

Cross-sectional study comparing different therapeutic modalities for cystic lymphangiomas in children

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OBJECTIVE: Here, we describe our experience with different therapeutic modalities used to treat cystic lymphangiomas in children in our hospital, including single therapy with OK-432, bleomycin and surgery, and a combination of the three modalities.

METHODS: We performed a retrospective, cross-sectional study including patients treated from 1998 to 2011. The effects on macrocystic lymphangiomas and adverse reactions were evaluated. Twenty-nine children with cystic lymphangiomas without any previous treatment were included. Under general anesthesia, patients given sclerosing agents underwent puncture of the lesion (guided by ultrasound when necessary) and complete aspiration of the intralesional liquid. The patients were evaluated with ultrasound and clinical examinations for a maximum follow-up time of 4 years.

RESULTS: The proportions of patients considered cured after the first therapeutic approach were 44% in the surgery group, 29% in the bleomycin group and 31% in the OK-432 group. These proportions were not significantly different. Sequential treatment increased the rates of curative results to 71%, 74% and 44%, respectively, after the final treatment, which in our case was approximately 1.5 applications per patient.

CONCLUSION: The results of this study indicate that most patients with cystic lymphangiomas do not show complete resolution after the initial therapy, regardless of whether the therapy is surgical or involves the use of sclerosing agents. To achieve complete resolution of the lesions, either multiple operations or a combination of surgery and sclerotherapy must be used and should be tailored to the characteristics of each patient.

KEYWORDS: Lymphangioma; Cystic; Picibanil; Bleomycin.

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■ INTRODUCTION

Lymphangiomas (LMs) are congenital malformations that occur in one in every 6000 births. Sixty percent of these malformations can be observed at birth, and 80%-90% do not arise until the patient reaches 2 years of age. Spontaneous resolution is very rare and expectant treatment is not recommended (1,2).

The most relevant classification system is the one that takes into account the size of the cysts. Using this system, lesions can be classified as macrocystic (cysts greater than 1 cm), microcystic (when most of the cysts are smaller than 1 cm), or mixed (2-7). This classification has clinical

implications because microcystic lymphangiomas appear to be less responsive to clinical treatments such as sclerotherapy.

Histologically, LMs are thin-walled vessels lined with lymphatic endothelial cells, which are immunopositive for podoplanin and lymphatic vessel endothelial hyaluronan receptor (LYVE-1) (8-10). LMs can be empty or filled with a serous fluid containing macrophages and lymphocytes.

Seventy to eighty percent of LMs typically occur in the cervico-facial region; they are observed less frequently in the axilla and thorax. The two main complications of LMs are intralesional bleeding and infections. The best diagnostic tool to establish a differential diagnosis with other cystic lesions of the neck is magnetic resonance imaging (MRI), although ultrasound (US) is commonly used to confirm the presence of a macrocystic LM.

Classical treatment consists of surgical excision with an attempt to preserve the nervous and vascular structures involved. However, this is not always possible because damage to these structures may occur during surgery and postoperative events such as fistula formation, infection and

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wound dehiscence may develop. Surgical mortality may be as high as 2% to 6%. Postoperative recurrence is described in up to 27% of patients (11,12). The limitations of surgical treatment led to the development of other forms of therapy, such as the application of sclerosing agents (SAs) aiming to obtain total or partial regression of the lymphangioma (13-17).

Sclerotherapy involves entering the cystic cavity by direct puncture, aspirating the fluid and injecting the SA. Several sessions may be required regardless of the SA used. In our department, we prefer to use US guidance to inject the SA. This therapeutic modality is also not free of complications, the most common of which are skin necrosis, local neuropathy and, in rare cases, dose-dependent cardiopulmonary toxicity.

Several SAs, such as ethanol, sodium tetradecyl sulfate and doxycycline have been tested; however, the two most extensively investigated SAs are bleomycin and OK432 (18-19).

Although published reports tend to attribute a better sclerosing effect to OK432, the statistical significance of this finding has not been demonstrated due to the lack of comparative studies.

The purpose of this report is to present the results of cervicofacial LM treatment in children using three different therapeutic modalities in a single Brazilian institution.

PATIENTS AND METHODS

Patients

This retrospective, descriptive, cross-sectional study included patients treated at our hospital from 1998 to 2011. Twenty-nine children with cystic lymphangiomas without any previous treatment were included.

The characteristics of the 29 patients included in the study are presented in Table 1.

All patients underwent a careful clinical examination that included measurement of the lesion and evaluation of possible complications, such as infection or bleeding. US was used to characterize the lesion (macrocytic in all cases) and also to obtain a more accurate evaluation of its volume. All the parents agreed with the proposed treatment and postoperative evaluation. This study was approved by local Ethics Committee (CEP: 1225/2010).

