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Clinical Research Paper

# Bleomycin electrosclerotherapy (BEST) of slow-flow vascular malformations (SFVMs) in children

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ABSTRACT

*Rationale and objectives:* Bleomycin electrosclerotherapy (BEST) is a promising treatment for slow-flow vascular malformations (SFVMs). Due to limited paediatric data, this study aimed to assess the safety, effectiveness, and patient-reported outcomes of BEST in children with SFVMs.
*Material and methods:* This monocenter cohort study included patients <18 years with symptomatic SFVMs treated by BEST. Patient records were analysed for procedural details and complications. Symptom severity was objectively classified before and after BEST. A treatment-specific, patient-reported questionnaire assessed mobility, aesthetic concerns, swelling, social participation, pain using a visual analogue scale (VAS), and post-procedural skin discoloration. Outcomes were compared between simple and infiltrative lesions.
*Results:* Overall, 68 BEST sessions were performed in 45 children. Total complication rate was 10/68 (14.7 %), most commonly pes equinus deformities (5/68, 7.4 %) after treating SFVMs in calf muscles. Physician-rated overall symptom severity improved significantly ($p < 0.001$). Treatment-specific, patient-reported questionnaire revealed improved mobility in 14/41 (34.1 %) and symptom-free patients in 10/41 (24.4 %). Outcome in both aesthetic measure and social participation was mostly rated as improved or perfect (33/41, 80.5 %; 35/41, 85.4 %). Median VAS pain scale improved significantly (2.0 vs. 0.0, $p < 0.001$). Postprocedural swelling occurred in all children, in 26/41 cases (64.4 %) persisting for 2–4 weeks. Postprocedural skin discoloration (41/41, 100 %) was mostly (25/41, 61.0 %) reported to fade over time. No differences between simple and infiltrative lesions were revealed in all outcome parameters.
*Conclusion:* BEST is effective for paediatric SFVMs by objective and subjective measures while maintaining low complication rates. Notably, BEST achieves therapeutic success even in infiltrative SFVMs expanding the range of available treatment options.


*Abbreviations:* BEST, Bleomycin electrosclerotherapy; COP, Current operating procedure; ISSVA, International Society for the Study of Vascular Anomalies; LIC, Localized intravascular coagulopathy; LM, Lymphatic malformation; MRI, Magnetic resonance imaging; SFVM, Slow-flow vascular malformation; VAS, Visual analogue scale; VM, Venous malformation.

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## 1. Introduction

Vascular malformations are classified according to the International Society for the Study of Vascular Anomalies (ISSVA) into simple (venous, capillary, lymphatic, arteriovenous) and combined, as well as into malformations associated with other anomalies (e.g. overgrowth of the affected limb). This system was last updated in 2025 and now includes more detailed data on the genetic causes of these diseases [1–5].

Slow-flow vascular malformations (SFVMs) represent the most common subgroup, mainly characterized by malformed venous (VMs) and/or lymphatic (LMs) vessels [1,6,7]. SFVMs are congenital and usually present at birth, though, mostly becoming clinically symptomatic during childhood, adolescence, or less often during adulthood. Consequently, diagnosis and treatment initiation are frequently carried out in the context of paediatric care [8–12]. The prognosis of the affected children depends not only on the localization and extent of the LFVM, but is also influenced by the treatment modalities, which are still limited for many infiltrative SFVMs [8,13,14]. Sclerotherapy, surgical resection or a combination of both is the gold standard procedure for most SFVMs, if conservative management fails [8,11,15]. However, surgery is typically restricted to lesions located within a compartment or tissue layer, particularly the subcutaneous tissue [8,16]. Sclerotherapy, however, may also have only limited effect, as some lesions show no or little clinical response even after repeated treatment [8,17–19]. Therefore, there is a great unmet therapeutic need especially in those children with large and infiltrative SFVMs [19,20].

Bleomycin electrosclerotherapy (BEST) has been described as a novel, highly effective treatment method [19,21,22]. Multiple, short electric pulses are delivered to the target tissue via thin needles, which renders cell membranes permeable for bleomycin, a large and hydrophilic molecule [23]. Hereby, the intracellular concentration and thus the effect of the bleomycin greatly increases [21,22,24–26].

Initial cohort data indicate that children tend to report better outcomes than adults [19]. Despite this promising results, there are hardly any studies to date that evaluate BEST as a treatment in a dedicated paediatric cohort [19,27]. The aim of this study, therefore, was to analyse the safety, efficacy, and patient-reported outcome of a paediatric cohort with SFVMs treated by BEST at a large academic paediatric medical center.

## 2. Methods

### 2.1. Study design

All paediatric patients (age <18 years at first intervention) presenting with symptomatic SFVMs (according to the ISSVA classification) at a tertiary care vascular anomalies center, treated with BEST between January 2022 and 2024 were included.

