Treatment of Ranula by OK-432: Pearls and Pitfalls

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Abstract: *Objectives*: Intralesional injection therapy with OK-432 was developed as a treatment modality for operatively difficult lymphangioma and is currently becoming a first choice treatment of this disease. The aim of this article was to evaluate the outcome and complications of the treatment of patients with ranula by OK-432 therapy.

Study Design and Setting: Case series with planned data collection at Yamagata University and Fukase clinic.

Subjects and Methods: We tried this therapy in 90 patients with ranula between January 2001 and February 2012. We injected OK-432 solution into the lesion with a 27 gauge needle to prevent the leak of the agent out of the ranula. This treatment was performed at an outpatient basis without hospitalization.

Results: Disappearance and marked reduction of the lesion were observed in 88 patients who had this therapy, and local scarring and deformity of the injection sites did not occur in any patients. As side effects, local pain at the injection site and fever (37to 39 °C) were observed in 40% cases of the patients who had this therapy, but such problems resolved within a few days.

Conclusion: These results may allow us to speculate that intralesional injection therapy with OK-432 is simple, easy, safe and effective, and can be used as a substitute for surgery in the treatment of ranula.

Keywords: Ranula, OK-432.

INTRODUCTION

Ranula is commonly encountered in the otolaryngological clinic. It occurs because of leakage of mucous from the sublingual gland and generally observed in the oral cavity. A plunging ranula occurring in the submandibular space is less common [1-4]. However surgical excision of ranula along with sublingual gland has been the first line treatment, surgical complications, including nerve injury, recurrence, and cosmetic problems, need to be considered [1-4]. These complications could be avoided by the use of nonsurgical procedures. Although simple aspiration of ranula is a satisfactory nonsurgical treatment, recurrence is commonly observed despite repeated aspiration. Thus, we have developed a new simple and safe method that can be used easily in private clinics and hospitals at an outpatient basis without hospitalization [5-7]. This method is intralesional injection therapy with OK-432. OK-432 (Picibanil) was originally developed as an immunotherapy agent for cancer. It is thought that its immunopotentiating actions are caused by strong local inflammation that promotes the release of various cytokines. It is widely accepted that OK-432 is very effective for reduction of ascites and pleural effusion in patients with carcinomatous peritonitis and pleuritis [8, 9] When it is injected into the peritoneal or pleural cavity, reduction of ascites and pleural effusion occurs and adhesion of the cavity develops. Ogita *et al.* firstly reported intracystic injection therapy with OK-432 for lymphangioma in 1987 [10]. This therapy has become a treatment of first choice for lymphangioma in Japan, because it is effective and safe. The purpose of this article is to study the effectiveness of OK-432 therapy in patients with ranula.

SUBJECTS AND METHODS

Subjects

This was prospective clinical study of patients with ranula receiving intralesional injection of OK-432 from January 2001 to February 2012 in Yamagata University Hospital and Fukase Clinic, Yamagata, Japan. Ninety patients were diagnosed as having ranula during the study. The patients ranged from 5 to 88 years of age. All patients were treated on an outpatient basis without hospitalization. No patients had penicillin allergy. This study was approved by the Institutional Review Board of our institution, and informed consent was obtained from each patient.

Intralesional Injection of OK-432

In plunging ranula, we aspirated as much of the fluid content of each lesion as possible. To aspirate the contents sufficiently, compression of the ranula was sometimes needed. After determining the capacity of

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the lesion, we prepared a sufficient quantity of OK-432 (Picibanil, Chugai Pharmaceutical Co., Tokyo, Japan) diluted with saline solution [0.5 to 5 Klinische Einheit (KE) per milliliter; 0.05 to 0.5 mg/mL]. With the same needle as that 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 ranula occurring in the oral cavity, we prepared 0.5 KE; 0.05mg of OK-432 diluted with 0.2 ml 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 2nd day after the injection, the swollen ranula was punctured by a syringe with a 20-gauge needle, and the intralesional fluid was aspirated as much as possible. The intralesional fluid was relatively viscous, so it was necessary to use a larger needle for aspiration at this time.

