Review Article

Intralesional treatment of lymphatic malformations with emphasis on Picibanil (OK-432) sclerotherapy: a systematic review

Tratamento intralesional de malformações linfáticas com ênfase na escleroterapia com picibanil (OK-432): revisão sistemática

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■ **ABSTRACT**

Introduction: We performed a retrospective systematic review of studies reporting the use of Picibanil for treatment of lymphatic malformations (LMs). **Methods:** We searched the PubMed database for available studies, including those published between January 1990 and April 14, 2013. The search strategy involved the use of the keywords "OK-432" or "Picibanil" and "lymphatic malformation." Information was compiled regarding the reported mechanism of action, indications, contraindications, efficacy, administration, side effects, complications, and advantages and disadvantages compared to those of other modalities. **Results:** Forty-four studies were found, of which 27 fulfilled the inclusion criteria. Picibanil is a lyophilized preparation of a low-virulence strain of *Streptococcus pyogenes* inactivated with penicillin G. Its mechanism of action is unclear, but it has been speculated that it causes a controlled inflammatory response with adhesion of cyst walls. Picibanil is almost unanimously indicated for the treatment of macrocystic LMs, which show a greater effectiveness response compared to that shown by microcystic or mixed LMs. Picibanil is usually administered by puncturing, either with direct visualization or guided by ultrasound, with the patient under general anesthesia. The most widely used preparation comprises 0.1 mg of Picibanil in 10 mL of saline. Side effects are mostly mild, with pain, swelling, and fever being the most frequently reported. **Conclusion:** The studies had low scientific evidence. A systematic review found that Picibanil is useful against any LM, with better results in macrocystic lesions. Efficacy was comparable to that of other therapies. No specific contraindication was presented. Although the mechanism of action has not been established, the inclusion of Picibanil as a treatment option is warranted.

Keywords: Lymphatic abnormalities; Therapeutics; Sclerotherapy; Picibanil; *Streptococcus pyogenes*.

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■ **RESUMO**

Introdução: Conduziu-se revisão sistemática retrospectiva da literatura incluindo estudos relatando o uso de picibanil para tratar malformações linfáticas (ML). **Métodos:** A pesquisa foi realizada com estudos publicados no PubMed de janeiro de 1990 a 14 de abril de 2013. Na estratégia de busca, usou-se os descritores "OK-432" ou "Picibanil" e "lymphatic malformation". Os seguintes elementos foram comparados aos de outras modalidades relatadas e, então, compilados: mecanismo de ação, indicações, contraindicações, eficácia, administração, efeitos colaterais, complicações, vantagens e desvantagens. **Resultados:** Foram encontrados 44 estudos, 27 dos quais atenderam aos critérios de inclusão. O picibanil é uma preparação liofilizada de uma cepa de baixa virulência de *Streptococcus pyogenes* inativada pela penicilina G. Seu mecanismo de ação ainda não definido claramente, mas especula-se que provoque uma resposta inflamatória controlada com adesão das paredes dos cistos. O picibanil é indicado quase que unanimemente para o tratamento da ML macrocística, cuja resposta é mais efetiva do que em lesões microcísticas ou mistas. Em geral, o picibanil é administrado por meio de punção com visualização direta ou guiada por ultrassonografia, com o paciente sob anestesia geral. A preparação comumente utilizada consiste em 0,1 mg de picibanil em 10 ml de soro fisiológico. Os efeitos colaterais são, em geral, leves; sendo dor, inchaço e febre os mais frequentemente relatados. **Conclusão:** Os estudos apresentam pouca evidência científica. A revisão sistemática identificou que o picibanil é útil no tratamento da ML de qualquer tipo, mas tem resultados melhores em lesões macrocísticas. A eficácia foi comparável à de outras terapias. Não foi apresentada nenhuma contraindicação específica. Embora o mecanismo de ação ainda não tenha sido determinado, o picibanil trata-se de opção de tratamento.

Descritores: Anormalidades linfáticas; Terapêutica; Escleroterapia; Picibanil; *Streptococcus pyogenes*.

INTRODUCTION

Lymphatic malformation (LM), previously known as lymphangioma or cystic hygroma, is a relatively uncommon congenital vascular anomaly[1,2]. The literature describes this condition as a benign hamartomatous lesion involving the skin and subcutaneous tissue, or as a benign cystic mass arising from abnormal development of lymphatic vessels[1-5].

More than half of LMs (50-75%) are clinically present at birth, but symptoms often become more evident during childhood. According to Zhou et al.[6], 80-90% of cases not noticeable at birth are diagnosed around the age of 2 years.

LMs are commonly found in the cervicofacial region (75% of cases). The tongue, lips, oral mucosa, and neck are the mainly affected sites[3,4,6]; other frequently affected sites are the axilla and mediastinum[2,5].

