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Treatments of Various Otolaryngological Cystic Diseases by OK-432: Its Indications and Limitations

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Objectives/Hypothesis: The aim of this study was to evaluate the indications for, and outcomes and limitations of, OK-432 therapy in various otolaryngological cystic diseases.

Study Design: A retrospective clinical study at Yamagata University School of Medicine and the Fukase Clinic in Japan.

Methods: Between April 1996 and November 2009 we tried OK-432 therapy in 148 patients with otolaryngological cystic diseases. In cases of plunging ranulas, lymphangiomas, branchial cleft cysts, thyroglossal duct cysts, thyroid cysts, and cervical lymphocele, we aspirated as much of the fluid content of each cystic lesion as possible, and we then replaced the volume of aspirated fluid with about half the volume of OK-432 solution.

Results: Disappearance of the lesion was observed in 119 of 148 patients (80%). Marked reduction was observed in 20 of 148 patients (14%). Partial reduction was observed in four patients (3%), and no response was seen in five patients (3%). Plunging ranula, lymphangioma, thyroglossal duct cyst, thyroid cyst, auricular hematoma, and salivary mucocele showed better responses to OK-432 therapy than did branchial cleft cyst. Serious complications with OK-432 therapy were infrequent, and the therapy seemed to have no influence on future surgery.

Conclusions: Our results confirmed that OK-432 therapy is simple, easy, safe, and effective and can be used as a substitute for surgery in the treatment of various otolaryngological cystic diseases.

Key Words: Neck cysts, OK-432, ranula, lymphangioma.

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INTRODUCTION

Although surgical excision has been the first-line treatment for otolaryngological cystic diseases such as lymphangioma, plunging ranula, branchial cleft cyst, thyroglossal duct cyst, salivary mucocele, auricular hematoma, and cervical lymphocele, surgical complications need to be considered. These complications, including nerve injury, cyst recurrence, and cosmetic problems, could be avoided by the use of nonsurgical procedures. Although simple aspiration of otolaryngological cysts is a satisfactory nonsurgical treatment, cyst recurrence is commonly observed despite repeated aspiration. Ogita et al. were the first to report OK-432 therapy for lymphangioma, in 1987.[1] OK-432 was originally developed as an immunotherapy agent for cancer.[2] It is thought that its immunopotentiating actions are caused by strong local inflammation that promotes the release of various cytokines.[2] It is widely accepted that OK-432 is very effective in reducing ascites and pleural effusion in patients with carcinomatous peritonitis and pleuritis.[3] When it is injected into the peritoneal or pleural cavity, reduction of ascites and pleural effusion occurs, and adhesion of the cavity develops. It is also widely accepted that OK-432 therapy is effective for lymphangioma,[1,4–6] but studies of the effectiveness of OK-432 in otolaryngological cystic diseases, including branchial cleft cyst, thyroglossal duct cyst, salivary mucocele, auricular hematoma, thyroid cyst, cervical lymphocele, and plunging ranula, have been few.[4,7–15] The purpose of this study was to investigate the indications for, and effectiveness and limitations of, OK-432 therapy in patients with these otolaryngological cystic diseases.

MATERIALS AND METHODS

Subjects

This study was a retrospective clinical study of patients with otolaryngological cystic diseases who

TABLE I.
Results of OK-432 Therapy.

Disease	Case	MS, cm (range)	TS, No. (%)	MR, No. (%)	PR, No. (%)	NR, No. (%)	Follow-up, mo (range)
Plunging ranula	48	3.6 (2.8–8.6)	40 (83)	6 (13)	0	2 (4)	12.5 (6–49)
Lymphangioma	14	5.4 (3.9–12.8)	10 (71)	4 (29)	0	0	13.1 (5–47)
Branchial cleft cyst	12	4.3 (3.9–10.7)	6 (50)	2 (16)	1 (8)	3 (25)	10.6 (7–44)
Thyroglossal duct cyst	15	2.7 (2.1–6.8)	12 (80)	1 (7)	1 (7)	1 (7)	14.8 (7–46)
Thyroid cyst	11	3.1 (1.5–6.4)	8 (72)	2 (18)	1 (10)	0	8.9 (4–37)
Cervical lymphocele*	3	8.9 (5.2–11.8)	3 (100)	0	0	0	11.3 (7–21)
Salivary mucocele	23	0.6 (0.5–1.2)	19 (83)	4 (17)	0	0	15.6 (8–47)
Auricular hematoma	22	3.8 (2.7–6.7)	21 (95)	1 (5)	0	0	13.1 (4–38)
Total	148	3.5 (0.5–12.8)	119 (80)	20 (14)	3 (2)	6 (4)	11.9 (4–49)