Treatment

The decision regarding what treatment the modality to use was based on the surgeons' preferences and the availability of drugs in the hospital. Before 2002, surgery was considered the initial treatment for every case of LM. However, in more recent years, it has become preferable to

utilize SA as an initial treatment for every patient exhibiting macrocytic lesions. Surgery has been employed mainly to treat microcytic lesions and small lymphangiomas or as an adjuvant therapy to remove residual lesions.

Sclerosing technique

Under general anesthesia, patients underwent puncture of the lesion (US guided, when needed) and complete aspiration of the intralesional liquid. Either OK-432 (equivalent volume of aspirated liquid) or bleomycin (2 mg/ml solution administered at a dose of 0.5 mg/kg) was injected (Table 2).

The patients were evaluated postoperatively with serial clinical examinations and US was performed in the 6th and 12th postoperative weeks. All US procedures were performed by an independent radiologist who was blinded to the medication given to each patient. If the response to this initial therapeutic approach was considered partial or unfavorable, then the patient was selected to receive another dose of the same SA, to receive a dose of the other SA, or to undergo surgery. Patients were followed up every three months thereafter for a maximum follow-up time of up to 4 years.

Analysis

Data were collected regarding the outcome after the first therapeutic intervention and also after completion of treatment in the cases in which the LM did not respond to initial therapy and the patient had to undergo further treatment. Response to the treatment (reduction in volume), the occurrence of adverse reactions (inflammation, infection, necrosis) and recurrence were observed and recorded. The response was classified as favorable (more than 90% reduction of the lesion), partial (reduction of 10% to 90% of the lesion), or unfavorable (less than 10% reduction of the lesion).

The primary endpoint of the study was the reduction in lesion volume 6 and 12 weeks after treatment and the secondary outcome was the occurrence of adverse reactions.

Due to the small number of patients included, no attempt was made to perform any statistical analysis.

RESULTS

The response to the initial treatment was evaluated at 6 and 12 weeks and the results are depicted in Table 3. The proportions of patients considered cured (not needing any further procedures) after the first therapeutic approach were 44% in the surgery group, 29% in the bleomycin group and 31% in the OK-432 group. These proportions were not significantly different.

Sequential treatment increased the rates of curative results to 71%, 74% and 44%, respectively, after an average of 1.5 applications per patient (or 1.5 operations in the surgery group) (Table 4).

Table 1 - Characteristics of the patients.

	Surgery	OK-432	Bleomycin	Combined
Number of patients	7	9	4	9
Age (months)	24	31.3	17.75	7.2
Gender (M/F)	4/3	1/2	1/3	4/5
Size of the lesion	5.58	6.4	6.47	11.31
Location:				
Cervicofacial	1	8	3	6
Axillary	2	1	1	1
Limbs	3			
Trunk	1			2

Table 2 - Doses of sclerosing agents.

	OK-432	Bleomycin
Diluent	0.1 KE/ml	2 mg/ml
Dose	0.1 KE/ml aspirated liquid	0.5 mg/kg
Maximal dose	2 KE/injection	5 mg/kg

**Table 3** - Use of surgery or injection as the initial procedure in each patient.

	Surgery	Bleomycin	OK-432	TOTAL
Favorable	4 (44%)	2 (29%)	4 (31%)	10 (34%)
Partial	3 (33%)	4 (57%)	9 (69%)	16 (55%)
Unfavorable	2 (22%)	1 (14%)	0	3 (10%)
TOTAL	9	7	13	29

A group of nine patients received a combined treatment that included at least two of the treatment modalities. The success rate in this group of patients was 44%.

At this point in the evaluation, when considering all of the therapeutic modalities, 56% of the patients are considered cured, whereas 44% have persistent or residual lesions and are awaiting further therapy.

Complications

There were two instances of serious surgical complications involving injury to the hypopharynx in one case and injury to the carotid artery in another case. These complications were detected and promptly treated during the operation. No complications were associated with the use of OK-432 or bleomycin.

DISCUSSION

Bleomycin was first described as anti-tumor agent that functioned by inhibiting DNA synthesis in 1966 (20). Later, this drug was also shown to have an effect on sclerosing endothelial cells via a non-specific inflammatory reaction. In 1977 (21), bleomycin was used for the first time as an SA in lymphangioma. For better control and targeting of the drug, it was used in the form of microspheres in an oil emulsion in 1987 (22). The side effects of bleomycin sclerotherapy are described as minimal, aside from local swelling and inflammation. The most feared complication is pulmonary fibrosis, which has been reported when bleomycin is administered as chemotherapy for cancer in a much higher cumulative dose (450 mg) (23,24). For sclerotherapy of hygroma, previous authors have suggested a dose of less than 1 mg/kg for a duration of 2 weeks or more, with a total dose of 5 mg/kg (14).