LMs are histologically characterized by cysts of varying size, constituted by endothelial cells and filled with lymphatic fluid[2]. The International Society for the Study of Vascular Anomalies (ISSVA) classification divides LMs into macrocystic, microcystic and mixed lesions. Clinically, LMs present as translucent lesions but may have a reddish or yellowish appearance when mucosal compromise occurs. In addition, lymphatic cysts may contain blood or purulent secretion when accompanied by bleeding or infection[6].

In addition to physical disfigurement, impairment of lymphatic flow in LMs can cause severe dysfunction[2,4,5]. Their progressive growth may cause compression of adjacent vital structures such as the trachea, major vessels, and nerves[1,6]. When present in thoracic or abdominal spaces, LMs can trigger effusions and ascites, eventually leading to respiratory failure[1].

Treatment of LMs includes a variety of procedures based on interventional radiology or surgery. There is no consensus regarding the most effective approach for all clinical presentations. However, intralesional agents seem to be at least less invasive than surgical options.

Several sclerosing agents have been used in the intralesional approach, including hypertonic glucose solution, ethanol, quinine, doxycycline, sodium morrhuate, corticosteroids, bleomycin, and Picibanil. The most commonly used agents nowadays are doxycycline, bleomycin, ethanol, and Picibanil.

Picibanil, also known as OK-432 (Chugai Pharmaceutical Co. Ltd., Japan), is a lyophilized preparation of a low-virulence strain (SU) of *Streptococcus pyogenes* (also known as *S. hemolyticus*) inactivated by heating with penicillin G. This drug was originally used as a non-specific immunostimulant in the treatment of malignancies, and especially in digestive and pleural tumors associated with ascites and hydrothorax[2,6,7].

Picibanil is not commercially available worldwide and is not currently approved by the US Food and Drug Administration (FDA). It has been studied in Europe, Japan, and South America, and has been recommended by some groups as a primary treatment for LMs owing to its ease of application, absence of scarring, and reduced aggression to adjacent structures[2,6,7]. However, the exact mechanism of action of this drug has not been fully elucidated[2].

The available trials are mostly case series using individual protocols. Consequently, these studies present low levels of scientific evidence, inhibiting a safe recommendation for this treatment method. Systematic review represents an important and useful methodology to provide more consistent data about the efficacy and safety of Picibanil use for the management of LMs.

The main purpose of this study was to perform a systematic review of studies reporting the use of Picibanil for treatment of LMs, including its mechanism of action, indications, contraindications, efficacy, administration, side effects, complications, advantages and disadvantages.

METHODS

The present study was approved by the Ethical Research Committee of the University of Sao Paulo Medical School (approval number 045/14).

A systematic review of studies available in PubMed database was performed, including those published between January 1990 and June 2014. The search strategy used the keywords: "OK-432" or "Picibanil" and "lymphatic malformation."

The inclusion criteria were:

- Articles included case reports, case series, comparative studies, original articles and reviews;
- Articles were available in their entirety;
- Articles were published in English;
- Articles dealt with intralesional treatment of soft tissue LM.

For each study and when available, information on the mechanism of action, indications, contraindications, efficacy, administration, side effects, complications, and advantages and disadvantages compared to other treatment options, was collected and analyzed.

RESULTS

Forty-four studies were found according to the search strategy and 27 fulfilled the inclusion criteria. The excluded studies did not have full text available (7 studies), were not written in English (1 study), or were outside the scope of this study (9 studies).

1. Definition: what is Picibanil?

Picibanil, produced exclusively by Chugai Pharmaceuticals (Tokyo, Japan)[8], is a preparation from a low virulence strain of *Streptococcus pyogenes* group A of human origin, pre-treated with benzylpenicillin G and heated. This lyophilized preparation loses its ability to produce streptolysin and consequently its toxic activities, but retains immunopharmacological properties responsible for LM retraction[2,3,6,7]. Different definitions and classifications of Picibanil have been reported and are described in Table 1.

Picibanil is also known in the literature as OK-432. It is noteworthy that although most authors preferentially use the "OK-432" nomenclature (19/21 articles), both terminologies ("OK-432" and "Picibanil") are presented in all the articles we reviewed (Table 1).

2. Mechanism of action

Treatment with Picibanil was introduced by Peter et al. in 1987, and according to these authors it has been shown to be a safe therapeutic modality, since adverse events are less frequent than with surgery[2,9].

The exact mechanism of action of Picibanil is not yet fully understood, but it is assumed to cause a controlled inflammatory response with cytotoxic effects leading to fibrosis, collapsing of the LM walls, cyst obstruction, and resolution[3,8]. The effect on the wall cysts is considered a sclerosing effect. Picibanil has been used in LM treatment based on its sclerosing

Table 1. Definitions of medication and nomenclatures used in cited articles.