Follow-Up

All patients were regularly observed for a mean of 14.1 months (range 9-49 months) after the final injection. To treat potential fever, we gave analgesics for 3 to 5 days to all patients. Analgesic suppositories were also used as needed. The skin at injection site became red and indurated on next day, we punctured the skin over ranula and aspirated the fluid on 2nd day after injection. We examined all patients on days 2, 7, 14 and 28 after OK-432 infection and judged the response between 4 and 6 weeks. In case, the response was insufficient, we repeated the same therapy with a 100% increase of OK-432. The “cure” and “marked reduction” of ranula were defined as a negative palpation and a decrease of more than one half compared with pretreatment size respectively.

RESULTS

A total of 90 patients with ranula were enrolled in this study. The demographic clinical data of 90 eligible patients are listed in Table **1**. The median age of patients was 33.1 years (range 5-88 years). Maximum ranula diameters ranged from 2.7 to 8.7 cm (median 3.9 cm). Eighty cases of ranula were cured (follow up for more than 9 months after the last injection with no recurrence) after injection OK-432 solution, administered one to five times. Typical cases of ranula treated by OK-432 are shown. Total shrinkage after a single OK-432 injection was observed in these two cases with ranula.

Table 1: Treatment Characteristic and Outcomes

Characteristic	Results
Treatment	
Previous surgery, no. (%)	5(6)
Injected OK-432 solution	
Median volume, ml (range)	1.2 (0.2-5)
Median dose, KE (range)	1.4(0.5-5)
Total dose, KE (range)	1.6(0.5-13.5)
No. of treatments, median (range)	1.8(1-5)
Follow-up, months	14.1(9-49)
Further treatment (%)	1(1)
Response, no. (%)	
Cure	80(89)
Marked volume reduction >50% #	8(9)
Minimal volume reduction <50%#	0
No response	2(2)
Recurrence after cure	0
Side effects	
Low grade fever, no (%)	36(40)
Tolerable pain and local tenderness, no (%)	40(44)
Local scar	0
Skin pigmentation	0

#Of original ranula size; no, number.
KE, Klinische Einheit.

Eight patients had a marked reduction of ranula even after receiving the maximum of five times injection of OK-432. The number of treatments ranged from once to 5 times (mean 1.8) and median follow-up period was 14.1 months (range from 9 to 49 months). The outcome of OK-432 injection in ranula seemed not to depend on the size and location, or the patient’s age. There were no serious complications, although patients experienced fever (37.5 to 39 degree centigrade) for a few days after injection, usually controlled by antipyretics. No infection or abscesses developed after OK-432 injections. None of the patients had evidence of scar on the skin at the injection site. Other side effects of the streptococcal preparation, such as post-rheumatic fever sequelae and glomerulonephritis, were not observed in any cases. This therapy was undergone for all patients with ranula at outpatient basis without hospitalization.

Two patients with dermoid cyst were excluded from this study.

DISCUSSION

There are variable conservative and surgical treatments for ranula, including simple aspiration, incision and drainage, excision and surgical excision of ranula along with sublingual gland [1-4]. Surgical complications, including nerve injury, recurrence, and cosmetic problems, need to be considered [1-4]. It has been reported that OK-432 therapy may become a first line treatment for lymphangioma [10]. OK-432 is a lyophilized streptococcal preparation made from the Su-strain of group-A Streptococcus pyogenes [5-13] It was originally developed as an immunotherapeutic agent for cancer [8, 9]. It was reported that OK-432 therapy is effective in the treatment of lymphatic malformation, thyroglossal duct cyst, auricular hematoma, bronchial cleft cyst, auricular hematoma and salivary mucocele [5-7, 11, 14-16]. 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 [5]. Although the complication rates of treatment with 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 epithelial lining of the lesion, have been observed. Bleomycin, in particular, can have serious side effects, including fibrosis of the lung, independent of the total dosage [5]. On the other hand, the complication rate of OK-432 is minimal, and use of this agent does not require local anesthesia or patient hospitalization and leaves no scar on the skin at the injection site. Benefits of OK-432 therapy over other surgical procedures are summarized as follows. 1) No local anesthesia was required during procedure. 2) The treatment was painless and time for procedure was brief, therefore children and anxious patients can be well tolerated. 3) The nerve injury and cosmetic problems could be avoided. 4) Secondary infection and hemorrhage are rare. 5) Recurrences are less frequent. 6) From the point of cost-performance, no hospitalization and no special equipment and medication was required. OK-432 therapy is economically and cosmetically more advantageous than surgery and could be considered as possible alternative therapy [5-7].

