Annals of Medicine and Surgery 81 (2022) 104531

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Case Series

Treatment of lymphangiomas by means of sclerotherapy with OK-432 (Picibanil®) is safe and effective – A retrospective case series

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ARTICLE INFO

Keywords:
Congenital cystic lymphangiomas
Lymphatic malformations
OK-432
Sclerotherapy
Case series

ABSTRACT

Introduction: Congenital cystic lymphangiomas (CCL) or lymphatic malformations (LMs) are benign malformations due to a developmental disorder of lymphatic vessels. Besides surgical excision, sclerosant therapy of these lesions by intracavitary injection of OK-432 (Picibanil®), a lyophilized mixture of group A Streptococcus pyogenes, is a common therapeutical option.

Methods: In a single center retrospective study we analyzed 37 consecutive patients (30 children, 3 adolescents and 4 adults) who were diagnosed with lymphangioma and subsequently treated with OK-432 (Picibanil®) in a general hospital between October 2000 and November 2021.

Results: The median follow-up period was 2.5 months (range 0.7–56.7 months). The lymphangiomas were localized in the head and neck region (n = 25), the thorax/abdomen (n = 6) and extremities (n = 6). The majority of patients had 1 injection with OK-432 (n = 28), five patients had 2 injections, three patients had 3 injections and one patient had more than 3 injections. The most common complications were swelling (89%), fever (81%), redness at the injection site (81%) and pain (73%). The response to therapy was excellent or good in 32 patients (86.4%), 2 patients had a medium response and 3 patients did not show any response. The clinical reaction after the instillation of OK-432 is not predictive for the quality of outcome.

Conclusion: The application of Picibanil is safe and without serious side effects. Parents and patients prefer local sclerotherapy versus surgery as it has less complications. We therefore suggest that Picibanil sclerotherapy should be the first-line treatment for macrocystic and mixed type lymphangiomas.

1. Introduction

Lymphatic malformations (LMs) are one type of vascular malformations and consist of masses of abnormal lymphatic vessels that occur in one out of 2000–4000 live births [1,2] and frequently involve the head and neck, oral cavity/pharynx, thorax and/or mediastinum. Occasionally they affect vital functions, frequently they cause disfigurement. They can be characterized as macrocystic (diameter >1 cm), microcystic (diameter <1 cm) or mixed cystic lesions [2,3]. On the basis of their histological appearance, lymphangiomas are classified as capillary, cavernous or cystic and contain dilated lymphatic vessels in size ranging from small channels to large cysts. Often the lesions are a combination of these subtypes and may also contain hemangiomatous components.

The principal goal of LM management is restoration or preservation of functional and aesthetic integrity. The standard treatment of lymphatic malformations has been ablative with variable success, sometimes necessitating multiple treatments and long-term management [3–5]. All treatment is based on a thorough initial assessment to detect the degree of functional impairment and/or disfigurement. When there is no significant functional deficit, treatment can be delayed well past infancy. Treatment timing relative to the age of the patient is somewhat debatable. LMs of small dimensions, without functional impairment or cosmetic disfigurement, do not necessarily require treatment. The possibility of spontaneous regression in low-stage macrocystic LM suggests that observational monitoring may also be appropriate in children with asymptomatic cervical LM, although this option is rare [6].

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https://doi.org/10.1016/j.amsu.2022.104531
Received 30 June 2022; Received in revised form 23 August 2022; Accepted 27 August 2022
Available online 2 September 2022
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Even small LMs can suddenly and impressively expand in size in the setting of intra-LM hemorrhage, infection or trauma. Extensive cervicofacial LMs have the potential for aerodigestive tract compromise, in addition to causing long-term sequelae such as mandibular distortion, dental malocclusion and speech impairment [7]. Complete and meticulous surgical excision is the textbook recommendation for the primary approach to lymphangiomas. However, complete excision is often impossible due to the risk of damage to vitally or functionally important surrounding structures. In addition, the cosmetic outcome after such radical surgery may be unacceptable, especially in children. To avoid complications of surgical therapy, several treatment options, including laser therapy, interferon alpha, propranolol, rapamycin, Kampo medicine and various intralesional sclerosing agents such as hypertonic saline, ethanol, bleomycin and OK-432 have been used to treat lymphangiomas.