Author	Preferential nomenclature	Definition
Boardman et al.[8] (2010)	OK-432	Sclerosant developed from a low-virulence strain of group A *Streptococcus pyogenes*
Breugem and Courtemanche[12] (2008)	OK-432	Lyophilized biological preparation containing cells of human-derived, low-virulence strain of group A *Streptococcus pyogenes* incubated with benzylpenicillin
Cabrera and Redondo[10] (2004)	OK-432	Preparation of human-derived *Streptococcus pyogenes* (group A, type III) with benzylpenicillin
Chen et al.[21] (2011)	OK-432	Sclerosing agent comprising lyophilized *Streptococcus pyogenes* incubated with penicillin
Claesson and Kuylenstierna[14] (2002)	OK-432	Streptococcal derivate
García et al.[7] (2012)	OK-432	Lyophilized substance of low virulence from *Streptococcus pyogenes* group A
Gilony et al.[23] (2012)	OK-432	Immunomodulator derived from low-virulence *Streptococcus pyogenes*
Giguère et al.[25] (2002)	OK-432	Lyophilized mixture of a low-virulence strain of group A *Streptococcus pyogenes* incubated with benzylpenicillin
Lin et al.[17] (2007)	OK-432	Lyophilized biological preparation containing cells of human-derived, low-virulence strain of group A *Streptococcus pyogenes* incubated with benzylpenicillin
Luzzatto et al.[26] (2000)	OK-432	A streptococcal derivative
Mello-Filho et al.[15] (2002)	OK-432	Lyophilized biological preparation of human-derived *Streptococcus pyogenes*, group A, type 3, treated with benzylpenicillin
Närkiö et al.[2] (2011)	OK-432	Biological preparation of *Streptococcus pyogenes* (group A, type 3) strain lyophilized and inactivated by benzylpenicillin
Ono et al.[1] (2010)	OK-432	Preparation of inactivated *Streptococcus pyogenes*
Peters et al.[13] (2006)	OK-432	Lyophilized mixture of group A *Streptococcus pyogenes* incubated with benzylpenicillin
Poldervaart et al.[3] (2009)	OK-432	Low-virulence strain of group A *Streptococcus pyogenes* of human origin treated with benzylpenicillin G and heating
Weitz-Tuoretmaa et al.[27] (2014)	OK-432	Preparation with lyophilized low-virulent group A *Streptococcus pyogenes* incubated with benzylpenicillin
Wheeler[16] (2004)	OK-432	Heat- and benzylpenicillin-treated preparation of human-derived *Streptococcus pyogenes*, presented as a lyophilized powder
Zhou et al.[6] (2011)	OK-432	Biologic preparation of lyophilized powder containing *Streptococcus pyogenes* strain cells (group A, type 3) treated with benzylpenicillin potassium

action[7], and is recommended as an elective treatment by many authors[2].

According to published studies, Picibanil administration produces an increase in natural killer cells, lymphokine-activated killer (LAK) cells, and even CD3 lymphocytes and macrophages. Furthermore, it is believed that this drug stimulates release of interferons (alpha, beta and gamma), TNF (tumor necrosis factor) and interleukins (IL1, IL2, and IL6)[1-3]. The combination of these factors increases the endothelial permeability of LMs and favors lymphatic drainage. Consequently, the cystic spaces become empty, leading to collapse and

Table 2. OK-432 mechanism of action described in the literature.

Author	Mechanism of action
Boardman et al.[8] (2010)	Gives rise to an intracystic acute inflammatory event with cytotoxic effects, subsequent fibrosis, and resolution
Cabrera and Redondo[10] (2004)	Diffusion through the stroma results in irritation and inflammation, promoting retraction and scar contracture of the lesion
Claesson and Kuylenstierna[14] (2002)	Increases permeability of cystic endothelial walls, which will shrink the cysts. Necrosis is histologically absent although OK-432 induces inflammation and activation of necrotizing cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha; increase of plasmin activity
García et al.[7] (2012)	Increases production of inflammatory cells, natural killer cells, CD3, interferon gamma, and interleukin-6, causing increased permeability of the endothelium and lymphatic drainage. Cystic spaces empty and collapse
Gilony et al.[23] (2012)	Stimulates an inflammatory response that causes local inflammation, resulting in regression of the lesion
Giguère et al.[25] (2002)	Effect by immunostimulation
Luzzatto et al.[26] (2000)	Destruction of the epithelium lining the cystic spaces, with subsequent decrease in lymph fluid production and collapse of the cysts
Mello-Filho et al.[15] (2002)	Anaphylatoxins and chemotactic factors cause inflammatory reaction - exchanging cell populations and activating natural killer cells - production of cytokines and interleukins, and endothelium, causing the lesion to diminish
Närkiö et al.[2] (2011)	Induces systemic immune response, with increased serum leukocyte count, elevated serum levels of IP-10 and C-reactive protein
Ono et al.[1] (2010)	Induces an inflammatory response at the site of injection, leading to sclerosis and occlusion of the sites of lymphatic leakage. Alternatively, OK-432-induced inflammation could lead to increased resorption/drainage of lymph fluid
Peters et al.[13] (2006)	Substance has been shown to remain confined within the malformation and to obliterate lymphatic channels without significant fibrosis
Poldervaart et al.[3] (2009)	A controlled inflammatory reaction that causes the walls of the lymphatic malformation (LM) to collapse
Weitz-Tuoretmaa et al.[27] (2014)	Induces a systemic inflammatory response; several cytokines, i.e., IL-6, -8, -12, interferon (IFN)-gamma, and TNF-alpha are produced locally in LM lesions and serum immune protein (IP)-10 levels are shown to increase after sclerotherapy. The exact sclerosing mechanism of OK-432 has not yet been completely clarified.
Wheeler[16] (2004)	Causes an inflammatory response on the endothelium lining of the cyst. Cellular content of the cysts changes from predominantly lymphocytes to predominantly neutrophils, with increased expression of TNF and IL-6. The cysts sclerose and involute as a result of this process.
Wiegand et al.[24] (2013)	Shrinkage of the cysts seems to be related to an immunomodulatory effect
Zhou et al.[6] (2011)	OK-432 remains confined within the malformations after injection and stimulates lymphatic endothelial cells, resulting in obliteration of lymphatic channels with minimal local fibrosis

