OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

PEDIATRICS

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| Journal: | *Pediatrics* |
| Manuscript ID | 2020-0566.R1 |
| Article Type: | Case Report |
| Date Submitted by the Author: | 01-Apr-2020 |
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| Keyword/Topic: | Birth Defects < Fetus/Newborn Infant, Surgery |
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# New treatment option for capillary lymphangioma: bleomycin-based electrochemotherapy of an infant

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**Short title:** Bleomycin-based electrochemotherapy in lymphangioma

**Funding Source:** This work was performed with the financial support of GINOP-2.3.2-15-2016-00015 (LK), EFOP-3.6.1-162016-00008 grant (ZSCS) and János Bolyai Research Scholarship from the Hungarian Academy of Sciences (ZSCS). The remaining authors have no financial relationships relevant to this article to disclose.

**Financial Disclosure:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**Conflict of Interest:** Authors have no conflicts of interest to disclose.

**Abbreviations:** LM: lymphangioma, ECT: electrochemotherapy, ESOPE: European Standard Operating Procedures of Electrochemotherapy, MR: magnetic resonance

**Table of Contents:** Microcystic and combined lymphangiomas are a real challenge to treat. Based on our results electrosclerotherapy should be considered as a feasible alternative treatment option.

**Word count:** 1411

**Figure count:** 3

**Video:** 1

**Contributors' Statement Page**

Szandra Dalmády conceptualized the treatment, drafted the initial manuscript and reviewed and revised the manuscript.

Zsanett Csoma and Krisztina Bottyán managed and controlled the patient as dermatologists and revised the results and reviewed and revised the manuscript.

Zsuzsanna Besenyi valued the results and designed the radiological imaging and reviewed and revised the manuscript.

Judit Oláh managed the patient as an oncologist and coordinated and supervised the treatment and designed the interpretation of the results and revised the result and reviewed and revised the manuscript.

Lajos Kemény coordinated and supervised the treatment and analyzed and revised the results and critically reviewed the manuscript for important intellectual content and revised the final version of the article.

Erika Kis designed the treatment and the evaluation of the results and performed the surgery as a plastic surgeon, expert of electrochemotherapy, and Head of the Hungarian Electrochemotherapy Team, also critically reviewed the manuscript for important intellectual content, revised and modified the final version of the article.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Abstract

The treatment of microcystic and combined lymphangiomas, especially in the head and neck region is still a challenge as they do not respond to conventional therapies, and their recurrence rate is high regardless of the treatment choice. The complete surgical resection is the best treatment for lymphangiomas, but due to the localization perioperative complications such as bleeding, neural damage or airway obstruction are common disadvantages of this method. Bleomycin based sclerotherapy is another common therapeutic approach, when the lymphocysts are aspirated and 25-50% of their volumes are replaced with sclerotisant drug. This is an effective treatment in those cases where the vessels are large enough for an intravascular or intracystic injection, but due to the small size of vessels and cysts, the microcystic and combined lymphangiomas are not suitable for sclerotherapy. Delivery of drugs for treating sclerosis to endothelial cells can be achieved by electroporation (electrochemotherapy) even for capillary malformations. A congenital, rapidly growing combined lymphangioma of the left cervicofacial region was treated with one session of bleomycin-based electrochemotherapy. Seven months after treatment, the growth-corrected target-volume decrease was 63% and the dislocation of the trachea and blood vessels previously observed had ceased. We suggest that bleomycin-based electrochemotherapy is a feasible alternative treatment option for capillary malformations.

## Introduction

Lymphangiomas (LMs) are rare benign congenital malformations of lymphatic vessels. The incidence of LMs is reported to be from 1.2 to 2.8 per 1000 newborns.[1] The most common localization of LMs is the cervicofacial region (95%), where vital structures can be compressed and infiltrated.[1] Spontaneous regression is not probable for microcystic (0%) and combined types (2%) of LMs,[2] and these types exhibit a high recurrence and complication rate such as hemorrhage (15%) or infection (27%), which can cause sudden enlargement, airway obstruction or death.[2,3] Complete surgical resection is the best treatment for LMs, but in lesions infiltrating main blood vessels complete resection is not possible and it may result in serious complications.[4-6] Bleomycin-based sclerotherapy is an effective treatment for LMs in cases where the vessels are large enough for an intravascular or intracystic injection. This therapy is not suitable for microcystic and combined LMs, due to the small size of the vessels and cysts.