OK-432 (Picibanil, Chugai Pharmaceutical Co., Ltd. Tokyo, Japan) is a freeze-dried biological product that is prepared from the Su strain of Streptococcus pyogenes (group A) by treatment with benzyl-penicillin and heat. Heating in the presence of penicillin at 37 °C for 20 min and 45 °C for 30 min increases the antitumor activity of the Su strain and eliminates its toxin-producing capacity. Since OK-432 is not subjected to further treatment, such as isolation, extraction or purification, the bacterial cells remain intact. However, proliferative activity is lost and streptococcal infection does not occur when it is administered to humans. Klinische Einheit (KE) is used as a unit of measurement for OK-432 doses. One KE corresponds to 0.1 mg of freeze-dried streptococci containing approximately 1×10^8 cells [8].

In Japan, OK-432 was approved as an immunotherapeutic agent for cancer by the Ministry of Health and Welfare in 1975. In the initial stage of development, OK-432 was considered to induce direct inhibition of RNA synthesis in tumor cells. Other reports of a direct action on tumor cells also appeared, but currently the main action is considered to be via stimulation of host immunity [7]. Its good efficacy in infantile LMs was first confirmed by Ogita et al., in 1987 [9]. The mechanism of OK-432 remains confined within the malformations after injection and stimulates lymphatic endothelial cells, resulting in obliteration of lymphatic channels with minimal local fibrosis [10].

In lesions which are near to the aero-digestive tract the patient must be closely observed in the postoperative period and the medical staff has to be aware of the possibility of local compression due to swelling. Also it is important to be aware of the possibility of allergy to benzylpenicilline.

2. Material and methods

2.1. Registration

The study was descriptive and conducted in accordance with the principles stated in the Declaration of Helsinki. It is registered at https://www.crd.york.ac.uk/prospero (UIN:CRD42022331779 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=331779) [11].

2.2. Ethical approval

The use of register data followed the General Data Protection Regulation of the European Union and was approved by the ethics committee of the government of Austria (EK – Number: S2022-07).

2.3. Material and methods

In a single center retrospective case series study we analyzed 37 consecutive patients (30 children, 3 adolescents and 4 adults) who were diagnosed with lymphangioma and subsequently treated with OK-432 (Picibanil®, Chugai Pharmaceutical Co, Tokyo) in a general hospital between October 2000 and November 2021.

We included in our study patients with macrocystic and mixed type lymphangioma. Patients with microcystic type lymphangioma were excluded.

The diagnosis was made by ultrasound or ultrasound and MRI in combination. The patients had no relevant comorbidities and did not need pre-surgical stabilization.

The procedures were performed either in general anesthesia (first choice) or in local anesthesia by the same two senior surgeons and a senior radiologist. Under sterile conditions and under ultrasound guidance one or more cysts were punctured and drained and afterwards an equivalent refilling of the cysts with 0.02–0.2 mg OK-432 (0.01 mg/ml in normal saline solution) was carried out (Fig. 1a and Fig. 1b).

The majority of patients had 1 injection with OK-432 (n = 28), five patients had 2 injections, three patients had 3 injections and one patient had more than 3 injections.

In the postoperative period the patients were observed for complications for one to three days in the hospital.

The patients were observed for a median time of 2,5 months after the last OK-432 injection (range 0.7–56,7 months).

For the interpretation of the results we used the Acevedo classification, according to which excellent results mean complete regression of the lymphangioma, good results if regression is more than 50%, poor results if regression is under 50% and no response [2].

We also wanted to show if the symptoms after treatment with OK-432 had a prognostic value for the outcome. All data regarding the patients was collected in an anonymized form.

Data were expressed as mean and range. Statistical analysis was performed using Fisher's exact test. A P value of less than .05 was considered statistically significant.

This case series has been reported in line with the PROCESS Guideline [12].

3. Results

There were no changes in the planned interventions. The median age in our study group was 6.9 years (range 0.5–39.9 years). The median follow-up period was 2.5 months (range 0.7–56.7 months). The lymphangiomas were localized in the head and neck region (n = 25), on the thorax/abdomen (n = 6) and extremities (n = 6).

The most common complications after treatment were signs of inflammation (fever (81%) for a few days, swelling (89%), redness at the injection site (81%) and pain (73%) for up to some weeks postoperatively). There was no airway obstruction complication because of the injection treatment.

Eight patients (21.6%) had an excellent response to therapy, 24 patients (64.8%) had a good response, 2 patients (5.4%) had a poor response and 3 patients (8.1%) did not show any response (Fig. 2a and Fig. 2b).