sclerosis, resulting in a decrease in lesion size[7,10]. Other studies claim that Picibanil's action remains confined within the lesion and consists of a non-specific immunostimulation, which includes activation of endothelial cells, resulting in obliteration of lymphatic channels with minimal local fibrosis[6]. Table 2 summarizes the information regarding the mechanism of action of this drug.

3. Indications

Picibanil was unanimously indicated in macrocystic lesions. Studies that exclusively use this drug in microcystic injuries are less common in the literature. Among the 23 clinical or meta-analytical studies, 19 contained information on indication for Picibanil use, and it was indicated exclusively for the treatment of macrocystic lesions in 248 patients, for isolated microcystic LM in 92 patients, and for mixed lesions in 27 cases (Table 3). Patients usually present complete resolution or favorable responses to treatment in macrocystic LM, irrespective of lesion size. While some authors report poor outcomes in microcystic LMs[10-16], others claim that repeated Picibanil injections can achieve good results[1,14].

Table 3. OK-432 indication according to lymphatic malformation classification.

Author	Publication year	Study	LM subtype		
			Macro	Micro	Mixed
Arenas et al.[18]	2011	Case report		1	
Boardman et al.[8]	2010	Retrospective case series		Not informed	
Chen et al.[21]	2011	Retrospective case series	1		
Churchill el al.[5]	2011	Review article		16	9
Claesson et al.[14]	2002	Prospective case series	18	4	10
García et al.[7]	2012	Case report	1		
Gilony et al.[23]	2012	Retrospective case series	14	5	1
Giguère et al.[25]	2002	Prospective randomized trial and case series	21	5	4
Hong et al.[4]	2009	Case report		1	
Lin et al.[17]	2007	Retrospective case series			2
Luzzatto et al.[26]	2000	Prospective	7	5	3
Melo-Filho et al.[15]	2002	Retrospective case series	5		1
Närkiö-Mäkelä et al.[2]	2011	Prospective case series	10	7	
Ono et al.[1]	2010	Case report		2	
Peters et al.[13]	2006	Retrospective case series	8	4	
Poldervaart et al.[3] (a)	2009	Review article		48	
Poldervaart et al.[3] (b)	2009	Review article	111		
Ravindranathan et al.[9]	2008	Retrospective case series	2		3
Stefini et al.[22]	2012	Case report	1		1
Weitz-Tuoretmaa et al.[27]	2014	Prospective, follow-up	33	1	2
Wheeler et al.[16]	2004	Retrospective case series		Not informed	
Wiegand et al.[20]	2009	Prospective case series		Not informed	
Wiegand et al.[24]	2013	Prospective case series		Not informed	
Total			248	92	27

LM: lymphatic malformation.

4. Contraindications

The use of Picibanil is formally contraindicated in patients with a history of allergy to beta-lactams due to risk of anaphylactic reactions[7,10]. Surprisingly, this contraindication was only mentioned in eight of 27 studies (29.2%).

Some authors consider that a lack of effective response after several injections is considered a contraindication for future attempts. Hong et al. stated that if after three attempts no response is observed, a contraindication for further injections is defined[4].

5. Effectiveness

Ogita .[11] first confirmed the successful treatment of LMs with Picibanil in 1996. Several studies have demonstrated the great efficacy of this drug, particularly for the treatment of macrocystic LM[12]. Macrocystic LM patients generally exhibit good or complete response to treatment, with resolution regardless of the size of the lesion[13]. On the other hand, patients with microcystic or mixed LM (macro- and microcystic) do not show satisfactory results[13]. Lymphatic-venous malformations also showed poor response when compared with pure LM[13].