During reversible electroporation, the application of short-term, high-intensity electric pulses induces transient permeabilization of cell membranes, which enables the delivery of large hydrophilic molecules, such as bleomycin, to the cytosol. The combination of reversible electroporation and intratumoral bleomycin injection — referred to as bleomycin-based electrochemotherapy (ECT) or electrosclerotherapy — facilitates drug delivery to endothelial cells, resulting in sclerosis of the vessels and cyst, and, eventually, to the regression of the lesion.

## Representative case report

A congenital, rapidly growing, soft-tissue mass was observed on the left side of the neck and cheek of a full-term baby boy. Magnetic resonance imaging demonstrated a prominent, heterogeneous, lobulated, multicystic mass. The trachea, left jugular vein and common carotid

artery were dislocated and compressed (Figure 2/ A-C). The T1-weighted contrast-enhanced MR images showed one large, high-lipid cyst (2x2 cm) at the level of the thyroid cartilage (Figure 2/A-B). The whole lesion volume was calculated by manual contouring and found to be 72.32 $cm^3$. Due to the location of the tumor and to the small size of the vessels neither complete resection by surgery nor traditional bleomycin sclerotherapy was not suitable. The rapid growth of the tumor, which could increase the risk of airway obstruction, ischemia and feeding difficulties, our multidisciplinary board decided to perform ECT on the mixed LM. Transmucosal application of electrode application to avoid scarring was ruled out because of the high risk of mucosal swelling with consequential airway obstruction, considerable postoperative pain [7] and feeding problems.[8]

## Methods

### *Treatment*

The first ECT session was performed when the child was 4 months old, according to the European Standard Operating Procedures of Electrochemotherapy (ESOPE) criteria.[9,10] The treatment was carried out under general anesthesia using intratumoral injection of bleomycin (1000IU/ml). Since this is a first case of using ECT in a child with LM, no guideline exists about the bleomycin dosage. In LM-s the advised dose of bleomycin is 0.3-0.5 mg/kg for sclerotherapy. In our case 0.5 mg/kg was calculated and used for the treatment according to the weight of the baby and information from the drug database of the National Institute of Pharmacy and Nutrition[12] (5.4 mg = 8100 IU, which is equivalent to 0.5 mg/kg). According to the ESOPE guideline the intratumoral bleomycin dose would have been 18000 IU based on the tumor volume[9], namely a reduced dose of bleomycin was used in our case. The ESOPE guideline was developed for cancer treatment in adults. [9] It should be noted that Groselj et al.[11] presented recently, that the antitumor effectiveness of electrochemotherapy is comparable when using standard or reduced bleomycin dose.

ECT was performed using a Cliniporator electric pulse generator (IGEA, s.r.l., Carpi, Italy) and row needle electrodes. [9,13] With every application eight consecutive pulses with duration of 100 μs and voltage-to-electrode distance ratio of 1000 V/cm were used for electroporation. During the first session of ECT 68 applications were performed to cover the whole lesion by the electric field. The average current was 5.27 A (2–14 A). Only one cyst (>2 cm) was aspirated, and the standard method (sclerotherapy) was used. During treatment, a biopsy was taken for histopathological examination, which was used to confirm the diagnosis of LM. Eight months after the first electrosclerotherapy a second session was performed with the same technique under intraoperative ultrasonography guidance. In this session the anterior triangle was treated, close to the main vessels. During the second session of ECT 74 applications were performed, the average current was 5.55 A (2–13 A). Follow up included visits with the patient on a weekly basis in the first month and, after the first three months, every fourth week. During visits, the general state of health, mental and physical development of the child, size and density of the lesion and skin scars were examined. The patient's parents gave their written informed consent prior to treatments.

*Therapeutic response evaluation*

To follow the therapeutic response, imaging evaluations were performed before treatment, seven months after the first ECT session and five months after the second ECT session. The lesion volume in units of $cm^3$ was manually determined from T2-weighted magnetic resonance (MR) slices. To evaluate objectively the therapeutic response, we corrected the absolute target volume reduction according to the growth of the baby. To measure the growth rate of the infant, the contralateral healthy parotid gland volume was determined by manual delineation in both time points.