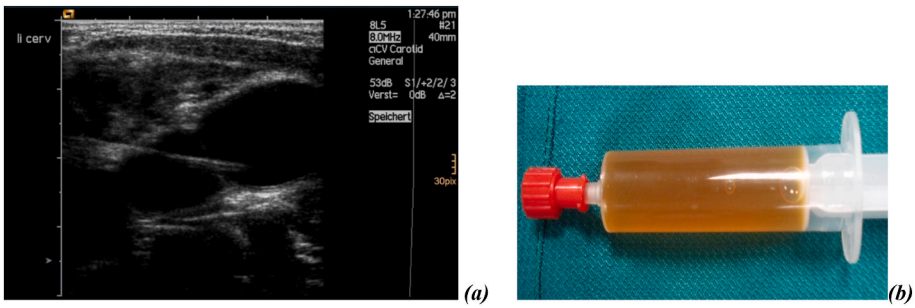
A Fisher's exact test showed that there was no statistical association between the symptoms after the injection and excellent/good outcome ($P < .05$).

4. Discussion

Lymphangiomas may cause marked disfigurement, recurrent infections, respiratory obstruction, malocclusion, dysphagia, dysphonia and dysarthria as a result of the infiltration and compression of neighbouring structures. Spontaneous regression is rare and sometimes followed by recurrence [13].

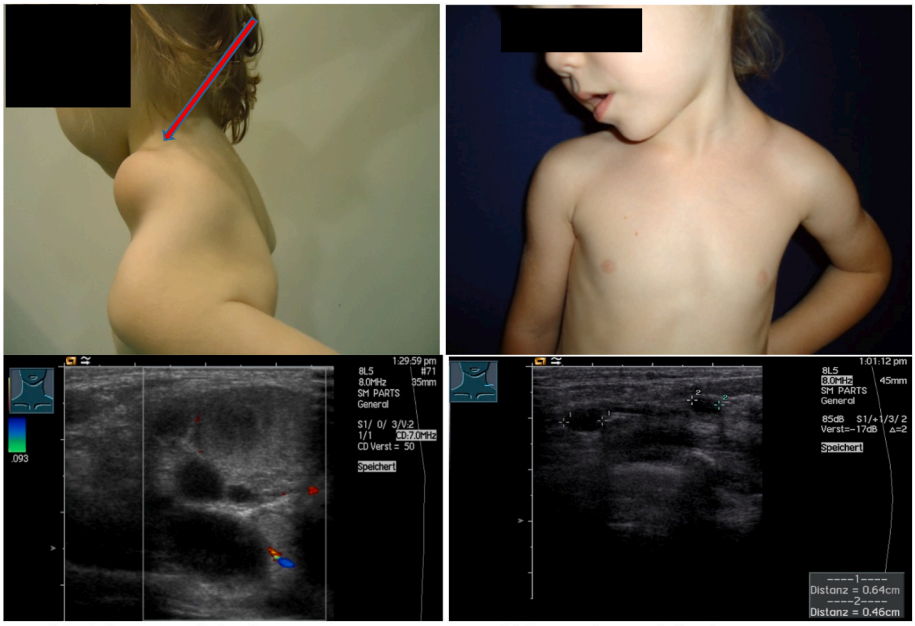
Histologically, these lesions are composed of dilated lymphatic vessels with one or two endothelial layers, with or without an adventitial layer. These dilated lymphatics can vary in size, depending on the location and surrounding tissues, representing the basis for classification. Cystic hygromas arise from lymphatic tissue in areas where expansion can occur. Cavernous lymphangiomas are found in areas such as the tongue and floor of the mouth.

In most cases diagnosis is not difficult. The neoplasms are usually



(a) *(b)*

Fig. 1. Ultrasound injection of OK -432 into lymphangioma (a), after aspiration (b).



(a) 4 days post-injection *(b)* 2 month post-injection

Fig. 2. 4-year-old girl with near complete regression at 2 months post-injection of OK-432.

characterized by the presence of a soft, compressible and ill-defined mass. The anterior triangle of the neck has been indicated as the most common site. Cystic hygroma may be localized in the parotid area, and is the second most common congenital mass of this area [13].

Ultrasound and MRI can be used to define the relationship of the lesion with the neighbouring structures and to help plan therapeutic strategies.

After Ogita reported the results of OK-432 sclerotherapy in lymphangioma in 1987, many reports around the world have concluded that OK-432 is a safe and effective treatment modality for lymphatic malformations. Also OK-432 can be used after surgery in case of recurrence of the lymphangioma. It was also used to treat a wound–healing impairment with good results [14].

