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Electrochemical sclerotherapy with bleomycin for the treatment of low-flow vascular malformations: a comprehensive review

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Abstract

Low-Flow Vascular Malformations (LFVMs) are a diverse group of abnormal vascular lesions characterized by slow blood flow that can involve veins, capillaries, or lymphatic vessels. These malformations, often diagnosed in childhood, may present with varying symptoms, including chronic pain, functional impairment, cosmetic deformities, and life-threatening complications. Electrochemical Sclerotherapy With Bleomycin (BEST) has emerged as a promising treatment. This technique combines bleomycin, a chemotherapeutic agent with sclerosing properties, with electrical pulses to enhance the drug's tissue penetration and targeting, thereby improving the efficacy of sclerotherapy. BEST has demonstrated significant success in treating venous, lymphatic, and capillary malformations, offering a minimally invasive option with fewer complications than conventional therapies like ethanol sclerotherapy or surgical excision. Recent studies have shown that BEST results in substantial lesion size reduction and symptom improvement, with reduced treatment duration and fewer side effects. Furthermore, electroporation allows for a reduction in the bleomycin dose, minimizing the risk of systemic toxicity. The safety and effectiveness of BEST, also certified by its decades of use in oncology, make it a safe and valuable tool in managing challenging LFVM cases. Given the variability in the extent and location of the pathologies treated the reported results should be interpreted with caution. Ongoing research and clinical trials will further establish BEST's role as a first-line treatment for vascular malformations, potentially revolutionizing the therapeutic landscape for these complex conditions.

Key words: vascular malformations, bleomycin, electrochemical sclerotherapy.

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Introduction

Vascular anomalies encompass a wide range of clinical and pathological characteristics. In 1982, Mulliken and Glowacki classified these anomalies into two main categories: tumors, which are true vasoproliferative neoplasms, and malformations, which result from defects in vascular development without endothelial cell proliferation.[1] Building upon this foundational work, the International Society for the Study of Vascular Anomalies (ISSVA) introduced a comprehensive classification system, most recently updated in 2018. This classification is widely recognized and utilized for standardizing the diagnosis and management of vascular anomalies.[2]

Vascular Malformations (VMs) are further categorized based on the types of vessels involved and can also be differentiated by their flow characteristics.[3-7]

Low-Flow Vascular Malformations (LFVMs) are a heterogeneous group of abnormal vascular lesions characterized by slow blood flow, and they can involve veins, capillaries, or lymphatic vessels.[8-11] These malformations often present during childhood and, clinically, can manifest as a range of conditions, from asymptomatic lesions to those causing significant functional impairment, chronic pain, cosmetic deformities, ulcerations, or life-threatening complications (such as recurrent infections, thrombosis, and hemorrhagic complications).[12-14] In addition to the clinical complications, the psychological impact of such malformations is non-negligible, especially in children and adolescents.

Treatment options for LFVMs have historically been limited and often suboptimal, particularly in cases where traditional surgical interventions are impractical due to the location or size of the malformation.

Electrochemical Sclerotherapy With Bleomycin (BEST) is a recent innovation in the treatment of these malformations. This technique combines the use of bleomycin, a chemotherapeutic agent with sclerosing properties, with electrical current to enhance the efficacy of the sclerosing agent. The synergistic effect of electrosclerosis with bleomycin is believed to improve tissue penetration and provide more specific targeting, leading to more effective obliteration of vascular lesions with reduced treatment duration and complication rates.[15]

Particularly of interest for bleomycin therapy delivered via electroporation are extratruncular malformations. These malformations develop between the first and third month of intrauterine life due to the failure of sectorial resorption of the primitive vascular network before the formation of the definitive circulatory trunks. Their characteristic feature is that, instead of endothelial cells, angioblasts are present, and, with traditional surgical techniques, they tend to recur locally in a manner similar to neoplastic disease.[3] This review aims to provide a comprehensive overview of BEST, focusing on its mechanism of action, clinical indications, comparative efficacy, and safety outcomes.