**Results**

Despite prominent post-operative edema, the treatment was well tolerated by the patient and breast feeding was constant. In this case, no perioperative complications were experienced. One and two months after treatment, erysipelas evolved on the cheek and was resolved with antibiotic therapy. During subsequent visits, a constant decrease in the volume of the LM was observed. Five months after the first ECT, a distinct decrease in the tumor volume was revealed with physical examination (Figure 3). Seven months after the first ECT treatment, MR images indicated significant decrease of the multicystic mass and, most importantly, the restoration of the dislocated trachea and compressed vessels (Figure 2/D). The volume of the cystic mass was reduced to 48.09 $cm^3$ from a 72.32 $cm^3$. The absolute target volume decrease was 33.5%. The normal right parotid gland growth was from 3.40 $cm^3$ to 6.08 $cm^3$, therefore 78.8% physiological growth rate of the parotid and the child was determined. Based on that calculation, 63% of growth corrected target volume decrease was achieved. To prevent the potential progression of the untreated area a second treatment was performed eight months after the first session of ECT. One year after the first session, the symmetry of the face was completely restored (Figure 3). After 17 months follow up no recurrence was observed. The mental and physical development of the child remained age-appropriate. Small skin scars and slight hyperpigmentation caused by the application of the electrodes remained visible on the treated area.



**Discussion**

ECT is a commonly used local treatment for cutaneous metastases and primary skin cancer of any histology. [14-16] Several recently published reports describe treatment of benign vascular malformations with bleomycin-based ECT. McMorrow et al. reported a case in which a venous malformation was managed successfully with intratumoral delivery of bleomycin using ECT [17] and referred to the procedure as bleomycin-based electrosclerotherapy. Endothelial cells are valid targets for electroporation, especially for vessels with diameters

smaller than 5 mm.[18] Therefore ECT, which is the combination of electroporation delivery of intratumoral bleomycin, facilitates drug delivery to endothelial cells even in microcystic cases, which leads to sclerosis of the vessels and cyst and regression of the tumor (Figure 1).[19] Moreover, electric pulses have an important immediate vascular effect which reduces blood flow transiently and prevents washout of the drug.[18] In case of benign vascular lesions, the aim of ECT is to enhance the sclerosing effect.[20] In our case, the growth-corrected target volume decrease was 63% after one session of ECT. This response considered to be very good, taking into account that the lesion was benign, and accordingly complete eradication was not necessary. Our major goal, to restore the position of the trachea and vessels, was achieved. The symmetry of the face was also restored, which is important for the social development of the child.

**Conclusion**

In our case, bleomycin-based ECT proved to be safe and effective in the treatment of a combined LM. Bleomycin-based ECT should be considered as a feasible alternative treatment option for microcystic and combined LMs for babies. Since this is the first use of bleomycin electrosclerotherapy in the management of capillary LMs in an infant, further studies are needed concerning the efficacy and safety of the method.

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**Figure 1.** Reversible electroporation.

Delivery of electric pulses to target cells enhances bleomycin uptake into the cytosol by permeabilizing the cell membrane. After the pulses cease, the membrane reseals, trapping bleomycin molecules in cells, where their effect is exerted.