Furthermore, many physicians have administered OK-432 sclerotherapy to ranula and branchial cysts and achieved successful results.

It has been reported that OK- 432 injection could provide a regression of lesions in up to 96% of patients [15].

In a study released by Protara Therapeutics in May 2022 they did a retrospective analysis in which they included 246 patients from a Phase 2 randomized study, and 275 patients from an open-label study. The majority of participants in both studies were six months to 18 years of age. In the first study, patients were randomized 2:1 to receive treatment immediately (immediate treatment group [ITG]) or delayed by six months (delayed treatment group [DTG]). In the open-label study, patients received four doses of OK-432 approximately six weeks apart. The primary efficacy endpoint was clinical success (defined as complete [90%–100%] or substantial [60%–89%] reduction in LM volume measured radiographically) in the ITG versus spontaneous resolution of the LM in the DTG. Efficacy was assessed two weeks post-treatment in the randomized study, and one to six months post-treatment in the open-label study.

Approximately 69% of patients in the randomized study ITG achieved clinical success after six months, while only 7.5% of patients in the DTG showed spontaneous resolution of LMs in the same time period ($p < 0.0001$). 73.1% of patients in the open-label study achieved clinical success.

In the randomized and open-label studies, 10 of 219 (4.6%) and 5 of 275 (1.8%) subjects, respectively, were reported to have treatment emergent serious adverse events that were assessed by the investigator as related to study drug. The most severe adverse events (SAE) were airway obstruction and facial paralysis due to swelling post-injection that required tracheostomy and hospitalization. Both of these events were reported as resolved. One SAE related to OK-432 led to discontinuation (proptosis of the eye). Local/systemic reactions peaked in the first few days and resolved within two weeks.

Patients were followed for up to three years post treatment with no significant safety concerns [16].

OK-432 seems to be safer and more effective than other sclerosing agents such as boiling water, hypertonic saline, ethanol, tetracycline, cyclophosphamide, sodium morrhuate, and bleomycin [14].

In a review study of 1876 MEDLINE articles by Acevedo et al. random-effects modeling revealed 43% of patients undergoing OK-432 for lymphangiomas achieved a complete/excellent response, 23.5% achieved a good response, 16.9% achieved a fair/poor response, and 15.4% observed no response. In the bleomycin group, the results were: 35.2% excellent, 37.1% good, 18.4% fair/poor, and 11.6% no response. Seven major complications were noted out of the 289 patients in the series, including two mortalities. They concluded that sclerotherapy for head and neck lymphangiomas achieves excellent/good clinical response in a majority of patients, with few complications, and anecdotally does not complicate future surgery [2].

A study by de De Maria et al. in which they searched PubMed, MEDLINE and Embase from 2000 to 2018 for studies evaluating the safety and efficacy of percutaneous sclerotherapy of head, face, and neck lymphatic malformations analyzed 25 studies reporting on 726 patients. The overall rate of complete cure of any pathologic type of lymphatic malformations after percutaneous sclerotherapy with any agent was 50.5%. Macrocystic lesions had a cure rate of 53.1% compared with cure rates of 35.1% for microcystic lesions and 31.1% for mixed lesions. Regarding agents, doxycycline had the highest cure rate (62.4%) compared with all other agents. Overall permanent morbidity or mortality was 1.2% (95% confidence interval, 0.4%–2.0%) with no deaths [17].

In a study by Olimpio et al. the authors concluded that no single sclerosing agent showed superiority over the other agents [18].

Although the complication rates after treatment with these sclerosing agents have been minimal, limited success and unpredictable local scarring, as well as systemic side effects caused by spread of the agents beyond the endothelial lining of the lesion, have been observed. Bleomycin, in particular, can cause serious side effects, including fibrosis of the lung [19,20].

On review of the literature, there were reports about bleomycin toxicity and hypersensitivity. In Niramis's study, leukopenia was noted in 3 patients below one year of age, which might be caused by bleomycin toxicity, and the author suggested the dosage of bleomycin should be reduced in infants [21].

Bleomycin hypersensitivity is a rare emergency. Until now, there was one reported case of pulmonary toxicity following 1.2 mg/kg single session dose in an 8-month-old infant. Therefore, it is essential to avoid injecting the drug into blood vessels and give close observation in the first 24 h, especially in infants [22].

