), surface (−42%; LSM −3.2, 95% CI −3.7 to −2.7; $P<0.01$) and overall opinion (−21%; LSM −1.5, 95% CI −1.8 to −1.2; $P<0.01$) were significantly improved at follow-up in the bleomycin-treated lesions. The POSAS observer score for pigmentation was 7.7 points at baseline, which was significantly worsened by 7% at follow-up (LSM 0.6, 95% CI 0.2–1.0; $P<0.01$).

Patient-reported pain and treatment satisfaction

The patient-reported NRS pain score during EPI treatment was similar for both treatments (bleomycin: LSM 5.4, 95% CI 4.5–6.3; placebo: LSM 5.6, 95% CI 4.5–6.3; $P=0.54$). The overall satisfaction of the treatment was most

Table 2 Results of three-dimensional imaging, perfusion and Patient and Observer Scar Assessment Scale (POSAS) measurements

	Volume (mm^3)	Height (mm)	Basal flow (AU)	Total POSAS observer	Total POSAS patient
Bleomycin					
Day 0	465	1.26	120	41.0	47.3
Δ Day 29	−46.6 (−76.8, −16.5)	−0.14 (−0.24, −0.04)	4.05 (−4.34, 12.4)	−1.5 (−2.9, −0.1)	−11.6 (−15.5, −7.7)
Δ Day 57	−76.3 (−107, −45.8)	−0.25 (−0.35, −0.15)	−7.19 (−15.6, 1.19)	−4.3 (−5.7, −2.9)	−11.3 (−15.2, −7.4)
Δ Day 85	−91.9 (−122, −61.5)	−0.30 (−0.40, −0.20)	−9.73 (−18.3, −1.18)	−8.4 (−9.8, −6.9)	−13.3 (−17.3, −9.4)
Placebo					
Day 0	465	1.26	120	41.0	47.3
Δ Day 29	−2.11 (−33.1, 28.9)	0.00 (−0.10, 0.10)	6.70 (−1.70, 15.1)	−1.6 (−3.1, −0.2)	−12.3 (−16.2, −8.4)
Δ Day 57	0.66 (−30.3, 31.6)	0.02 (−0.08, 0.13)	−3.69 (−12.1, 4.70)	−1.6 (−3.1, −0.2)	−9.7 (−13.6, −5.9)
Δ Day 85	13.4 (−17.0, 43.9)	0.05 (−0.05, 0.15)	−2.18 (−10.7, 6.37)	−1.6 (−3.0, −0.1)	−7.8 (−11.8, −3.9)
P-value[a]	< 0.01	0.002	0.16	0.001	0.03

Data are presented as the least-squares mean with 95% confidence interval. Δ represents the change from baseline. [a]*P*-value comparing the Δ-values at the day 85 follow-up in the control vs. intervention.

frequently reported as 'satisfied' (69%, 9 of 13; Table S2; see Supporting Information). Moreover, the majority of patients (85%, 11 of 13) preferred EPI over conventional needle injections. All patients (100%, $n=13$) would recommend EPI treatment with intralesional bleomycin to others.

Microcirculation

Cutaneous microcirculation of the lesions was quantified using LSCI. No statistically significant differences in cutaneous microcirculation were observed with bleomycin vs. placebo at follow-up (Figure 2b and Table 2).

Residue formation

The extent of drug spillage was evaluated by collecting the residual fluid on the skin surface. In total, the mean residual fluid observed was 50.0% (SD 11.8%) of the injected volume with bleomycin and 43.6% (SD 8.6%) with physiological saline.

Safety and tolerability

Overall, intralesional bleomycin treatment with the EPI was well tolerated (Table S3; see Supporting Information). No severe adverse events or treatment discontinuations occurred during the study. However, 2 out of 14 patients (14%) developed transient superficial necrosis at the injection site, which recovered in approximately 4 weeks. Furthermore, in the bleomycin-treated lesions, temporary bruising occurred in two patients (14%), and mild hyperpigmentation was observed in most patients (71%, 10 of 14) at the 4-week follow-up. No infection or ulceration was observed. All adverse events were mild and transient.

Discussion

This randomized controlled trial evaluated the efficacy and tolerability of EPI-assisted intralesional bleomycin treatment in patients with severe keloids. We found a significant decrease of 20% in keloid volume after three consecutive bleomycin EPI treatments, whereas placebo-treated lesions remained unchanged. Importantly, this decrease was paralleled by a substantial improvement of POSAS scores after bleomycin treatment, with patient and observer scales improved by 28% and 20%, respectively. Contrary to our hypothesis, the effect of bleomycin does not occur through permanent changes in microcirculation.

Importantly, no severe adverse events occurred. Notably, in the majority of patients, mild hyperpigmentation was observed in the bleomycin-treated keloids. This phenomenon was previously observed in other intralesional bleomycin studies, but was not regarded as bothersome by most patients.[23] In line with our previous findings, 85% of the patients preferred treatment with the jet injector over conventional needle injections, which supports the use of needle-free injector devices as patient-friendly alternative delivery methods in this patient group.[21,22,24]

A previous study by Rijsbergen *et al.* showed that the 3D imaging technique that was used in our study is an accurate and reliable method for the clinical visualization of human papillomavirus-induced skin lesions.[25] No previous trials have been published that used highly sensitive objective 3D measurements in conjunction with patient-reported outcomes to assess the clinical effects of intralesional bleomycin treatment in patients with keloids. Khan *et al.* compared six treatments of intralesional bleomycin vs. TCA using conventional needle injections, and found significant improvements in mean combined POSAS scores (sum of patient and observer scores) of 72% vs. 67%, respectively.[26] When intralesional bleomycin was compared with intralesional 5-fluorouracil with or without TCA, mean improvements of 73%, 54% and 55% on the Vancouver Scar Scale were observed after two to six treatments.[27]