The retrospective, monocenter study was conducted in adherence to the 1964 Helsinki Declaration and its subsequent amendments and received approval from the local ethics committee (Protocol No. 24–1056, 07/01/2025). Data were collected using electronic patient records and the picture archiving and communication system. Diagnosis, based on patient history, ultrasound and magnetic resonance imaging (MRI), and clinical examination, including indications for electrosclerotherapy, was made through an interdisciplinary consensus at our Vascular Anomalies Center. Decisions for BEST treatment were made following discussions in a multiprofessional vascular anomaly board, which included at least an interventional radiologist and a paediatric surgeon specialized in the management of vascular anomalies. Additional specialties, such as paediatric orthopaedics, paediatric thrombosis and haemostasis, maxillofacial surgery, head and neck surgery, and plastic surgery were included in the discussion when necessary.

Indications for BEST treatment included pain, swelling, bleeding, recurrent infections, repetitive thrombosis, aesthetic disfigurement, functional impairment, and localized intravascular coagulopathy (LIC). Pre-procedural laboratory screening for LIC (fibrinogen, D-dimer, platelets) was routinely performed in children with extensive or infiltrative SFVM. Given the heterogeneity of the disease and the variable ages of the patients, screening for LIC was not based on a specific lesion size but was determined through a multifactorial, interdisciplinary decision involving the pediatric hemostaseology team.

Selection criteria for BEST instead of conventional sclerotherapy were untreated lesions not considered suitable for conventional sclerotherapy (e.g. microcystic LMs) as well as therapy-refractory or recurrent SFVMs defined as lesions that persisted or worsened clinically and/or radiologically despite prior invasive treatment. BEST was not used in patients with known intolerance to bleomycin, previous bleomycin-related toxicity, a cumulative bleomycin dose of 100 mg or more, chronic pulmonary dysfunction, history of epilepsy/seizures as well as prior chest irradiation, or if the parents of the children did not consent to the intervention [28]. *Bleomycin electrosclerotherapy* The procedure was performed under general an aesthesia. Lesion were punctured using guidance. For complex lesions or in cases where venous drainage was unclear, a direct percutaneous injection of contrast agent into the malformation under fluoroscopic guidance was carried out. Following the intravenous or intralesional bleomycin injection, electrodes were positioned, and reversible electroporation pulses were applied. The type of electrode used (hexagonal, finger, or freely positionable needle electrodes) was chosen based on the lesion's size, location, and tissue composition. Needles were inserted within the borders of the malformations, with distances ranging from 0.5 to 3 cm. When technically feasible, the target volume was totally covered using repeated punctures while avoiding both gaps or overlaps. For large, deeply located lesions, various needle electrodes were employed to allow flexible positioning in multiple geometries. The maximum administered bleomycin dose (both intralesional and intravenous) was 0.2 mg per kg body weight per treatment session, with a cumulative dose of less than 1 mg/kg body weight, following the current operating procedure (COP) of BEST in SLVMs [29]. The electroporation was performed using the Cliniporator™ VITAE system (IGEA S.p.A., Carpi, Italy), which delivers multiple independently controlled, isolated outputs, each capable of reaching up to 3000 V (maximum current: 50 A). This resulted in electrical pulses with a duration of 100 μs between each pair of electrodes. Electroporation was carried out immediately after intralesional bleomycin injection or 8 min after the initiation of intravenous bleomycin administration. No anticoagulation is routinely administered during BEST or in the post-procedural phase. *Follow-up* Patients underwent a standardized follow-up schedule including the first follow-up at 3 months after each BEST treatment. The follow-up consisted primarily of a clinical examination and a medical history, as well as ultrasound. Due to the need for anaesthesia for MRI in children <6 years, MRI was not used as standard examination during follow-up. Only in certain scenarios, such as inadequate response to therapy, extensive/deep lesions difficult to visualize by ultrasound, or postprocedural complications, additional MRI examination was performed. In case of insufficiently resolving symptoms after treatment, and if residual perfused lesions persisted allowing further BEST, additional BEST treatments were scheduled. *Procedure-related complications* Peri- and post-interventional complications were classified according to the Clavien-Dindo classification [30]. Skin discoloration following BEST as well