However, until now, it has reached a consensus that bleomycin is a safe sclerosant because there were no complications when no more than 15 U in adults or 0.5 U/kg per session in children and a cumulative dose $<$90 U in adults or 6 sessions of 0.5 U/kg in children were administrated [23,24].

Yang et al. conducted a study on 65 patients with cervicofacial lymphangiomas. They found that intralesional bleomycin A5 was reasonably effective in shrinking both macrocystic and microcystic LMs. More than 81% of the macrocystic lesions and nearly 63% of the microcystic lesions exhibited greater than 90% size reduction. Only 2 of the 65 lesions responded poorly to the treatment with less than 50% reduction [25].

The precise mode of action of OK-432 has not been fully understood, but it seems to be related to an immunomodulatory effect. Picibanil induces cytokines and activates many inflammatory cells, such as neutrophils, macrophages, lymphocytes and T-cells. The cytokines induce strong local inflammatory reactions in the cyst wall, resulting in fluid drainage, shrinkage, and fibrotic adhesion of the cyst [26]. During the early postinjection period, acute inflammatory cells (neutrophils and macrophages) predominate, but 4 days later activated lymphocytes and natural killer cells represent the majority and TNF and IL-6 levels are elevated. Another proposed mechanism is that picibanil induces apoptosis of the lymphatic endothelium. This hypothesis concurs with the finding that the local inflammatory reaction induced by picibanil does not involve the skin or cause scar formation. No necrosis is seen histologically although the OK-432 induces inflammation and activation of IL-6 and TNF alfa [27–29]. OK-432 can diffuse even into small cysts. This might explain why OK-432, unlike other sclerosing agents, has effect even on small-cystic LM.

OK-432 leads to complete or near-complete response in macrocystic lesions, with a lower degree of response in mixed, microcystic lesions or polycystic lesions, which concurs with our findings [30–34].

Which factors favor a good response or define a non-responder is unclear. Reismann concludes that a dynamic TLR4-expression may represent a predictive parameter [35].

Statistically, we could not confirm that a good reaction after the instillation of OK-432 with swelling, reddening, pain or fever is associated with an excellent or good outcome.

No major complications were encountered in our patients, the treatment was well tolerated and with no local scarring and it had a high rate of excellent/good response (86.4%), so that in our hands it is the first-line therapy in the treatment of lymphatic malformations. Parents and patients prefer local sclerotherapy versus surgery as it has less complications.

The limitations in our study were the relatively small number of cases, but this has to be attributed to the rarity of the pathology and the fact that patients with microcystic type of lymphangioma were excluded.

Directions of future research should be a multicentric study to address the limitations in the current study. Also future research should involve a search for new predictive parameters that can guide future therapies and predict which patients can benefit from a specific type of treatment.

5. Conclusion

Sclerotherapy of lymphatic malformations with OK-432 achieves excellent to good clinical response in the majority of patients. The application is safe and without serious side effects. Swelling, redness at the injection site, low-grade fever and pain are to be expected after the therapy with OK-432. Symptoms after injection do not correlate with the outcome.

A low recurrence rate and good response to repeated injections in recurrent or primary failed cases yielded good long-term response. To summarize, we found that Picibanil is a good sclerotherapeutic agent with only minor complications and high long-term efficacy for lymphangioma. We therefore suggest that Picibanil sclerotherapy should be the first-line treatment for macrocystic and mixed type lymphangiomas.

Ethical approval

Ethical approval was given by the Ethikkomission Kärnten.
EK – Number: S2022-07.

Please state any sources of funding for your research

Nothing to declare.

No funding or grant support. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

Author contribution

Guenter Fasching: Data curation, Formal analysis, Conceptualization, Methodology, Reviewing and Editing, Project administration, Supervision, Christine Dollinger: Data curation, Formal analysis, Investigation, Stephan Spendel: Data curation, Investigation, Narcis Flavius Tepeneu: Investigation, Data curation, Formal analysis, Writing, Reviewing and Editing.

Registration of research studies

1. Name of the registry: PROSPERO
2. Unique Identifying number or registration ID: CRD42022331779
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=331779

Guarantor

Guenter Fasching.

Patient consent

Written informed consent for the treatment was obtained in every single patient. Consent to publish the article was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Ethical approval was given by the Ethikkomission Kärnten
Reference number EK – Number : S2022-07

Please state any conflicts of interest

Nothing to declare.
There are no conflicts of interest.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104531.

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