Mechanism of action

The underlying principle of electrochemical sclerotherapy lies in the application of an electric current to enhance the delivery and effect of a sclerosant agent. Bleomycin, a chemotherapeutic agent, has been shown to possess sclerosing properties when used in the treatment of vascular malformations. When administered through a catheter or injection into the malformation, bleomycin induces endothelial cell damage and fibrosis, resulting in the obliteration of the malformation over time. Electrochemical sclerotherapy amplifies this effect by generating localized heating and electrochemical reactions at the site of treatment. This is facilitated by an electrical current applied through electrodes placed near or within the lesion. The current induces chemical reactions at the interface between the sclerosant and vascular endothelium, enhancing tissue penetration and promoting endothelial damage (Figure 1-3).[16,17] Additionally, the electrochemical reaction may also lead to the production of Reactive Oxygen Species (ROS), which further enhance cellular damage and fibrosis. Thanks to electroporation, which, as previously mentioned, facilitates the drug's entry into cells, electrochemical sclerotherapy significantly reduces the required dosage of bleomycin compared to traditional sclerotherapy, thereby minimizing the risk of side effects, and enhancing the safety of the treatment.[18] This is particularly useful when treating patients with extensive vascularization or when it is necessary to reduce the risks of systemic toxicity.[19]

Safety of treatment

In terms of safety, we can certainly refer to the experiences with BEST in cutaneous oncology, where it is known as

Figure 1. Mechanism of action of electrochemical sclerotherapy.

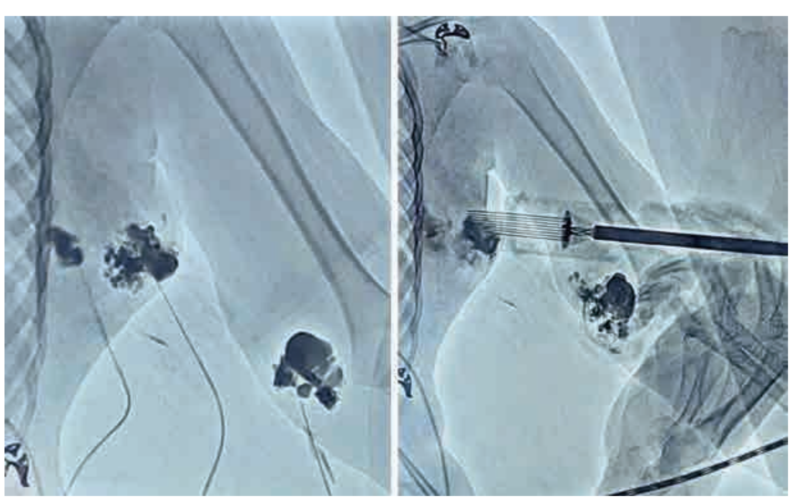

Figure 2. Mechanism of action of electrochemical sclerotherapy.

Electrochemotherapy (ECT).[20,21] The technology and the bleomycin agent are the same, and their rationale for use is based on the inhibition of neoangiogenesis to control the tumor, exactly as the control of angioblasts in the sclerotherapy of low-flow vascular malformations. The safety profile of ECT has been supported by numerous clinical studies that have shown the procedure to be generally safe, with a minimal occurrence of serious adverse events. Notably, severe complications such as nerve damage, skin necrosis, or other life-threatening outcomes have not been reported in significant numbers. For instance, studies by Marty *et al.*[22] and Campana *et al.*[23] have highlighted that the incidence of severe side effects remains exceedingly low, underscoring the relative safety of the procedure in clinical practice. These findings are crucial when considering the use of bleomycin in conjunction with electroporation, as bleomycin itself can sometimes present risks, such as pulmonary toxicity, in other settings. However, in the context of electrochemotherapy, the local application, the reduced dosage, and controlled delivery mitigate the risk of systemic complications, thus improving the overall safety profile.

Moreover, ECT has also shown broad efficacy across various tumor histologies, such as Basal Cell Carcinoma (BCC), melanoma, squamous cell carcinoma, and Kaposi's sarcoma,[24,25] but also in various solid tumors, including vulvar tumors,[26] breast metastases,[27] sarcomas,[28] and mucosal tumors of the head and neck region.[29] In palliative settings, ECT has significantly improved quality of life, with a positive clinical response in patients where other therapeutic options are limited.[26]

Clinical applications and indications

BEST is primarily indicated for the treatment of low-flow vascular malformations, including Venous Malformations (VMs), Lymphatic Malformations (LMs), and Capillary Malformations (CMs), which typically exhibit slow blood or lymph flow. Ideal candidates for BEST include: i) patients with LFVMs who have not responded to two or more previous invasive treatments; ii) patients with debilitating symptoms such as pain, swelling, or significant aesthetic and functional dysfunctions; iii) both children and adults, as clinical benefits have been observed across all age groups.[19]

Efficacy and clinical outcomes in vascular malformations

Several studies have demonstrated the efficacy of BEST in the treatment of LFVMs. For instance, a prospective observational study conducted by Li JH *et al*. in 2013 showed that, out of a total of 505 patients with venous malformations, 95.4% experienced significant improvements following BEST treatment. Of these, 30.1% had an almost complete response, 46.3% showed a reduction of 50-75% in lesion size, and 19.0% exhibited symptom improvement associated with a 25-50% reduction in lesion extent.[30] Similar results have been reported by other studies. In a retrospective observational study conducted by Wohlgemuth *et al*. in 2021, a total of 17 patients previously treated with at least two ineffective invasive procedures were analyzed. Following treat-