as significant post-interventional swelling after treatment of microcystic LMs are well known frequent side effects [19,27,29]. Patients and their parents were consented in detail about these manifestations prior to treatment while they were not classified as complications. Special attention was given to the documentation of further skin alterations (e.g., necrosis, blisters) and peripheral nerve damage (e.g., paresis, sensory and motor disturbances), as well as orthopaedic issues, wound complications, and bleeding. *Effectiveness and outcome assessments* The overall severity of the symptoms associated with the lesion was classified by the treating physician using a 3-stage Likert scale (mild, moderate, severe) before and after BEST according to following pre-defined clinical anchors. 'Mild' = mild, occasional symptoms without functional loss or complications (bleeding/infection); 'moderate' = recurrent symptoms with partial functional impairment and/or sporadic complications; 'severe' = persistent severe symptoms with marked functional impairment, frequent complications, or rapid progression. For the subjective evaluation of effectiveness and outcome after BEST, a treatment-specific patient-reported questionnaire (see Supplementary Appendix 1) was utilized, which was completed 3–6 months after treatment. The dedicated questions queried include the outcome related to mobility, aesthetic concerns, swelling, social participation, pain before and after BEST, as well as the assessment of post-procedural skin discoloration. Patient-reported mobility outcomes were categorized as follows: worsened compared to baseline, stable, improved, and symptom-free. Aesthetic outcomes were classified into four groups: impaired compared to baseline, stable, improved, and perfect. Duration of procedure-related swelling was graded according to its persistence into <2, 2–4, 4–8, and 8–12 weeks post BEST. Social participation of children was rated by parents as impaired compared to baseline, stable, improved, and perfect. Pain levels were assessed using a 10-point visual analogue scale (VAS). Postprocedural skin discoloration was recorded dichotomously (yes/no). The further course of occurred skin changes was classified by the patient as unchanged, reduced, or fully resolved. *Statistical analysis* To analyse the distribution of patients within the various categories descriptive statistics were applied. Data are presented as mean (± standard deviation) or median (range, minimum–maximum). Two subgroups of the cohort with SLVMs were defined using preprocedural ultrasound and/or magnetic resonance imaging (MRI): lesions were termed "simple" if the SFVM was confined to a single tissue layer, while the term "infiltrative" was used if multiple tissue layers or compartments were involved. Subgroup analyses between simple and infiltrative lesions were performed using Pearson's chi-square test for categorical data (objective overall severity of symptoms before and after BEST, subjective outcome in mobility and aesthetic concerns, postprocedural swelling, social participation) while continuous data was tested with Mann–Whitney U test (pain VAS score pre- and postprocedural). Regarding the total cohort, the Wilcoxon test was used to compare the physician-rated overall severity of the symptoms before and after BEST. P-values <0.05 were considered statistically significant. Statistical analysis was performed with SPSS (version 26.0, IBM Corp., USA).

## 3. Results

### 3.1. Patients characteristics

A total of 45 consecutive children, 23 males and 22 females, with symptomatic, extracranial SFVMs underwent a total of 68 BEST treatments. The median age was 6.5 years (range, 0–17 years) at time of first treatment. A total of 44/68 (65.7 %) patients received one procedure, 16/68 (23.5 %) two procedures, and 8/68 (11.8 %) three or more procedures. In general, 29/45 (64.4 %) patients presented with VMs (Fig. 1), 8/45 (17.8 %) children with LMs