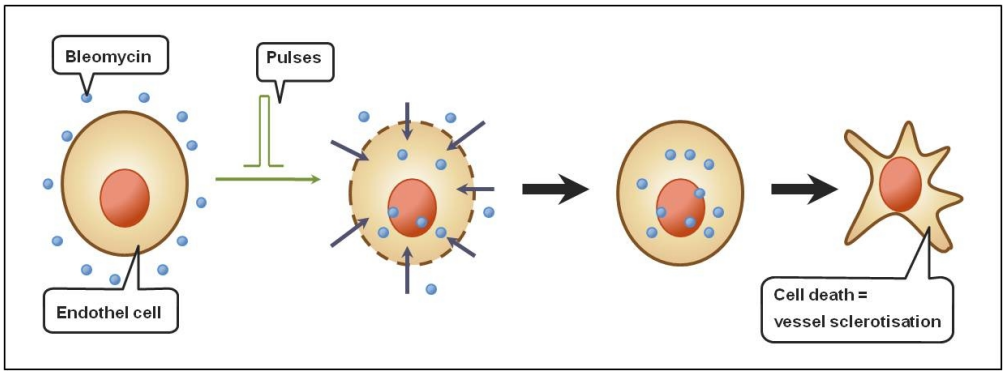
**Figure 2.** MR images

A. T1-weighted, contrast-enhanced coronal MR slice before the treatment shows dislocation of pharyngeal structures (red arrow). The midline of the head is indicated with a green broken line. One large, high-lipid cyst is indicated with a white arrow.
B. T1-weighted, contras-enhanced MR coronal view of the 3D reconstructed image before treatment shows the compressed and dislocated jugular vein and common carotid artery (red arrow).
C. T2-weighted axial MR slice before treatment shows compression of surrounding structures and dislocation of the pharyngeal structures (red arrow).
D. T2-weighted axial MR image 7 months after the treatment shows restored position of the pharynx .

**Figure 3.** Photos of the patient

A. One week old: soft-tissue mass on the left side of the neck and cheek.
B. Two months old: rapidly growing combined lymphangioma.
C. Four months old, at the time of ECT.
D. Nine months old, 5 months after ECT: significant decrease of the malformation.
E. Eleven months old, 7 months after ECT: further volume decrease.
F. Sixteen months old, 1 year after ECT: symmetry of the face is restored.

**Video:** T2 weighted STIR coronal image of first examination with before (red) and after (green) treatment target volumes in 3 dimensional view.




Reversible electroporation. Delivery of electric pulses to target cells enhances bleomycin uptake into the cytosol by permeabilizing the cell membrane. After the pulses cease, the membrane reseals, trapping bleomycin molecules in cells, where their effect is exerted.

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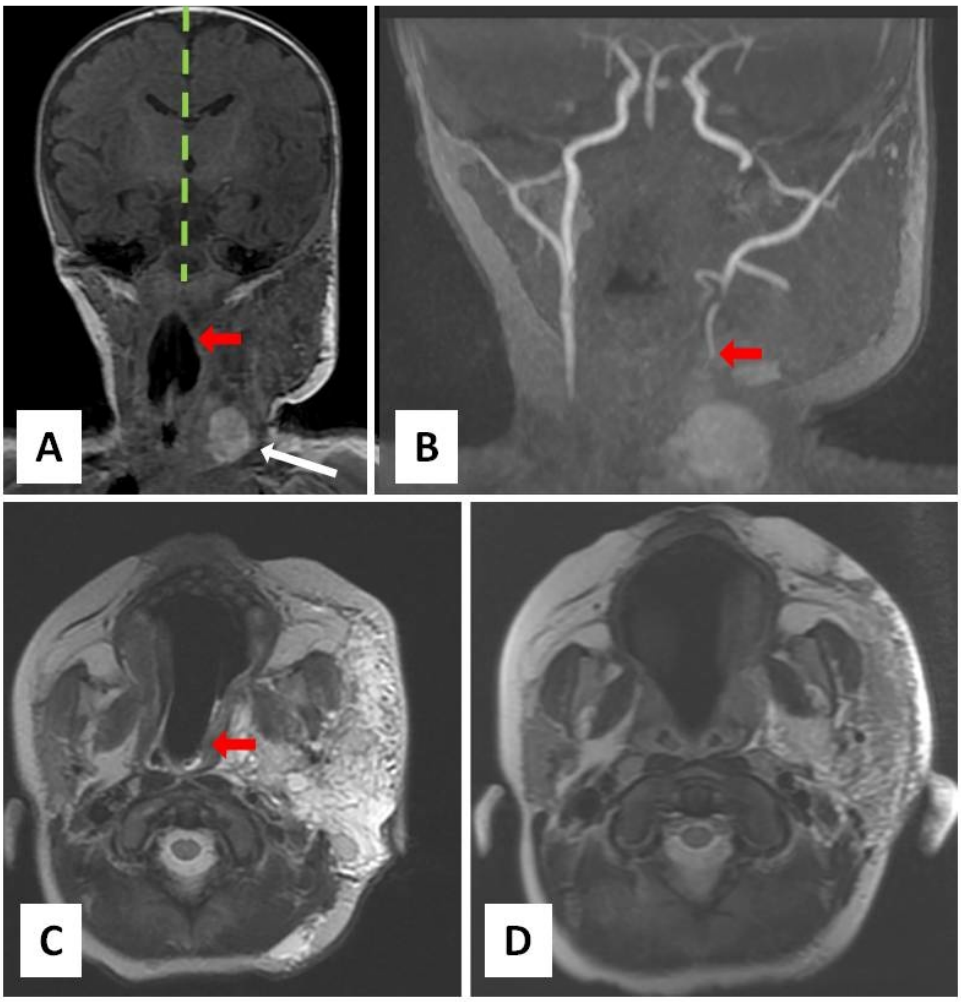