*Cervical lymphocele after neck dissection for head and neck cancer.
MS = mean size; TS = total shrinkage; MR = marked reduction; PR = partial reduction; NR = no response.

received OK-432 therapy between April 1996 and November 2009. Data reviewed were patient age, sex, type of cystic disease, number of treatments, outcomes, recurrence, and complications. The patient ages ranged from 4 to 91 years. Sixty-eight patients were female and 80 patients were male. All patients except a few with potential risk of airway obstruction were treated on an outpatient basis without hospitalization. No patient had penicillin allergy. This study was approved by the institutional review board of our institution, and informed consent was obtained from each patient.

OK-432 Therapy

In patients with plunging ranulas, lymphangiomas, branchial cleft cysts, thyroglossal duct cysts, thyroid cysts, and cervical lymphocele after neck dissection for head and neck cancer, we aspirated as much of the fluid content of each cystic lesion as possible. To aspirate the contents sufficiently, compression of the cyst was sometimes needed. After determining the capacity of the lesion, we prepared a sufficient quantity of OK-432 (picibanil; Chugai Pharmaceutical Co., Tokyo, Japan) diluted with saline solution (0.1–0.5 Klinische Einheit [KE] per milliliter; 0.01–0.05 mg/mL). With the same needle as was used for aspiration, we injected OK-432 solution (at a volume equal to about half that of the fluid removed) into the cyst by changing the syringe.

In salivary mucocele or auricular hematoma, we prepared 0.5 KE (0.05 mg) of OK-432 diluted with 0.2 mL of saline solution and injected the solution into the lesion with a 27-gauge needle to prevent leakage of the agent out of the lesion. There was no resistance in cases of successful injection into the cystic lesion.

Aspiration

On day 2 after the injection, the swollen benign neck cyst was punctured by a 20-gauge needle with syringe, and as much of the intralesional fluid as possible was aspirated. The intralesional fluid was highly viscous, so it was necessary to use a larger needle for this aspiration.

Follow-up

All patients were regularly observed for a mean of 11.9 months (range, 4–49 months) after the last injection. To treat potential fever, analgesics were prophylactically given to all patients. Analgesic suppositories were also used as needed. The skin at the injection site became red and indurated on the day after injection; we punctured the skin over the cyst site and aspirated the fluid on day 2. We examined all patients on days 2, 7, 14, and 28 after OK-432 injection and judged the response at 6 to 8 weeks. If the response was insufficient, we repeated the same therapy with a 100% increase in OK-432. Cure, marked reduction, and partial reduction of neck cysts were defined as complete absence, a decrease of more than half, and a decrease of less than half compared with the pretreatment size, respectively, as determined clinically or by computed tomography.

Pathological Examination

We examined the pathology slides of branchial cleft cysts excised after patients had received OK-432 to look for histologic changes. The histopathology of the cysts after the patients had undergone OK-432 therapy was compared with that of excised thyroglossal duct cysts in patients that had not been treated with OK-432.

RESULTS

A total of 148 patients were enrolled in this study. Demographic clinical data for these 148 eligible patients are listed in Table I. Of these patients, 48 (32%) had plunging ranulas, 14 (9%) had lymphangiomas, 12 (8%) had branchial cleft cysts, 15 (18%) had thyroglossal duct cysts, 11 (7%) had thyroid cyst, three (2%) had cervical lymphocele, 23 (15%) had salivary mucocele, and 22 (14%) had auricular hematoma. The mean age was 26.4 years (range, 4–91 years). Maximum diameters of the otolaryngological cysts ranged from 0.5 to 12.8 cm (mean, 3.5 cm). A total of 119 (76%) cases of otolaryngological cystic disease were cured (follow-up of more than 4 months after the last injection with no recurrence)

TABLE II.
Injection of OK-432 Therapy.