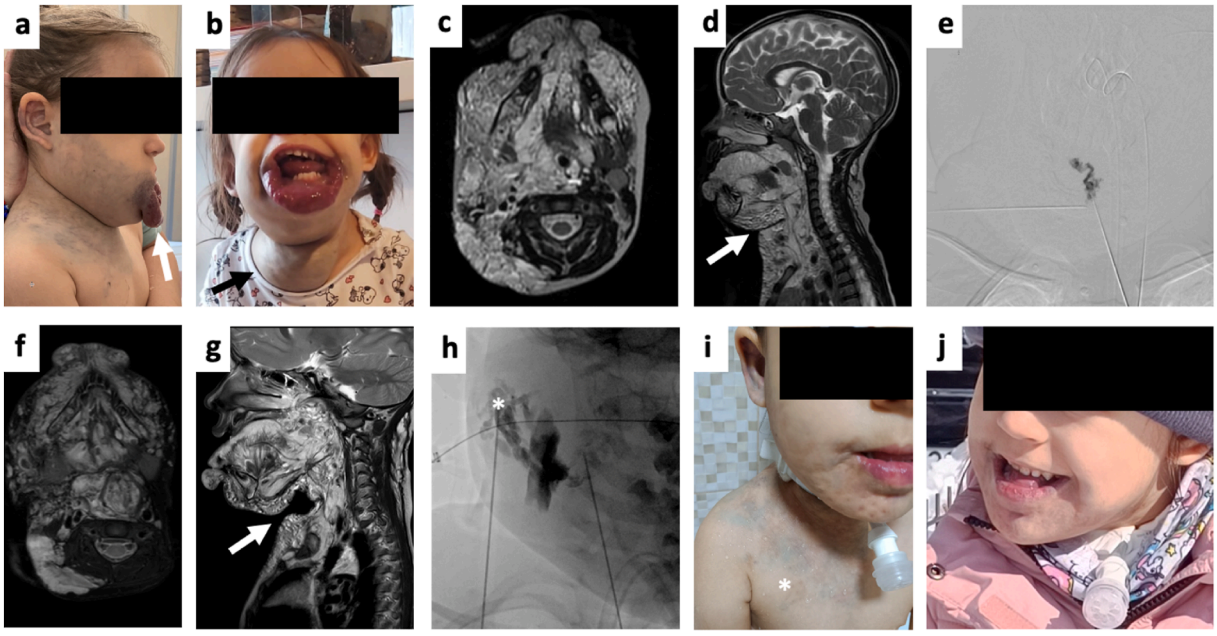


**Fig. 1.** Three-old year female patient with extensive, infiltrative venous malformation (VM) of the head and neck area treated with three bleomycin electrosclerotherapies (BESTs). a, b, Clinical photographs before BEST treatment, note the involvement and consecutive deformity of the lips (white arrow) as well as the relevant swelling of the neck (black arrow). c, d, T2-weighted, axial and sagittal magnetic resonance images prior to treatment shows the infiltrative character of the lesion involving multiple tissue layers; note the lack of submandibular space due to the extensive VM (arrow, d). e, Periprocedural digital subtraction image during first BEST session. f, g, T2-weighted, axial and sagittal magnetic resonance images after first BEST session revealing significant lesion regredience, note the postprocedural gained submandibular space (arrow). h, Periprocedural digital subtraction image during third BEST session, note the puncture of the right cheek and filling of vascular structures after contrast administration (asterisk). i, j, Clinical photographs after three BEST sessions; before third session preventively tracheostomy was performed to cope with postprocedural swelling after treating laryngeal structures. Note the clinical success particularly the relevant decreased swelling of neck and lips. Slight postprocedural skin discoloration is noted (asterisk).

(Fig. 2) as well as in 8/45 (17.8 %) with combined veno-lymphatic SFVMs. Involvement of anatomical areas was present as followed: the lower extremities in 21/45 (46.7 %) cases, the head/neck area in 16/45 (35.6 %) cases, the upper extremities in 4/45 (8.9 %) cases as well as the trunk/buttock area in 4/45 (8.9 %) cases.

Thereby, 29/45 (64.4 %) patients presented with infiltrative lesions expanding into more than one tissue layer (Table 1). Both therapy-naive children (11/45, 24.4 %) and children having undergone previous invasive treatments (34/45, 75.6 %) by debulking surgery (5/45, 11.1 %), sclerotherapy (20/45, 44.4 %), or both (9/45, 20.0 %) without sufficient symptom improvement, were included.

### 3.2. Procedural characteristics

The mean number of BESTs per patient was 1.5 (±0.8) (Table 2). If more than one procedure was performed in a child, the median interval between them was 6 months (range, 3–17 months). Finger electrodes (max. 400 V/cm) were primarily used in 42/68 (61.8 %) procedures while in 26/68 (38.2 %) treatments hexagonal electrodes (max. 730 V/cm) were predominantly applied. In 12/68 (17.6 %) cases a switch to another electrode geometry was performed. The median number of electroporation cycles per treatment was 20 (4–141). Among the 68 BEST treatments, in 64/68 (94.1 %) cases bleomycin was applied intralesionally with a mean dose of 5.9 mg (±3.9 mg) per session, in 2/68 (2.9 %) cases bleomycin was applied intravenously with a mean dose of 3.4 mg (±1.8 mg) per session.

Thus, in 2/68 (2.9 %) treatments children received both intravenous and intralesional bleomycin application with an overall dose of bleomycin of 6.5 mg (±4.9 mg) per session (Table 2).

### 3.3. Procedure-related complications

In total, procedure-related complications were reported after 10/68 (14.7 %) BESTs (Clavien-Dindo I-IV). The most common complication was the development of equinus deformity (5/68; 7.4 %) occurring in all patients who underwent BEST treatment of the calf muscles (5/5, 100 %). Of these five children, three were treated with physiotherapy (3/68, 4.4 %, Clavien-Dindo I), while two patients underwent surgery in form of achilles tendon lengthening (2/68, 2.9 %, Clavien-Dindo IIIb). Two children experienced post-interventional bleeding (2/68, 2.9 %), one mild case without any hemodynamic relevance or need for intervening measures (1/68, 1.5 %, Clavien-Dindo I), while the other patient presented with h aemodynamic relevant and life-threatening bleeding, necessitating transfusion and intensive care treatment (1/68, 1.5 %, Clavien-Dindo IV). In the latter case BEST was performed in an extensive, infiltrative VM with 141 electroporation