Claesson and Kuylenstierna[14] described their experience in the treatment of 32 LM patients (28 children, three teenagers and one adult). The results were excellent in all 28 macrocystic LM patients, except for one, who had previously been treated with ethanol. Moreover, none of the four patients with microcystic LMs required additional therapy, and, for two of them, results were considered excellent. An additional study by Wheeler et al.[16] conducted a chart review of seven children undergoing Picibanil therapy. Four children had lesions involving the axilla and/or chest wall, two had involvement of extra-mylohyoid neck tissues and only one child had an LM involving the tongue, floor of the mouth and an extra-mylohyoid component. The authors concluded that macrocystic lesions showed excellent

response to Picibanil therapy but that the effectiveness for microcystic lesions was disappointing.

Mello-Filho et al.[15], performed a retrospective study of six children diagnosed with head and neck LM treated with Picibanil. The most frequently encountered type was macrocystic LM. All patients showed regression of the mass and in three patients there was complete resolution.

In 2006, Peters et al.[13] reported a series of 12 patients, of whom six had macrocystic malformations and six microcystic or mixed venous-lymphatic malformations. Ten abnormalities were located in the head and neck and the remaining two in the extremities. All patients with macrocystic abnormalities showed complete resolution or good response to treatment with Picibanil, without additional treatment. In contrast, those with microcystic malformations or mixed lymphatic-venous lesions responded poorly. Interestingly, the size and location of the lesion did not correlate with treatment response.

Poldervaart et al.[3] performed a literature search of studies in English with five or more LM patients who had never been treated before. The results showed that 27% of microcystic LM patients showed an excellent result (i.e. more than 90% regression); 33% a good result (reduction by more than 50%) and 40% a poor outcome (less than 50% reduction). In contrast, studies dealing with macrocystic LM showed 88% excellent results. Similarly, Churchill et al.[5] conducted a literature review of LM treatment with Picibanil sclerotherapy in pediatric patients (n = 318 cases). Sixty-six percent of patients with macrocystic lesions had excellent results with sclerotherapy, while only 23% of patients with microcystic lesions showed the same results.

Although LM is congenital and usually located in the cervicofacial region, satisfactory responses could be observed in any location, including large retroperitoneal lesions, without limitation with respect to age[10] (Table 4).

Ono et al.[1] reported successful Picibanil treatment of two patients with microcystic LM and pleural effusion or ascites. In the first case, a newborn had a large microcystic LM occupying the abdominal cavity, surrounding the portal vein and extending to the retroperitoneum. At 5 months of age, the child developed a large pleural chylous effusion and ascites that was drained, and 0.1 mg of Picibanil (10 mL) was injected through the drainage tube into the abdominal cavity and into the pleural cavity through thoracoscopy.

The ascites and pleural effusion gradually decreased over the next two months. After six months, the child showed no pleural effusion or ascites, despite the persistence of abdominal microcystic LM. The second case was a 26-year-old patient who presented chylous ascites and diffuse microcystic LM in groin and thigh. Through laparoscopy, 0.1 mg Picibanil (10 mL) was injected directly into the retroperitoneal LM. The chylous ascites resolved completely after 2 months and the patient remained stable without ascites for five years[1].

Although the above studies support the efficacy of OK-432, evidence for its effectiveness has not been gathered from randomized controlled trials. There is no study that objectively evaluates success, for instance by an observer who is independent from the treating physician, to increase clinical evidence.

6. Administration

Skin testing for beta-lactam allergy is recommended before administration[6].

In children, the procedure is usually performed under general anesthesia[3,12] and the most widely used preparation is 0.1 mg of Picibanil mixed with 10 mL of saline[3,10,11]. Airway patency must be maintained by endotracheal intubation during sclerotherapy of extensive cervicofacial LMs involving the tongue, floor of mouth, soft palate, or parapharyngeal region, because edema may develop and obstruct the airway[6].

The most widely used access is ultrasound-guided direct puncture. After the contents of the lesion are aspired, the needle (gauge 7)[6] must be left in place for injection of the same volume of Picibanil solution[3,12]. This injection is usually performed at different points and in different directions until cystic expansion is achieved. Most studies advocate not exceeding a total amount of 20 mL[6,10]. Table 5 describes the average number of applications, doses and indication for tracheal intubation.

According to García et al.[7], a new treatment session, when indicated, is performed between 3 and 6 weeks after the first procedure. The dose is increased to 0.3 mg (30 mL). Afterwards, if additional treatment is necessary, the appropriate interval is 1-1.5 months. Other authors who suggest a therapeutic dose of 0.02 mg of Picibanil suggest a second dose of the same amount, after 10-15 days.

Picibanil use in microcystic LM is controversial since there are reports of unsuccessful results in the treatment of this kind of lesion[12]. Other authors, however, claim that repeated intralesional Picibanil injections achieve good results[6]. In these cases, the injection is not considered fully intracystic and Picibanil effects can occur within the microcysts or in the lesion interstitium.

