Otolaryngology–Head and Neck Surgery (2009) 140, 120-123

ORIGINAL RESEARCH–PEDIATRIC OTOLARYNGOLOGY

OK-432 sclerotherapy in head and neck lymphangiomas: Long-term follow-up result

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INTRODUCTION: Nonsurgical treatments, such as sclerotherapy have been attempted for head and neck lymphagiomas. Of the available sclerosing agents, picibanil has shown satisfactory short-term treatment results in many studies, but no study has presented long-term treatment results. Accordingly, in the present study, the authors retrospectively reviewed the long-term treatment results of picibanil sclerotherapy.

MATERIALS AND METHODS: Fifty-five lymphangioma patients who underwent picibanil sclerotherapy were enrolled. Data about initial and long-term response, recurrence, and excision rate were collected.

RESULTS: Initial response rates were 83.5 percent and long-term response rates were 76.3 percent.

CONCLUSION: Initial and the long-term response rate were equally good for lymphangioma.

Surgical excision is regarded as the treatment of choice for head and neck lymphangiomas. However, these lesions sometimes present otolaryngologists with challenging conditions. Although they are benign in most cases, they frequently infiltrate adjacent structures, such as, vessels and nerves,[1,2] which makes total resection difficult; furthermore, surgeons are often confronted with serious complications, such as bleeding, wound infection, nerve damage, and recurrence.[3] Accordingly, other nonsurgical methods with less morbidity have been attempted to treat these lesions like radiation, diathermy, cryotherapy, and sclerotherapy. However these methods have achieved only limited success and have introduced other complications, such as fever, inflammations, and other systemic side effects. Furthermore, the use of sclerosing agents sometimes causes unpredictable scarring due to the penetration of adjacent tissues, to the extent that subsequent surgery is difficult or impossible.

Recent reports have revealed that OK-432, a lyophilized mixture of low-virulence group A *Streptococcus* containing penicillin G potassium, could be useful for the treatments of lymphangioma and that it has minimal adverse effects. However, reports on this topic are limited and contain no information about long-term follow-up results.[4-8] Accordingly, we reviewed the long-term treatment results of picibanil sclerotherapy.

MATERIALS AND METHODS

We retrospectively reviewed 55 patients who underwent picibanil sclerotherapy for head and neck lymphangiomas at Seoul National University Hospital from January 1993 through August 2006. Demographics are described in Table 1. Diagnoses were confirmed by computed tomography (CT) or magnetic resonance imaging (MRI), or both. Once a diagnosis had been made, cystic content aspiration and picibanil sclerotherapy were performed in an outpatient clinic, except for some (n = 12) pediatric patients who required general anesthesia due to poor cooperation. Picibanil was prepared by diluting 0.1 mg picibanil in 10 ml normal saline solution. If the volume of aspirate was less than 30 ml, this was replaced with the equal quantity of the diluted picibanil. The maximum volume of picibanil used was 30 ml regardless of the amount of fluid aspirated from a lesion. When a lesion was composed of several noncommunicating cavities (multiple microcystic lesions), 1 to 2 ml of picibanil solution was injected into each cavity grossly or using ultrasonography. Cyst size reductions were evaluated at one month after the final injection and if the size reduction was insufficient, we repeatedly injected picibanil. Temporary mild fever and a local heating sense were observed in most cases during the first 48 hours after final injection. We assessed initial and long-term responses. Long-term follow-up was defined as more than 2.5 years after final injection. This study was approved by the institutional review board of Seoul National University Hospital.

Received September 7, 2008; revised October 13, 2008; accepted October 15, 2008.