Disease	Case	Treatments, No. (range)	Median Dose* (range)	Total Dose* (range)	Further Treatments, No. (%)
Plunging ranula	48	1.8 (1–5)	1.4 (0.5–5)	1.5 (0.5–13.5)	1 (2)
Lymphangioma	14	1.9 (1–5)	2.1 (1–7)	2.9 (1–13)	0
Branchial cleft cyst	12	2.9 (1–7)	2.7 (2–7)	6.8 (2–32)	3 (25)
Thyroglossal duct cyst	15	2.1 (1–3)	1.2 (1–3)	2.4 (1–8)	0
Thyroid cyst	11	2.1 (1–3)	1.2 (0.5–2)	1.6 (0.5–3.5)	1 (9)
Cervical lymphocele†	3	1.3 (1–2)	3.3 (2–5)	3.3 (2–7)	0
Salivary mucocele	23	1 (1–2)	0.5 (0.5–1)	0.5 (0.5–1)	0
Auricular hematoma	22	1.3 (1–5)	0.55 (0.5–1)	0.55 (0.5–3.5)	0
Total	148	1.8 (1–7)	1.3 (0.5–7)	1.6 (0.5–32)	5 (3)

*Doses are given in Klinische Einheit (KE) (1 KE = 0.1 mg).
†Cervical lymphocele after neck dissection for head and neck cancer.

after one to seven injections of OK-432 solution. Thirteen (16%) patients had marked reduction in the size of their benign neck cysts after receiving a maximum of five injections of OK-432.

The number of treatments ranged from one to seven (mean, 1.8), and the mean follow-up period was 11.9 months (range, 4–49 months). The outcome of OK-432 injection in otolaryngological cystic disease seemed not to depend on the cyst size or location or the patient's age. Six patients showed no response to OK-432 therapy after three to seven OK-432 injections. Five of these six patients underwent surgery without any technical difficulties and were eventually cured, and the remaining one was observed (Table II).

There were no serious complications, although patients experienced fever (37.5°–38.5°C) for a few days after injection. It was usually controlled by antipyretics. No infection or abscesses developed after OK-432 injection. None of the patients had evidence of scarring on the skin at the injection site. Other potential side effects of the streptococcal preparation, such as post–rheumatic fever sequelae and glomerulonephritis, were not observed. All patients received the therapy on an outpatient basis without hospitalization, except for a few patients who had a potential risk of airway obstruction.

Plunging ranula, lymphangioma, thyroglossal duct cyst, thyroid cyst, auricular hematoma, and salivary mucocele showed better responses to OK-432 therapy than did branchial cleft cyst. In plunging ranula, lymphangioma, thyroglossal duct cyst, thyroid cyst, auricular hematoma, salivary mucocele, and cervical lymphocele after neck dissection, 225 treatments were performed on 136 lesions. However, 86 of 136 patients required only one treatment. The 12 patients with branchial cleft cysts required more treatments, a high median dose, and a high total dose of OK-432; three of these patients needed further surgery despite repeated OK-432 therapy. The surgery was performed without difficulty, and wound closure and healing were uneventful. Specimens from these three patients were submitted for further histologic examination. Nonkeratinizing stratified squamous epithelium and reactive germinal centers beneath the lining epithelium were found in one patient in a branchial cleft cyst that had not been treated with OK-432. However, in the patient's excised branchial cleft cyst that had received prior OK-432 therapy, abundant lymphocytic aggregates, along with hyperplastic germinal centers and abundant collagen deposition, were found beneath the epithelium or around the lymphoid stroma. The stratified squamous epithelium lining of the cyst was partly damaged and thin or absent; however, most of the stratified squamous epithelium was preserved despite the repeated OK-432 therapy.