7. Side effects and complications

Reported side effects can be categorized as local or systemic (Table 6). Pain, swelling and erythema with

Table 4. OK-432 use and effectiveness according to lesion locations.

Author, year	n	Localization	Previous treatment	Concurrent treatment	Lesion reduction	Evaluation method	Relapse
Arenas et al.[18], 2011	1	Cervicofacial = 1	No	No	Small or none = 1	Magnetic resonance imaging (MRI)	No
Boardman et al.[8], 2010	37	Cervicofacial = 37	Not informed	Surgery (number of patients not reported)	Not informed	Clinical	Not informed
Chen et al.[21], 2011	15	Cervicofacial = 15	No	Fibrin glue and bleomycin	Complete = 7; partial = 8	Computed tomography (CT)	No
Churchill el al.[5], 2011	318	Cervicofacial = 326; trunk = 38; limbs = 99	Not informed	Not informed	Complete = 178; partial = 88; small or none = 52	MRI or CT	No
Claesson et al.[14], 2002	32	Not specified	Aspiration only (2); ethanol and laser (2); multiple surgeries (1)	Not informed	Complete = 26; partial = 5; small or none = 1	MRI or CT	No
García et al.[7], 2012	1	Cervicofacial = 1	No	No	Small or none = 1	CT	No
Gilony et al.[23], 2012	20	Cervicofacial = 19; limbs = 1	Not informed	No	Complete = 9; partial = 10; small or none = 1	Clinical and ultrasound (US)	No
Giguère et al.[25], 2002	30	Cervicofacial = 29; limbs = 1	Not informed	Surgery (3)	Complete = 17; Partial = 4; small or none= 8; Spontaneous regression = 1	MRI or CT	Not informed
Hong et al.[4], 2009	1	Cervicofacial = 1	Surgical reduction of macroglossia (2)	Not informed	Partial = 1	MRI	1
Lin et al.[17], 2007	2	Cervicofacial = 2	No	No	Complete = 2	Clinical and CT	No
Luzzatto et al.[26], 2000	15	Cervicofacial = 11; Trunk = 4	Surgery (5)	Surgery (2), after OK-432 treatment	Complete = 7; Partial = 3; small or none = 5	Not specified	1
Melo-Filho et al.[15], 2002	6	Cervicofacial = 6	Not informed	Not informed	Complete = 4; partial = 2	MRI, CT, and/ or US	No
Närkiö-Mäkelä et al.[2], 2011	17	Cervicofacial = 17	No	No	Complete = 7; partial = 8; small or none = 2	Clinical	No
Ono et al.[1], 2010	2	Trunk = 2	Diuretic; short-chain triglycerides	Not informed	Complete = 1; partial = 1	MRI	1
Peters et al.[13], 2006	12	Cervicofacial = 10; limbs = 2	No	Não	Complete = 4; partial = 2; small or none = 6	Clinical	Not informed
Poldervaart et al.[3] (a), 2009	48	Cervicofacial = 46; trunk = 40; limbs = 32	No	Não	Complete = 13; partial = 16; small or none = 19	Not specified	Not informed
Poldervaart et al.[3] (b), 2009	111	Cervicofacial = 111; trunk = 165; limbs = 160	No	Não	Complete = 98; partial = 9; small or none = 4	Not specified	Not informed
Ravindranathan et al.[9], 2008	5	Cervicofacial = 5	Sclerotherapy sessions	Fibrovein injection	Partial = 4; small or none = 1	MRI, CT, or radiography	1

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Table 4. OK-432 use and effectiveness according to lesion locations.

Stefini et al.[22], 2012	2	Cervicofacial = 2; trunk = 1	Surgical excision and laser	No	Partial = 1; small or none = 1	Not specified	1
Weitz-Tuoretmaa et al.[27], 2014	36	Cervicofacial = 27; Trunk = 9	Surgery (2)	No	Complete = 24; partial = 7; small or none = 5	MRI	2
Wheeler et al.[16], 2004	7	Cervicofacial = 2; trunk = 5	Not informed		Complete = 3; partial = 3; small or none = 1	MRI	1
Wiegand et al.[20], 2009	1	Cervicofacial = 1	Not informed	Not informed	Not informed	Not specified	Not informed
Wiegand et al.[24], 2013	1	Cervicofacial = 1	No	No	Partial = 1	Clinical	1

3-7 days duration are frequently reported[2,6,12]. Almost all patients experience a slight degree of hyperthermia (38-39 °C) up to 6 hours after injection, which improves after 2-4 days. In the literature review conducted by Poldervaart et al.[3] in 2009, almost all patients (48) had fever (38-39 °C) associated with local inflammation and lethargy after treatment. These adverse events disappeared in about one week.