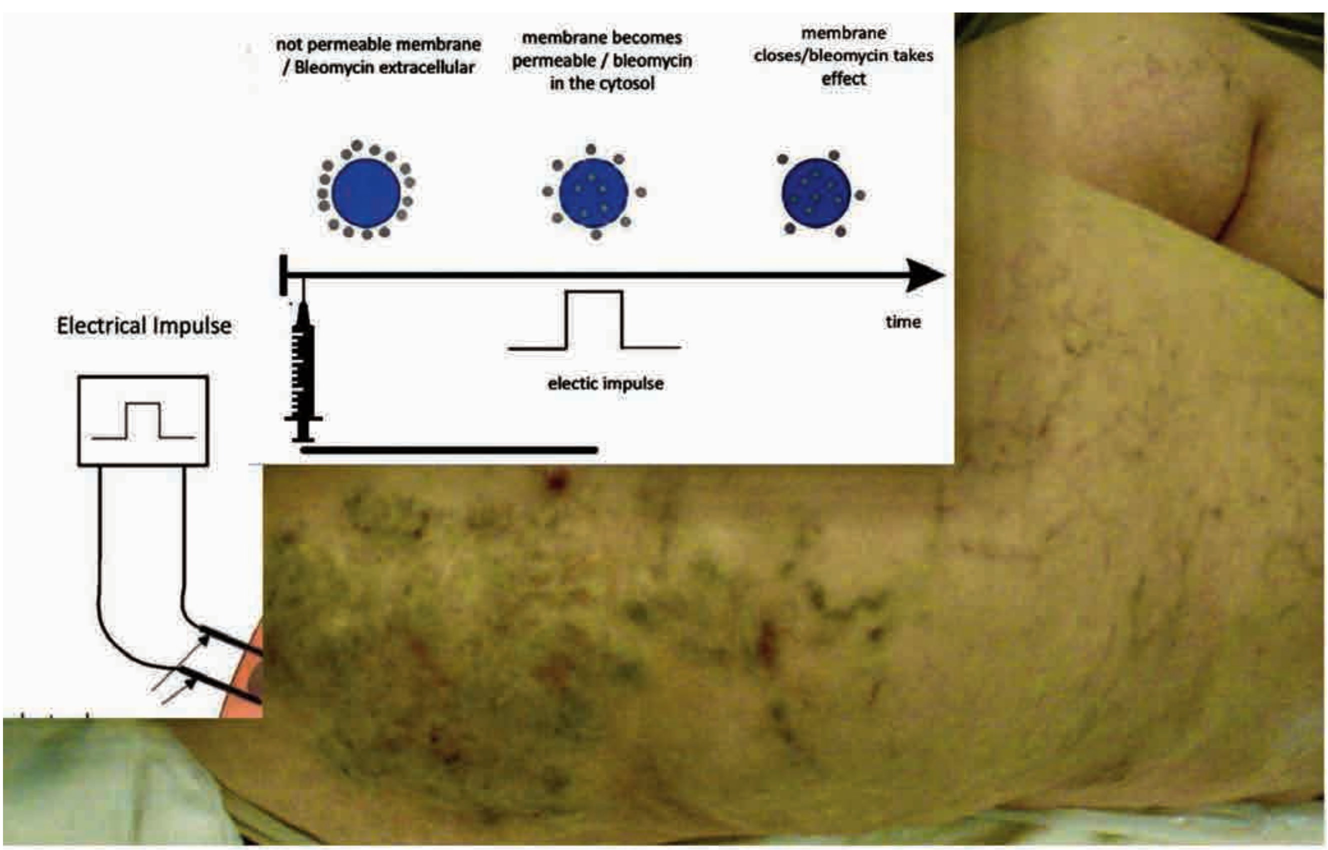

Figure 3. Mechanism of action of electrochemical sclerotherapy.

ment with BEST, 100% of the patients showed improvement, with 8 patients becoming completely asymptomatic and 9 patients demonstrating significant clinical symptom improvement.[31]

In a retrospective study by Bouwman *et al.* (2021) involving 116 children with Lymphatic Malformations (LM) or Venolymphatic Malformations (VLM), bleomycin sclerotherapy resulted in clinical improvement in 91% of the procedures.[32]

In the prospective observational study by Kostusiak *et al.* (2022), involving thirty patients with predominantly low-flow vascular malformations, 57% achieved a complete response and 23% showed significant improvement.[33] Another recent retrospective study conducted by Brandao showed a lesion volume reduction of at least 50% on Magnetic Resonance Imaging (MRI) over 50 patients treated with Bleomycin, with no major complications during follow-up.[34]