It is worth mentioning that, in the majority of keloid studies, a dosage of 0.375 U intralesional bleomycin was injected per cm^2 using conventional needle injectors or spring-loaded jet injectors.[15,26–28] Despite the good efficacy achieved in these studies, bleomycin treatment led to a high rate of treatment discontinuations and mild-to-moderate adverse events, including ulceration, necrosis, infection, pain and hyperpigmentation. Another randomized controlled trial in keloids also found good efficacy without adverse events with a lower dosage of bleomycin of 0.1 U cm^{-2}.[23] That study also showed that with this dosage, no systemic uptake of bleomycin takes place. Therefore, in our study we chose to use the lower bleomycin dose of 0.1 U cm^{-1}, which we considered to be safer for repeated administrations.

As a result, bleomycin treatment was generally well tolerated, with only two patients developing transient superficial necrosis of the treated keloid, which did not lead to treatment discontinuation. However, we recommend using a concentration of 0.2 U cm^{-2} when administering bleomycin via EPI for the treatment of severe keloids due to the spilled volume of 50%.

In the study by Erlendsson *et al.*, a single treatment with 5-fluorouracil and TCA was administered using an EPI in patients with hypertrophic scars.[29] Remarkably, in their study, a lower median procedure-related NRS pain score of 2.0 was observed, compared with 5.6 in our trial. However, in general, hypertrophic scars are less painful than severe keloids. In a previous study by our group with intralesional EPI-assisted TCA treatment in keloids, we found a lower mean NRS pain score of 3.8.[22] The higher pain scores in the present study could be related to the burning pain sensation that bleomycin can cause.[30] However, EPI-assisted injections with placebo also resulted in a higher NRS pain score of 5.4. Therefore, the higher injection-related pain scores in our current study are more likely related to our specific patient population who had extremely severe keloids, some of which were already very painful upon palpation.

One of the strengths of this study is the design of the trial. In addition, we incorporated both objective outcomes such as volume reduction measured with a 3D camera using a standard operating procedure[25] and subjective outcomes such as POSAS, NRS pain and patient satisfaction. Moreover, to minimize recall bias of adverse events, patients were instructed to take pictures of the treated area and report potential adverse events via an e-diary mobile application on a daily basis.

A theoretical limitation of this study includes a crossover effect of bleomycin treatment from one side of the lesion to the other side of the split lesion in larger keloids (≥ 4 cm).

Therefore, in all divided keloids, an exclusion zone of 1 cm was respected to minimize the potential crossover effect. Additionally, our study is constrained by a relatively short follow-up time, which limits the evaluation of recurrences. However, a previous meta-analysis has already shown that recurrence rates with bleomycin are low, and therefore we did not prioritize a longer follow-up time.[31] Another limitation is the substantial residual fluid (around 50% of the injected volume) observed on the skin after EPI treatments, which was higher than previously reported in other studies (around 10–20% of the injected volume).[29,32] This might be related to the rigid nature of the severe keloids that were included in this study, which are more difficult to penetrate with EPI.

Our results indicate that intralesional EPI-assisted bleomycin administration is a promising treatment modality for patients with severe keloids. However, as there is a small risk for local adverse events such as transient necrosis, we believe it should primarily be considered if standard of care (intralesional TCA) fails or leads to quick recurrence. Furthermore, intralesional bleomycin cannot be used in pregnant or lactating patients, and therefore extra caution is needed when selecting patients for this treatment. Finally, when performing EPI-assisted intralesional bleomycin treatment, it is important to use protective safety measures such as smoke evacuators and face masks to prevent the inhalation of potentially harmful bleomycin aerosols by patients and practitioners.[33]

Future technical innovation of EPI devices may lead to more efficient, more precise and less painful drug delivery with minimal residue formation. However, until this next generation of devices arrives, the addition of local anaesthetics such as lidocaine may be considered to decrease procedure-related pain.

To conclude, in this study we demonstrated that three 1-monthly EPI treatments with bleomycin significantly decreased keloid volume and keloid-related symptoms, and EPI was preferred over needle injection by patients with severe keloids. A well-powered randomized controlled trial with parallel design, extended treatments and longer follow-up time is warranted to confirm our findings.

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Conflicts of interest

V.Z.B., K.M.Z., L.B., W.T.V., P.A., F.O., R.B., E.P.P., R.R. and M.B.A.vD. declare no conflicts of interest. M.H. declares no conflicts of interests related to this work and declares the following conflicts of interest outside of this work: Cherry Imaging (Equipment), Cynosure (Equipment), Galderma (lectures, teaching, research), GME Medical (equipment), LEO Pharma (research grant), L'Oréal/La Roche Posay (research grant, consulting), Lutronic (equipment), MiraDry (equipment), Procter & Gamble (consulting) and Venus Concept (research grant, equipment).

Data availability

Additional data that support the findings of this study are available in the Supporting Information.

Ethics statement

This study was reviewed and approved by the ethics committee of Erasmus MC, approval #MEC-2021-0661. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This trial was registered with ClinicalTrials.gov, listing NCT04582305, registered on 5 October 2020.

Patient consent

All participants provided oral and written informed consent prior to their inclusion in the study. The authors affirm that the participants provided informed consent for publication of the images in the figures.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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