Other complications have been also described, including cervical cellulitis and proptosis requiring urgent decompression, cervical abscess requiring surgical drainage and injury to adjacent nerves, and skin necrosis over the LM[9]. When cystic cavities are very small, the sclerosing agent can be injected, imperceptibly, into surrounding tissue. Extravasation may also be inevitable and may ultimately produce damage to nerves and adjacent healthy tissues[17].

Segado Arenas et al.[18], in 2011, reported a case of a tongue microcystic LM in a five-year-old boy, still in an early stage of Picibanil infiltration, who presented with severe diffuse edema, progressive obstruction of the upper airway, and respiratory distress, requiring emergency tracheal intubation. The authors concluded that although Picibanil injections are considered safe and effective as a treatment of choice for LM, local edema with potentially fatal airway compromise should be considered.

Although advantageous for its ease of application and absence of scarring, local inflammatory reactions make Picibanil controversial for specific sites[7].

DISCUSSION

Lymphatic malformations are defined as low-flow vascular malformations. Microcystic, macrocystic and mixed subtypes have different behaviors in response to various treatment options. Outdated descriptive terms as cystic hygroma, lymphangioma or cavernous malformations must be avoided.

Microcystic LM has a large amount of fibrous connective tissue between small cysts. It tends to be more diffuse, poorly defined, with digitiform protrusions into adjacent tissues. It is difficult to treat by sclerotherapy or to remove completely by surgery. Macrocystic LM tends to be better defined and often responds better to sclerotherapy, regardless of the affected area.

LMs are most commonly located in the cervicofacial region. De Serres et al.[19] proposed a classification for cervicofacial LM with therapeutic implications, correlating location and severity.

De Serres Classification:

- Stage 1: Unilateral Infrahyoid;
- Stage 2: Unilateral Suprahyoid;
- Stage 3: Unilateral Suprahyoid and Infrahyoid;
- Stage 4: Bilateral Suprahyoid.

The tongue, lips, oral mucosa and oral floor are mainly affected[20]. Special attention should be given to extensive lesions involving the floor of the mouth, oropharynx and neck, which may compromise airway patency either by their anatomic location or as a consequence of management. Delayed[21] tracheal intubation is advocated by some authors after sclerotherapy for extensive microcystic LM to overcome the expected airway obstruction caused by inflammatory edema[3,6,12].

The evolution of LM can lead to macroglossia, tongue protrusion, bone deformities, and orthodontic abnormalities such as mandibular prognathism, malocclusion and esthetic deformities. Functional impairment of breathing, chewing, swallowing and speaking as well as psychological problems can occur as a consequence. LMs are unstable lesions, and can grow rapidly after infection, trauma, radiation therapy, bleeding or changes in hormonal levels.

Spontaneous remission has been described in the literature, but can be followed by recurrence. Hence, the most judicious approach is to indicate a treatment modality that has a rapid and effective response.

Historically, treatment for LM was limited to surgical excision. Although this treatment is reasonably

Table 5. Administration - number of applications, dose used, and need for intubation.

Author	N	Average number of sessions per patient	Dose per administration (mg)	Endotracheal intubation (ETI) and general anesthesia
Arenas et al.[18], 2011	1	1	Not informed	0
Boardman et al.[8], 2010	37	Not informed	0.1-0.2	37
Chen et al.[21], 2011	15	1	2.0-6.0 (average 3.6)	0
Churchill el al.[5], 2011	318	Not informed	0,1-0,5	0
Claesson et al.[14], 2002	32	3	0,1-0,2	0
García et al.[7], 2012	1	1	0,02	1
Gilony et al.[23], 2012	20	1.85	(1-3 kilo equivalents)	0
Giguère et al.[25], 2002	30	2.33	0.1mg/10ml (max. 20 ml)	30
Hong et al.[4], 2009	1	15	Not informed	Not informed
Lin et al.[17], 2007	2	2	0,1	2
Luzzatto et al.[26], 2000	15	3	0.1-0.2 mg/dose	0
Melo-Filho et al.[15], 2002	6	2.5	0,1	0
Närkiö-Mäkelä et al.[2], 2011	17	1.9	0,1	17
Ono et al.[1], 2010	2	2	0,1	0
Peters et al.[13], 2006	12	Not informed	0,1	1
Poldervaart et al.[3], 2009	159	Not informed	0.1 (recommendation)	0
Ravindranathan et al.[9], 2008	5	2.6	Up to 0.5 ml/kg (average = 38.4 ml)	5
Stefini et al.[22], 2012	2	4.5	Not informed	1
Weitz-Tuoretmaa et al.[27], 2014	36	2.5	0.01 mg/ml (max. 10 ml)	2 (tracheostomies - TCT)
Wheeler et al.[16], 2004	7	3.43	0,015	0
Wiegand et al.[20], 2009	1		0,1	7
Wiegand et al.[24], 2013	1	1	Not informed	Not informed
Zhou et al.[6], 2011	Not applicable	Not applicable	0.1-0.3 (recommendation)	Not applicable
Total	720	2.947		101 (103 ETI +TCT)

effective, poor lesion demarcation, close association with adjacent vital structures, high recurrence rates and risk of complications motivated the development of less invasive approaches[22-24].