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doi:10.1016/j.otohns.2008.10.026

Table 1
Demographic findings

	Number	M	F	Mean age (y)	Follow-up duration duratop duration (mo)
Lymphatic malformation	55	27	28	11 (0.2~34)	63 (30~144)

RESULTS

For initial response analyses, "complete response" was defined as no lesion at inspection by palpation or by imaging studies, and "near complete" was defined as grossly no lesion at inspection but a minimal remaining lesion by palpation or imaging studies. We defined "marked" as a marked decrease in size of more than one half, and "partial" as a decrease of less than one half at palpation, by inspection, or by imaging (Table 2). For analyses of long-term follow-up results, we classified patients in four groups, namely, the complete response group, the symptomless group, the symptom group, and the excision group. We defined "marked to complete response" as grossly no lesion at inspection or by palpation or imaging. "Symptomless follow-up" was defined as a decrease in mass size of less than one half at palpation, inspection, or by imaging and without symptoms. Symptom group members included subjects with symptoms (neck discomfort, swallowing difficulty, disfigurement of face, dyspnea) or a remnant mass. and excision group members underwent surgery regardless of response to sclerotherapy (Table 3).

Table 2
Classification of initial response

Response	Definition
Complete response	No lesion at inspection, palpation, or imaging studies
Near complete response	Grossly no lesion at inspection but minimal remaining lesion by palpation or imaging studies
Marked response	Decrease in size of more than one half
Partial response	Decrease of less than one half
No response	no change or increase in size

After initial treatment, we analyzed initial responses to sclerotherapy. Success was defined as better than partial response. Success rates was 83.5 percent (46 of 55) (Fig 1). We assessed reductions in mass sizes after weeks to months. If mass size did not decrease after 2 to 3 months, we injected picibanil repeatedly. Picibanil was applied up to three times when a cyst showed no response, and when a cyst showed more than partial response, we injected picibanil until patients complained of no clinical symptom or discomfort. Consequently sclerotherapy was performed from 2 to 7 times, and the mean injection number was 2. Periods between injections ranged from 2 weeks to 3 months. We also investigated response rate of repeated injections, which was 83 percent (19 of 23 patients).

Excision was performed when injections produced no response or patients complained about the remaining mass or symptoms or firming requested surgery. Excision after picibanil injection resulted in some difficulties such as adhesion with adjacent tissues and bleeding during surgery but total removal of mass was possible in all cases. Excision rates was 8.7 percent (5 of 55).

We analyzed success rates on the basis of mass septation and location. Unilocular lesions showed more than partial response in 94 percent of cases, multilocular lesions were treated successfully in 69 percent of cases ($P = 0.08$) (Fig 2). According to cyst size, macrocystic lesions showed more than partial response in 92 percent of cases, while microcystic lesions were treated successfully in 62 percent of cases ($P = 0.10$) (Fig 3). With respect to lymphatic malformation locations, lesions located below mylohyoid muscle (deSerres classification type I) were treated successfully in 77.8 percent of cases, whereas masses located above mylohyoid muscle (type II) or of the mixed type (type III) were treated successfully in only 21.7 percent and 20.3 percent of cases, respectively ($P = 0.002$, below mylohyoid muscle versus others).

Table 3
Classification of long-term response

Response	Definition
Marked to complete response	Grossly no lesion at inspection, palpation, or imaging studies
Symptomless follow-up	Decrease of less than one half at palpation, inspection, or imaging studies and without symptom
Follow-up with symptom	Remaining persons such as who had symptoms or remnant mass
Operation	People who received operation regardless of the repose to the sclerotherapy

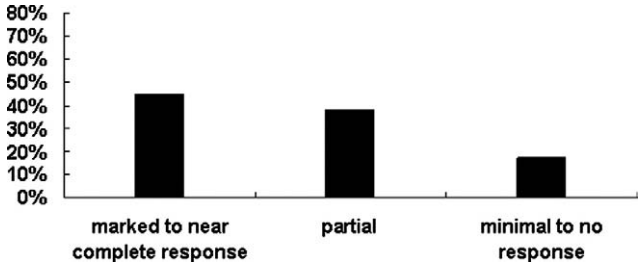

Figure 1 Initial response to OK-432 sclerotherapy.

After long-term follow up, 30 (54.8%) of 55 patients showed marked to complete response and 12 (21.7%) were asymptomatic during follow-up.