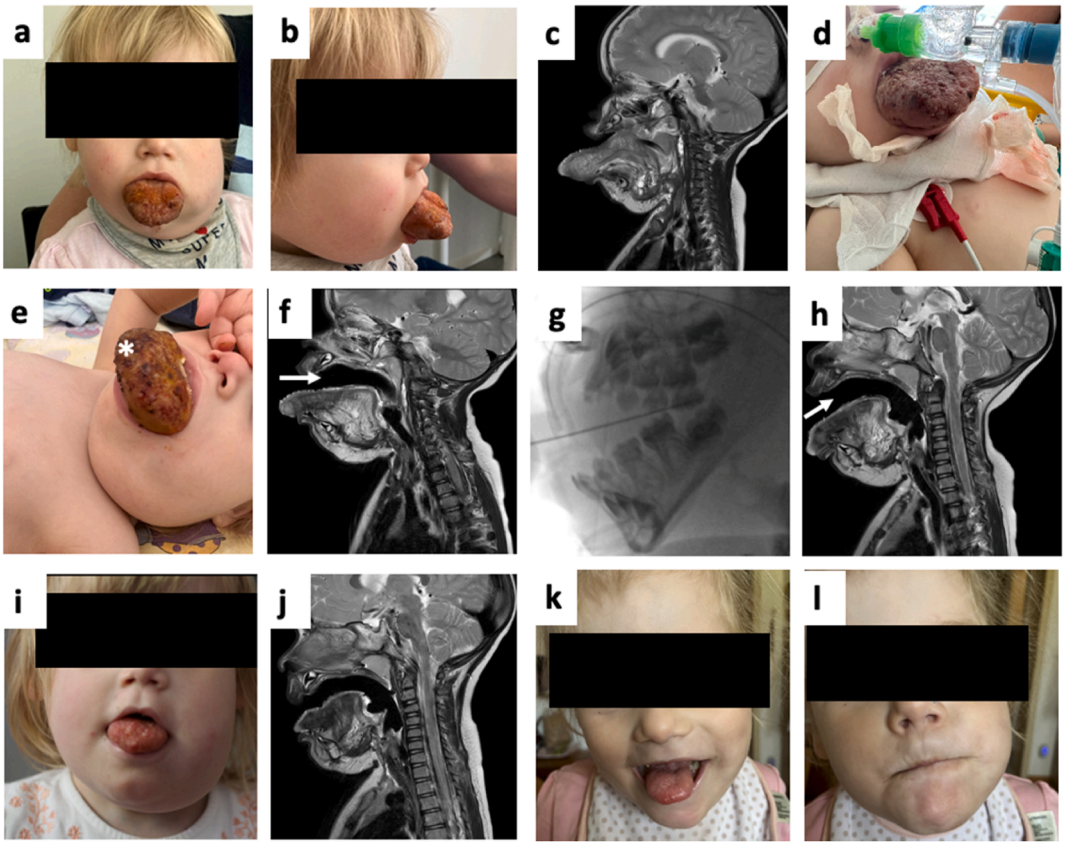


**Fig. 2.** Two-year-old female patient with extensive microcystic lymphatic malformation (LM) of the left tongue after partial tongue resection without sufficient symptom improvement undergoing three bleomycin electrosclerotherapies (BESTs).
a, b, Clinical photographs before BEST treatment; note the extensive swelling of the tongue. The child was unable to place her tongue in the oral cavity as well as food intake and speech development was impaired. c, T2-weighted, sagittal magnetic resonance image prior to treatment shows the microcystic LM of the tongue, that consecutively extends outside the oral cavity. d, e Clinical photographs after first BEST present the immediate postprocedural course including protective intubation for 8 days (d) due to relevant postprocedural swelling (asterisk, e). f, T2-weighted, sagittal magnetic resonance image after first BEST session revealing significant regredience of the lesion, note the newly defined distance to the palate (arrow). g, Periprocedural digital subtraction image during second BEST session. h, T2-weighted, sagittal magnetic resonance image after second BEST session revealing further lesion regredience (arrow). i, Clinical photographs after 2 BEST sessions, note the significantly improved clinical picture. j, T2-weighted, sagittal magnetic resonance image after the third BEST session, the tongue nearly reached a normal size. k, l, Clinical photographs after three BEST sessions, the tongue could be completely positioned in the oral cavity while normal food intake and speech development was achieved.