Thus, the development of therapeutic alternatives, in recent decades, is important. Although several sclerosing agents have been described, Picibanil has emerged in the literature as an effective option with regard to LM sclerotherapy. Picibanil and OK-432 have been used as synonyms in almost all studies, but the term OK-432 predominates.

The exact mechanism of action remains unclear since the hypotheses can be pooled into two partially contradictory theories that need to be better clarified: increased endothelium permeability causing drainage or absorption of cystic contents[7,10]; and endothelium response by obliteration or sclerosis of malformed lymphatic channels with minimal fibrosis[3,6,7,8].

Patients who do not show complete resolution after sclerotherapy with Picibanil are candidates for surgery. Picibanil pretreatment does not compromise surgical dissection. Since there is no method that can provide optimal lymphatic malformation treatment with full resolution in 100% of cases, multimodal therapy, including a combination of sclerotherapy and surgery, should be available as a treatment option.

Reported adverse events after Picibanil sclerotherapy are less frequent, compared with surgery or other sclerosing agents. However, the published studies have a low level of evidence. Prospective controlled trials are necessary to define the real status of long-term effects and efficacy[25-27].

Damage to nerves and adjacent tissues may occur when treating microcystic LMs by sclerotherapy. Tissue ischemia and neurotoxicity does not appear to occur with Picibanil. Transient changes in facial nerve function following Picibanil application have been reported after injections in the parotid region. Stretching and compression of nerve branches are considered the causative mechanisms[17]. Overdose effects related to absorption of Picibanil, such as cardiotoxicity, are rare but have been described.

Table 6. Complications and side effects after Picibanil use.

Author	N	Number of patients with side effects and/or complications	Reported side effects	Complications
Arenas et al.[18], 2011	1	1	-	Severe diffuse edema and airway obstruction
Boardman et al.[8], 2010	37	4	Pain and local edema	-
Churchill et al.[5], 2011	318	-	Fever, pain, and edema	Intracystic hemorrhage, airway obstruction, and infection at the site of puncture
Claesson et al.[14], 2002	32	32	Fever and local inflammation	-
García et al.[7], 2012	1	1	Local inflammation and edema	Intralesional hemorrhage
Gilony et al.[23], 2012	20	-	Fever and inflammation	Local infection
Giguère et al.[25], 2002	30	30	Erythema, swelling, discomfort at the site of the injection, and pyrexia	Proptosis secondary to intracystic hemorrhage 4 weeks after injection (1), cervical cellulitis (1), and stridor and impending airway obstruction with urgent tracheostomy needed (1)
Hong et al.[4], 2009	1	1	-	Intralesional hemorrhage
Lin et al.[17], 2007	2	2	Edema and mild fever	-
Luzzatto et al.[26], 2000	15	15	Fever and local inflammation	Feeding tube needed because of cervical swelling (1)
Melo-Filho et al.[15], 2002	6	6	Fever and hyperemia	-
Närkiö-Mäkelä et al.[2], 2011	17	17	Fever and edema	Peritonsillar abscess
Peters et al.[13], 2006	12	-	Fever and edema	Airway obstruction, dysphagia, arthralgia, intubation, and tracheostomy
Poldervaart et al.[3] (a), 2009	48	48	Local edema	Intralesional hemorrhage
Poldervaart et al.[3] (b), 2009	111	111	Local edema	Respiratory distress, intralesional hemorrhage, cellulitis, stridor and airway obstruction, and dysphagia
Ravindranathan et al.[9], 2008	5	3	Intralesional edema	-
Weitz-Tuoretmaa et al.[27], 2014	36	36	Local swelling and fever	-

It is noteworthy that this review presents important limitations for the generalization of findings, since most studies consist of case reports, retrospective studies and literature reviews, which do not allow for statistical evaluation of all collected data. However, this represents the extent of the literature currently available to support discussion and practice.

Although studies have individually shown little scientific evidence, this systematic review finds that Picibanil can be used in any lymphatic malformation, although better results are seen in macrocystic lesions, with reported efficacy comparable and even superior to other treatment modalities. No specific contraindication has been presented and, while the mechanism of action is not yet perfectly established, the inclusion of this drug as a treatment option is warranted.

COLLABORATIONS

OHGP Analysis and/or interpretation of the data; statistical analysis; final approval of the manuscript; formulation of the hypotheses and study design; performance of the surgeries and/or experiments; manuscript preparation and critical review of the content.

DCG Analysis and/or interpretation of the data; statistical analysis; final approval of the manuscript; formulation of the hypotheses and study design; performance of the surgeries and/or experiments; manuscript preparation and critical review of the content.

RG Final approval of the manuscript; critical review of its contents.

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