DISCUSSION

After Ogita reported the results of OK-432 sclerotherapy in lymphangioma in 1987,[4] many reports[4-11] have concluded that OK-432 is a safe and effective treatment modality for lymphatic malformations. Furthermore, many physicians have administered OK-432 sclerotherapy to ranula and achieved successful results.

The precise mode of action of OK-432 has not been fully established, but it seems to be related to an immunomodulatory effect.[6,7] Picibanil induces cytokines, such as, IFN-γ, IL-1 and IL-2, or TNF, and activates many inflammatory cells, such as, neutrophils, macrophages, lymphocytes, and T-cells. 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.[8] Another proposed mechanism is that picibanil induces apoptosis of the lymphatic endothelium.[12] This hypothesis concurs with the finding that the local inflammatory reaction induced by picibanil does not involve the skin or cause scar formation.

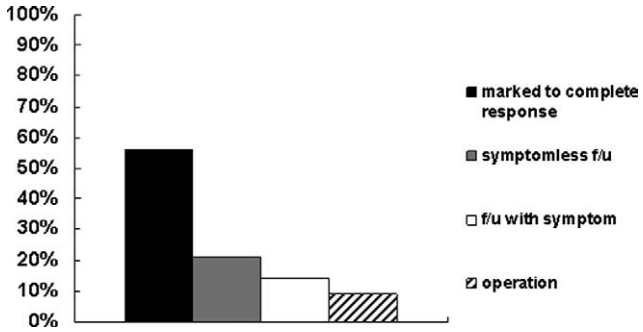

Figure 2 Response according to septation.

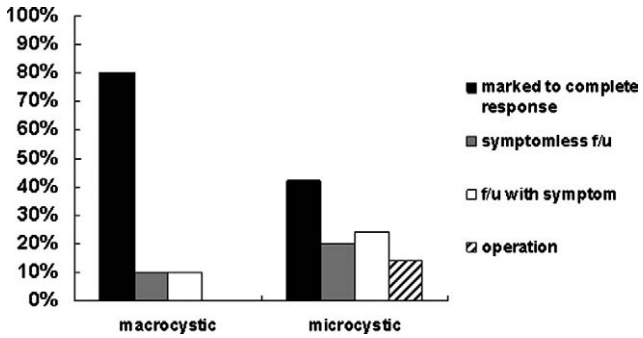

Figure 3 Response according to cyst size.

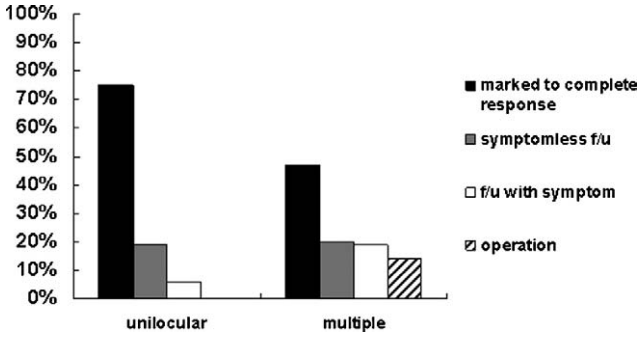

Figure 4 Long-term follow-up result of OK-432 sclerotherapy.

Previous studies have shown that macrocystic lesions respond well to sclerotherapy, which concurs with our findings. In terms of anatomic location, the present study shows a good response rate (76.8%) for type I lesions (below the level of mylohyoid muscle) and a relatively low response rate for type II lesions (above the level of mylohyoid muscle) and mixed (type I + type II) lesions, which again agrees with previous reports.

According to previous studies, short-term responses to the picibanil sclerotherapy are 50 percent to 85 percent for lymphangioma. The short-term result in our study population was similar (83.5%). And long-term response was also good (76.3%). It seems that a low recurrence rate and good response to repeated injection in recurrent cases caused good long-term response.