**Table 1**
Patient characteristics of pediatric Study cohort.

| Characteristic | | Cohort (total, n = 45) |
|---|---|---|
| Age at treatment | *median (range)* | 8.0 (0–17) |
| Men | | 23 (51.1 %) |
| Slow-flow vascular malformations | | 45/45 (100 %) |
| VMs | | 29/45 (64.4 %) |
| LMs | | 8/45 (17.8 %) |
| VLMs | | 4/45 (8.9 %) |
| CVMs | | 2/45 (4.4 %) |
| CVLMs | | 2/45 (4.4 %) |
| Involved anatomical areas | | |
| Head/neck | | 16/45 (35.6 %) |
| Lower extremity | | 21/45 (46.7 %) |
| Upper extremity | | 4/45 (8.9 %) |
| Trunk/buttocks | | 4/45 (8.9 %) |
| Complexity of lesions[a] | | |
| Simple | | 16/45 (35.6 %) |
| Infiltrative | | 29/45 (64.4 %) |
| Previous invasive treatments | | 34/45 (75.6 %) |
| Debulking surgery only | | 5/45 (11.1 %) |
| Sclerotherapy only | | 20/45 (44.4 %) |
| Both | | 9/45 (20.0 %) |

CLM = capillary-lymphatic malformation. CM = capillary malformation. CVLM = capillary-veno-lymphatic malformation. CLM = capillary-lymphatic malformation. LM = lymphatic malformation. VLM = veno-lymphatic malformation. VM = venous malformation.
[a] A simple lesion is defined to a single tissue layer, while an infiltrative lesion involves multiple tissue layers.

cycles using a hexagonal electrode and 15 mg intralesionally admistered bleomycin. Imaging during emergency setting showed diffuse arterial bleeding in the treated area requiring interventional embolization, blood transfusions as well as supplemental coagulation factors. Furthermore, two patients experienced wound infections, both requiring antibiotic therapy (2/68, 2.9 %, Clavien-Dindo II). One child developed a flexion contracture of the wrist successfully treated with physiotherapy (1/68, 1.5 %, Clavien-Dindo I). No pulmonary complications or allergic reactions to bleomycin occurred during and after BEST.

### 3.4. Effectiveness and outcome assessment

The physician-rated overall severity of the symptoms improved significantly (Wilcoxon test, $p < 0.001$) with moderate or severe symptoms in nearly all children (44/45, 97.8 %) before BEST and only 16/45 cases with moderate symptoms (16/45, 35.6 %) and no cases with severe symptoms (0/45, 0 %) after BEST.

The treatment-specific, patient-reported questionnaire was completed in 41/45 (91.1 %) patients. The outcome in mobility was described as improved in 14/41 (34.1 %) children and as symptom-free in 10/41 (24.4 %) cases while 13/41 (31.7 %) children were found to have no change. Regarding both in aesthetics and social participation, the outcome was mostly rated as improved or perfect (33/41, 80.5 %; 35/41, 85.4 %) (Table 3). The median VAS pain scale was rated as 2.0 (0–10) preprocedural, and as 0.0 (0–5) at post-procedural follow-up ($p < 0.001$). Postprocedural swelling mostly persisted for 2–4 weeks (26/41, 64.4 %) and for less than 2 weeks in 9/41 children (22.0 %). Persistent postprocedural swelling of 4–8 and 8–12 weeks was reported in 3/41 (7.3 %) children, respectively. Postprocedural skin discoloration occurred in all children (41/41, 100 %). Though, the further course of the skin alterations was reported as mostly reduced in 25/78 (61.0 %) and as stable in 16/41 patients (39.0 %) 3–6 months after BEST.

The comparison of simple and infiltrative lesions revealed no significant differences regarding the outcome in all assessed objective and subjective parameters (Pearson's Chi-squared test, $p > 0.05$) (Table 3).

## 4. Discussion

To date, this is the largest single-center studies comprehensively describing the effects of BEST therapy on SFVMs in children and adolescents. The findings suggest that BEST is an effective therapy, leading to a significant reduction in symptoms including pain and mobility aspects as well as a relevant improvement in social participation in both simple as well as infiltrative lesions. The overall complication rate was low. However, pes equinus deformity being the most frequent postinterventional complication, and bleeding complications, although rare can be potentially severe. The entire cohort developed postprocedural skin discoloration to some degree, with about two thirds reporting fading in the further postprocedural course. Moreover, all children reported significant postprocedural swelling while two thirds of the patients stated that the swelling persisted for about two to four weeks, while in few cases the swelling lasted up to twelve weeks before finally resolving. Compared to data in adults, post-interventional swelling lasted longer in this cohort, though complete recovery was achieved in all cases [19,22,28,29]. Careful informed consent of parents and children regarding these side effects is thus essential.