MR images: A. T1-weighted, contrast-enhanced coronal MR slice before the treatment shows dislocation of pharyngeal structures (red arrow). The midline of the head is indicated with a green broken line. One large, high-lipid cyst is indicated with a white arrow. B. T1-weighted, contras-enhanced MR coronal view of the 3D reconstructed image before treatment shows the compressed and dislocated jugular vein and common carotid artery (red arrow). C. T2-weighted axial MR slice before treatment shows compression of surrounding structures and dislocation of the pharyngeal structures (red arrow). D. T2-weighted axial MR image 7 months after the treatment shows restored position of the pharynx .

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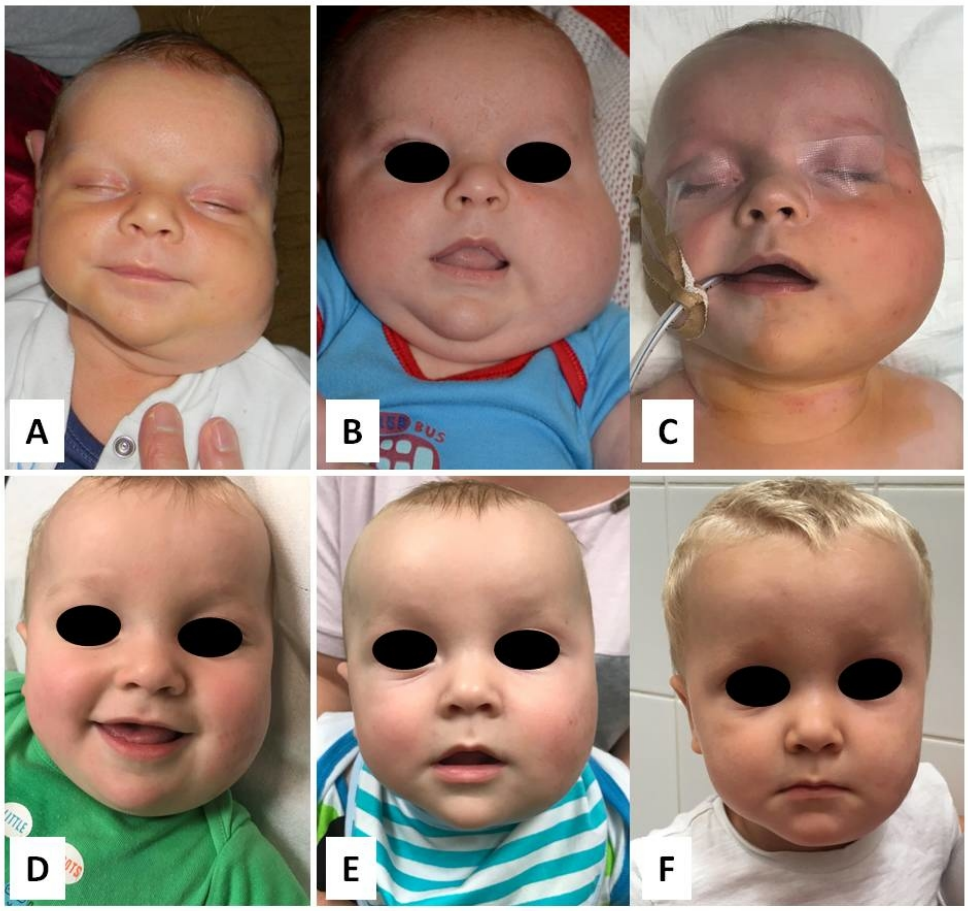


Photos of the patient: A. One week old: soft-tissue mass on the left side of the neck and cheek. B. Two months old: rapidly growing combined lymphangioma. C. Four months old, at the time of ECT. D. Nine months old, 5 months after ECT: significant decrease of the malformation. E. Eleven months old, 7 months after ECT: further volume decrease. F. Sixteen months old, 1 year after ECT: symmetry of the face is restored.

164x161mm (150 x 150 DPI)