Finally, in the multicenter retrospective study conducted by Schmidt *et al.* in 2024, 325 BEST treatments were performed, with 54.9% reporting significant improvement and 9.7% showing a complete response.[19] Although the large number of reported patients demonstrates the efficacy of BEST treatment, the great variability in location and extent of the disease, as well as the lack of homogeneous diagnoses in some articles, could represent a limitation of the conclusions and the data should therefore be interpreted with caution; nevertheless, the authors reserved the right to cite the reported data in order to request AIFA (Agenzia Italiana del Farmaco) authorization to use the drug in the cited pathology.

Comparative effectiveness

There are no randomized controlled trials comparing the safety and efficacy of BEST with other therapeutic options. Liquid or foam sclerotherapy remains the most commonly used treatment.[35]

In many cases, patients require repeated treatments, sometimes without achieving significant reductions in lesion size or pain. The most commonly used agent, due to its potency and efficacy, is ethanol; however, it is associated with a high morbidity rate. Notably, in the most qualified literature, the incidence of skin necrosis ranges between 10% and 18%, along with reports of potential peripheral nerve damage and thromboembolic events, despite its effectiveness.[36-39] In this context, BEST offers a significant therapeutic alternative for achieving sclerosis of malformed tissues while maintaining the low invasiveness of sclerotherapy, yet reducing the complications associated with ethano.[19,40,41]

Surgical excision is generally indicated only for localized lesions, as it carries high risks of complications and recurrence, especially for extensive malformations[19,41] and the previously mentioned extratruncular malformations.[3] Moreover, it comes with the risks of scarring, prolonged recovery, and potential functional impairment.

Finally, laser therapy is more limited to superficial capillary malformations, whereas it has limitations in treating deeper or larger malformations, where electrochemical sclerotherapy may prove more effective.

Electrosclerotherapy is capable of treating a wide range of VM patients, including those with lesions that are difficult to treat or resistant to other therapies. These include microcystic and macrocystic lymphatic malformations, as well as trunk vascular malformations, which are often refractory to traditional sclerotherapy techniques.[31,41] The technique has proven particularly effective in treating recurrent vascular malformations or those difficult to approach surgically.[33] Moreover, thanks to electroporation, which facilitates the entry of the drug into cells, electrosclerotherapy allows for a significant reduction in the dosage of bleomycin compared to traditional sclerotherapy, minimizing the risk of side effects and improving treatment safety,[18] making it particularly useful when treating patients with extensive vascularization or when it is necessary to reduce the risks of systemic toxicity.

It has been shown that electrosclerotherapy requires fewer sessions compared to conventional sclerotherapy, improving treatment efficiency.[42] In general, only one session of bleomycin is often needed to achieve complete resolution of the VM or significant reduction, even in patients who have previously undergone sclerotherapy with bleomycin without electroporation.[31,41] Indeed, in the aforementioned analysis by Schmidt *et al.* (2024), out of a sample of 233 patients (325 VMs), the average number of sessions required was 1.4.[19]

Discussion

Low-flow vascular malformations, both venous and lymphatic, represent a heterogeneous group of malformative extratruncular conditions that require accurate diagnosis and a personalized therapeutic approach.

The use of electrochemical sclerotherapy with bleomycin in these types of lesions is a rapidly evolving field. Early results suggest that this approach is effective, minimally invasive, and has a favorable safety profile.

Regarding safety, the large number of cases treated, including within Randomized Controlled Trials (RCTs), allows us to conclude that, in terms of safety, this is now an established and incontrovertible element. The sclerosing properties of bleomycin, especially in oncology for neoplasms characterized by primitive or secondary neovascularization, have led to its recognition as an innovative and promising therapeutic technique for treating vascular malformations. By combining the local application of bleomycin with electrical pulses (reversible electroporation), this method optimizes drug penetration into tissues, significantly reducing both the administered dose and the number of sessions required.

While ethanol sclerotherapy continues to be a fundamental therapeutic cornerstone for these types of lesions, the treatment is associated with a significant percentage of skin necrosis, fibrotic scarring of the treated tissues, and nerve damage. In contrast, BEST has proven to be safer and better tolerated in both pediatric and adult populations,[36,37] while still providing comparable or even superior results.

Conclusions

BEST is a promising treatment modality for low-flow vascular malformations. It offers a safe, effective, and minimally invasive alternative to traditional therapies, with significant clinical benefits in terms of symptom relief, lesion reduction, and patient satisfaction. Ongoing research and clinical experience will continue to define its role in the management of these complex vascular conditions.

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