Following the low overall complication rate as well as the lack of Clavien-Dindo grade V events with just one grade IV event in a

**Table 2**
Procedural data of pediatric BEST Study.

| Characteristic | | Cohort (total, n = 45) | BESTs (total, n = 68) |
|---|---|---|---|
| BESTs per child | *mean (±SD)* | 1.5 (±0.8) | |
| Total BESTs | | | |
| 1 | | 44/45 (64.7 %) | |
| 2 | | 16/45 (23.5 %) | |
| 3 | | 6/45 (8.8 %) | |
| 4 | | 1/45 (1.5 %) | |
| 5 | | 1/45 (1.5 %) | |
| Primarily used electrode | | | |
| Finger | | | 42/68 (61.8 %) |
| Hexagonal | | | 26/68 (38.2 %) |
| Dose [mg] of Bleomycin | | | |
| Intralesional (n = 64) | *mean (±SD)* | | 5.9 (±3.9) |
| Intravenous (n = 2) | *mean (±SD)* | | 3.4 (±1.8) |
| Both (n = 2) | *mean (±SD)* | | 6.5 (±4.9) |
| Cycles of electroporation | *median (range)* | | 20 (4–141) |
| Depth of electrodes (mm) | *median (range)* | | 20 (10–40) |

BEST=Bleomycin electrosclerotherapy. SD = standard deviation.

**Table 3**
Comparison of outcome according to complexity of SFVMs (Simple versus infiltrative).

| Characteristic | Total cohort (n = 45[a]/n = 41[a]) | Simple (n = 16[a]/n = 14[b]) | Infiltrative (n = 29[a]/n = 27[b]) | p-value[c] |
|---|---|---|---|---|
| Objective overall severity of the symptoms before BEST[a] | | | | 0.272[d] |
| Mild | 1/45 (2.2 %) | 0/16 (0.0 %) | 1/29 (3.4 %) | |
| Moderate | 22/45 (48.9 %) | 11/16 (68.8 %) | 11/29 (37.9 %) | |
| Severe | 22/45 (48.9 %) | 5/16 (31.3 %) | 17/29 (58.6 %) | |
| Objective overall severity of the symptoms after BEST[a] | | | | 0.127[d] |
| Mild | 29/45 (64.4 %) | 12/16 (75.0 %) | 17/29 (58.6 %) | |
| Moderate | 16/45 (35.6 %) | 4/16 (25.0 %) | 12/29 (41.4 %) | |
| Severe | 0/45 (0.0 %) | 0/16 (0.0 %) | 0/29 (0.0 %) | |
| Subjective outcome in mobility[b] | | | | 0.676[d] |
| Decreased | 4/41 (9.8 %) | 1/14 (7.1 %) | 3/27 (11.1 %) | |
| Stable | 13/41 (31.7 %) | 4/14 (28.6 %) | 9/27 (33.3 %) | |
| Improved | 14/41 (34.1 %) | 4/14 (28.6 %) | 10/27 (37.0 %) | |
| Symptom-free | 10/41 (24.4 %) | 5/14 (35.7) | 5/27 (18.5 %) | |
| Subjective outcome in aesthetic concerns[b] | | | | 0.541[d] |
| Impaired | 1/41 (2.4 %) | 0/14 (0.0 %) | 1/27 (3.7 %) | |
| Stable | 7/41 (17.1 %) | 1/14 (7.1 %) | 6/27 (22.2 %) | |
| Improved | 23/41 (56.1 %) | 9/14 (64.3 %) | 14/27 (51.9 %) | |
| Perfect | 10/41 (24.4 %) | 4/14 (28.6 %) | 6/27 (22.2 %) | |
| Postprocedural swelling[b] | 41/41 (100 %) | 14/14 (100 %) | 27/27 (100 %) | 0.290[d] |
| <2 weeks | 9/41 (22.0 %) | 4/14 (28.6 %) | 5/27 (18.5 %) | |
| 2–4 weeks | 26/41 (63.4 %) | 10/14 (71.4 %) | 16/27 (59.3 %) | |
| 4–8 weeks | 3/41 (7.3 %) | 0/14 (0.0 %) | 3/27 (11.1 %) | |
| 8–12 weeks | 3/41 (7.3 %) | 0/14 (0.0) | 3/27 (11.1 %) | |
| Social participation[b] | | | | |
| Impaired | 4/41 (9.8 %) | 1 (7.1 %) | 3/27 (11.1 %) | 0.428[d] |
| Stable | 2/41 (4.9 %) | 0 (0.0 %) | 2/27 (7.4 %) | |
| Improved | 18/41 (43.9 %) | 5 (35.7 %) | 13/27 (48.1 %) | |
| Perfect | 17/41 (41.5 %) | 8/14 (57.1 %) | 9/27 (33.3 %) | |
| Pain VAS score preprocedural, median (range)[b] | 2.0 (0–10) | 2.0 (0–10) | 2.0 (0–10) | 0.320[e] |
| Pain VAS score postprocedural, median (range)[b] | 0.0 (0–5) | 0.0 (0–5) | 0.0 (0–5) | 0.714[e] |
| Postprocedural skin discoloration[b] | 41/41 (100 %) | 14/14 (100 %) | 27/27 (100 %) | |
| Stable | 16/41 (39.0 %) | 5/14 (35.7 %) | 11/27 (40.7 %) | |
| Reduced | 25/41 (61.0 %) | 9/14 (64.3 %) | 16/27 (59.3 %) | |
| Completely resolved | 0/41 (0.0 %) | 0/14 (0.0 %) | 0/27 (0.05) | |

BEST=Bleomycin Electrosclerotherapy. VAS = visual analogue scale.
[a] Physician-rated.
[b] Patient-rated questionnaire (by parents and/or child itself).
[c] Subgroup analyses between simple and infiltrative lesions.
[d] Pearson's Chi-squared for categorical data.
[e] Mann–Whitney U test for continuous data.

cohort of 45 children, BEST can be regarded as an overall safe therapeutic approach for SFVMs in paediatric patients.