To summarize, we found that picibanil is a good sclerotherapic agent with only minor complications and high long-term efficacy for lymphangioma, and, accordingly, we suggest that picibanil sclerotherapy be viewed as a promising first-line treatment for lymphangioma (Figs 4, 5).

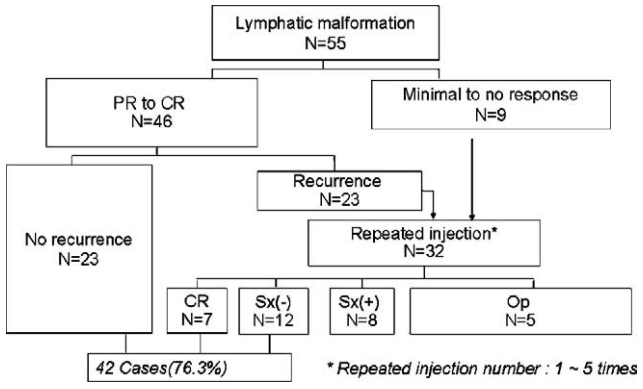

Figure 5 Long-term follow-up result of OK-432 sclerotherapy.

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AUTHOR CONTRIBUTION

Jae Chul Yoo, collection and assembly of data, data analysis and interpretation, manuscript writing; **Youngj in Ahn,** manuscript review and editing; **Yune Sung Lim,** data collection; **J. Hun Hah,** manuscript review; **Tack-Kyun Kwon,** data analysis and interpretation; **Myung-Whun Sung,** final approval of manuscript; **Kwang Hyun Kim,** administrative support.

FINANCIAL DISCLOSURE

None.

REFERENCES

1. de Serres L, Sie KCY, Richardson MA. Lymphatic malformations of the head neck. Arch Otolaryngol Head Neck Surg 1995;121:577–82.
2. Orvida LJ, Kasperbauer JL. Pediatric lymphangioma of the head and neck. Ann Otol Rhinol Laryngol 2000;109:411–21.
3. McGill TJI, Forsen JW JR, Mulliken JB. Hemangioma and vascular anomalies of the head and neck. In: Cummings CW, et al, eds. Otolaryngology–Head Neck Surgery, 3rd ed. St. Louis: Mosby; 1998 p. 66–80.
4. Ogita S, Tsuto T, Nakamura K, et al. OK-432 therapy in 64 patients with lymphangioma. J Pediatr Surg 1994;29:784–5.
5. Greinwald JH Jr, Burke DK, Sato Y, et al. Treatment of lymphangiomas in children: an update of Picibanil (OK-432) sclerotherapy. Otolaryngol Head Neck Surg 1999;121:381–7.
6. Sung M-W, Lee DW, Kim DY, et al. Sclerotherapy with picibanil (OK-432) for congenital lymphatic malformation in the head and neck. Laryngoscope 2001;111:1430–3.
7. Kim KH, Sung MW, Roh JL, et al. Sclerotherapy for congenital lesions in the head and neck. Otolaryngol Head Neck Surg 2004;131: 307–16.
8. Greinwald JH, Burke DK, Sato Y, et al. Treatment of lymphangiomas in children: an update of picibanil (OK-432) sclerotherapy. Otolaryngol Head Neck Surg 1999;121:381–7.
9. Claesson G, Kuylenstierna R. K-432 therapy for lymphatic malformation in 32 patients (28 children). Int J Pediatr Otorhinolaryngol 2002; 65(1):1–6.
10. Okazaki T, Iwatani S, Yanai T, et al. Treatment of lymphangioma in children: our experience of 128 cases. J Pediatr Surg 2007;42(2): 386–9.
11. Luzzatto C, Lo Piccolo R, Fascetti LF, et al. Further experience with OK-432 for lymphangiomas. Pediatr Surg Int 2005;21(12):969–72. Epub 2005 Oct 25.
12. Hase T, Kodama M, Sano H, et al. Successful treatment of a recurrent large cystic hygroma in a child with intracystic injection of OK-432. Eur J Pediatr 1996;155:424.