DISCUSSION

Surgery is considered to be the treatment of choice for various otolaryngological cystic diseases, but surgical complications, including nerve injury, cyst recurrence, and cosmetic problems, need to be considered. It has been reported that OK-432 therapy may become a first-line treatment for lymphangioma,[1,4–6] and Ogita et al. reported that OK-432 therapy was effective for lymphangioma.[1] OK-432 is a lyophilized streptococcal preparation made from the Su strain of A-group *Streptococcus pyogenes* incubated with penicillin. It was developed as an immunotherapeutic agent for cancer.[1–3] We reported previously that OK-432 therapy is effective in the treatment of ranula,[9] and Roh et al. have demonstrated that OK-432 therapy is effective in the treatment of branchial cleft cyst.[10] OK-432 seems to be more safe and effective than other sclerosing agents such as boiling water, hypertonic saline, ethanol, tetracycline, cyclophosphamide, sodium morrhuate, and bleomycin.[10] Although the complication rates with treatment by these sclerosing agents are 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, independent of the total dosage.[9,10] Benefits of OK-432 therapy as compared with other surgical procedures are summarized as follows: 1) In regard to cost performance, no hospitalization is required. 2) The treatment is painless and the time required for the procedure was brief, which means it can be well tolerated by children and nervous patients. 3) No local anesthesia is required during the procedure. 4)

Nerve injury and cosmetic problems are avoided. 5) Secondary infection and hemorrhage are rare. 6) Recurrences are less frequent.

The mechanism underlying the effectiveness of OK-432 therapy is very strong production of IL-6, IL-8, IFN-γ, TNF-α, and vascular endothelial growth factor in aspirated fluids after the therapy. When OK-432 is administered locally, inflammatory cells, such as neutrophils and monocytes, infiltrate the cyst; various cytokines, including IL-6, IL-8, IFN-γ, and TNF-α, are secreted.[14] These cytokines induce strong local inflammatory reactions in the cyst wall, resulting in fluid drainage, shrinkage, and fibrotic adhesion of the cyst.[15,16]

With regard to long-term follow-up results, Yoo et al. reported that in 55 lymphangioma patients who underwent OK-432 therapy, initial response rates were 83.5%; long-term follow-up (30–144 months) response rates were 76.3%. The initial and long-term response rates were equally good for lymphangioma.[17]

To our knowledge, this study is the first to show the indications for, and limitations of, OK-432 therapy in various otolaryngological cystic diseases in a larger patient series. Plunging ranula, lymphangioma, thyroglossal duct cyst, thyroid cyst, auricular hematoma, and salivary mucocele show a better response to OK-432 therapy than does branchial cleft cyst. To clarify the differences in efficacy among these diseases, from a histopathologic point of view, we considered the architectural components of the epithelium in these diseases. Thyroglossal duct cyst may be lined with pseudostratified columnar epithelium. Histologically, salivary mucocele and ranula demonstrate cystlike spaces lined by inflammatory granulation tissue or fibrous tissue. The epithelia in these diseases are basically thin and can be damaged easily by the inflammation evoked by OK-432 therapy. A strong inflammatory reaction in the cyst wall might result in epithelial damage, shrinkage, and fibrotic adhesion of the cyst. On the other hand, branchial cleft cysts are well circumscribed, with fibrous walls usually lined by stratified squamous or pseudostratified columnar epithelium containing lymphoid tissue with prominent germinal centers. The cyst wall is thicker than in other cystic diseases and might be more resistant to inflammatory reaction by OK-432.

CONCLUSION

OK-432 therapy did not require patient hospitalization, except in a few patients who were at potential risk of airway obstruction, and it did not scar the skin at the injection site. OK-432 therapy has economic and cosmetic advantages as compared with surgery and can be used several times, if needed, as a primary treatment for various otolaryngological cystic diseases. Surgery is recommended only for limited cases with poor or no response to OK-432 therapy. Any cyst recurring after a remission produced by OK-432 therapy can be treated by the same procedure without difficulty, unlike with other treatment methods.

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