The occurrence of pes equinus deformities after BESTs is a relevant finding of this study, noted in all cases with treatment of the calf musculature. Studies on conventional sclerotherapy report joint dysfunction due to muscle fibrosis and subsequent contractures as a relevant postprocedural complication, and SFVM in the lower extremity has been identified as a significant risk factor compared to lesions of the upper extremity [31,32]. These findings were reported to be more relevant in young patients (age <10 years) [32,33]. Physiotherapy is the first line of treatment in these cases, failing with surgery is recommended. These complications stress the importance of multi-professional approach to this group of patients [34]. As there are no comparable data of pes equinus deformities after BEST to date, evaluation in further studies is needed. Treatment of the calf muscles with BEST should therefore be performed with caution using strict indications, particularly in children.

In our cohort, one potential life-threatening bleeding (Clavien-Dindo IV) occurred after treatment of an extensive, infiltrative VM. Despite this complicated course, the patient showed an overall improvement in symptoms and quality of life four months after the intervention, without any neurological or other systemic sequelae related to the complication. We hypothesize, that the key to this event may be the disproportionately high number of electroporation cycles (141) compared to the average number of cycles (mean 26 cycles) in this cohort. The excessive electroporation may have led to overproportioned tissue damage, subsequent resulting in diffuse bleeding. Another point that may have aggravated the bleeding complication was an accompanying LIC in the described patient. Important indicators for LIC in SVLMs are hypofibrinogenemia, elevated D-dimers, and, in some cases, thrombocytopenia. The larger the malformation, the higher the risk of LIC within the malformation [35,36]. The risk of bleeding due to generalized coagulopathy following interventions is higher in SFVMs with LIC [37,38].

Thus, in children with extensive, infiltrative SFVMs and associated predisposition for coagulation disorders, peri-interventional coagulation management should be performed, and a maximum number of electroporation cycles may be considered in general to particularly meet the high risk of bleeding events in these patients.

Studies of BEST in SFVMs including both children and adults indicate similar safety [19,21,22] with children even appearing to benefit more than adults [19]. However, no study has analysed the therapeutic effect of BEST in a paediatric cohort excluding adults and to date, paediatric data of BEST are limited to case reports [39]. Conventional sclerotherapy and surgery are established treatment methods for slow-flow vascular malformations (SFVMs). However, the therapeutic effect in extensive, infiltrative SFVMs remains limited. There is still a lack of effective therapeutic options for the affected children [10,18,40,41]. A key novel insight from our study

is that BEST appears to be effective not only in simple, but also in infiltrative SFVMs. This observation could lead to an expansion of treatment indications for BEST, making it an especially promising option for previously challenging SFVMs subtypes. Future studies should investigate these findings in a prospective, controlled manner.

Several limitations of our study must be acknowledged. The retrospective study design introduces inherent biases, particularly in patient selection and outcome assessment. Additionally, imaging-based follow-up was not systematically performed in this paediatric cohort, limiting objective radiological evaluation of treatment response. This is due to the fact that MRI was performed in only about 50 % of cases, owing to the need for general anaesthesia during MRI in childhood. The patient-reported questionnaires, while providing valuable insights into subjective outcomes, were not psychometrically validated, as no validated quality-of-life assessment tools currently exist specifically for BEST. Follow-ups by telephone-based interviews may further introduce recall bias and variability in patient responses.

Despite these limitations, the real-world data from this cohort provides valuable insights into the effectiveness and safety of BEST in paediatric patients.

## 5. Conclusion

Our study shows that BEST has the potential to provide both objective and subjective clinical improvement in paediatric patients with SFVMs. It generally seems to be a safe treatment modality, adding to the previously limited armamentarium to treat vascular malformation in children. Caution is required treating lesions involving the calf muscles due to the risk of pes equinus deformity. Furthermore, BEST does not replace established therapeutic options such as sclerotherapy and surgery for their respective indications. Rather, this study suggests, that BEST expands the range of available treatment options, particularly for children with infiltrative SFVMs who previously had limited options for effective treatment.

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## Declaration of competing interest

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2025.162631.

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