OK-432, produced by lyophilization of *Streptococcus pyogenes* group A strains with low virulence that were treated in culture with penicillin G potassium, has also been used with favorable results (4,5,13,17). OK-432 was approved by the Japanese Ministry of Health for use as a biological response modifier. It was first used in clinical trials for the treatment of head and neck cancers in 1987; since then, it has been used in the treatment of lymphangioma (25) in 22 countries, including Japan. In Brazil, the use of OK-432 was approved by the Brazilian National Agency of Sanitary Control-ANVISA (26) in February 2009.

The clinical effect of OK-432 occurs via damage to the endothelium of lymphangiomas secondary to activation of the immune system. It has been demonstrated, both *in vitro* and *in vivo*, that OK-432 promotes the induction and augmentation of activated macrophages, NK cells and LAK cytotoxic T lymphocytes. Sclerosis is confined to the interior of the cysts without damaging the surrounding tissue. Due to this mode of action, the use of OK-432 does not appear to increase the difficulty of a subsequent operation to remove any residual lesion (9).

The most complete review of the literature comparing bleomycin with OK-432 was a meta-analysis performed in 2008 (16). The authors selected 22 papers reporting large series but could only find one prospective randomized study. The conclusions of this meta-analysis were as follows: OK-432 showed a tendency to be a better SA than bleomycin; however, there was no statistically significant difference between OK-432 and bleomycin. Seven serious complications occurred in seven different studies and two children died from pulmonary complications in the groups treated with bleomycin; however, a direct cause-effect relationship could not be demonstrated. Sclerotherapy appears safe; however, a small number of patients have developed acute respiratory failure requiring tracheostomy, regardless of the SA used. Apparently, this event is associated with the presence of bulky lymphangiomas possibly invading the chest.

Despite the low number of applications (average of 1.55 per patient), there were no unfavorable results among the patients receiving OK-432 as the sole therapy (Table 1), meaning that all patients have displayed at least a partial response. However, it should be noted that only 4 patients have reached complete remission of the lesion, whereas 5 are still under treatment and should receive additional treatment with OK-432 until they are considered cured. Data from the literature indicate that as many as 5 applications may be needed to achieve complete resolution. Additionally, in the bleomycin group, 3 out of 4 patients have shown a favorable response to treatment after one or two applications.

In our small sample, bleomycin did not lead to systemic complications, especially the most feared (in the case of overdose): pulmonary fibrosis.

Overall, forty-four percent of our patients are still waiting for some type of therapy (34% with partial results, 10% with poor results).

As previously stated, surgery was previously the first-line therapy for all lymphangiomas. With the introduction of sclerotherapy, surgical excision is now reserved either for the resection of remaining fibrotic tissue after sclerotherapy or, after an informed joint decision with the family, as a first-line therapy for lymphangiomas localized outside the cervicofacial region, where the risk of injuring nervous structures is smaller and the resulting scars less important from an aesthetic point of view.

Table 4 - Final response to treatment.

	Surgery	Bleomycin	OK-432	Combined	TOTAL
Favorable	5 (71%)	3 (75%)	4 (44%)	4 (44%)	16 (56%)
Partial	1 (14%)	0	5 (56%)	4 (44%)	10 (34%)
Unfavorable	1 (14%)	1 (25%)	0	1 (11%)	3 (10%)
TOTAL	7	4	9	9	29
Average number of surgeries/applications	1.57	1.5	1.55	3	2



The groups that included surgery as a therapeutic modality were the ones with a higher rate of poor outcome (surgery and combined groups). The less favorable results observed in patients undergoing surgery, especially in the cervicofacial region, may be attributed to the efforts to spare the neural and vascular structures that cross this anatomic region, which very often precludes the complete resection of this malformation. Overall, we encountered two serious intraoperative complications (one carotid lesion and one lesion of the hypopharynx) that were promptly corrected in the same operation.

In conclusion, despite the limitations inherent in a retrospective study including a small number of patients, the results of this study indicate that most patients with cystic lymphangiomas do not show complete resolution after initial therapy, regardless of whether the therapy is surgical or involves the use of SAs. To achieve complete resolution of the lesions, either multiple operations or a combination of surgery and sclerotherapy must be used and should be tailored to the characteristics of each patient. Although the number of patients is too small to draw any definitive conclusions, no single sclerosing agent showed superiority over the other agents. Prospective randomized clinical trials should be designed to investigate this issue.

AUTHOR CONTRIBUTIONS

Olimpio HO, Bustorff-Silva J and Oliveira Filho AG reviewed the data and wrote the manuscript. Araujo KC performed all the ultrasounds.

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