The mechanism underlying the effectiveness of OK-432 therapy is very strong production of IFN-γ, TNF-α, IL-6, IL-8 and VEGF, as found in fluids aspirated after OK-432 therapy. When OK-432 is administered locally, inflammatory cells such as neutrophils and monocytes infiltrate the cyst and various cytokines, including IFN-γ, and TNF-α, IL-6, IL-8 are secreted [5, 8, 9, 13]. These cytokines induce strong local inflammatory reactions in the cyst wall, resulting in fluid drainage, shrinkage, and fibrotic adhesion of the cyst.

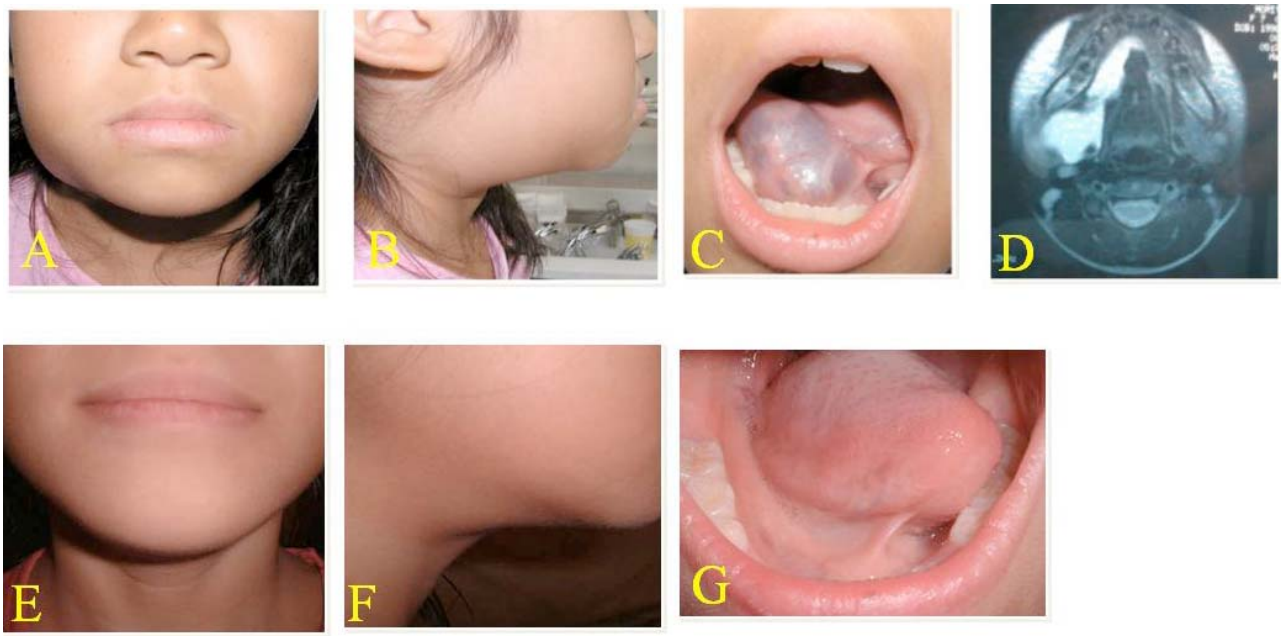

Figure 1: There was total shrinkage after a single OK-432 treatment at a dose of 2 KE in this 8-year-old woman with right submandibular swelling. (**A**, **B**, **C**); Local findings before OK-432 therapy, showing a plunging ranula in the left submandibular and oral floor regions (about 7.3 × 6.6 cm); (**D**) Initial T1-weighted magnetic resonance image before treatment, showing a plunging ranula in the left submandibular space; (**E**, **F**, **G**) Local finding after OK-432 therapy, showing absence of marked swelling in the right submandibular and oral floor regions (6 weeks after treatment).

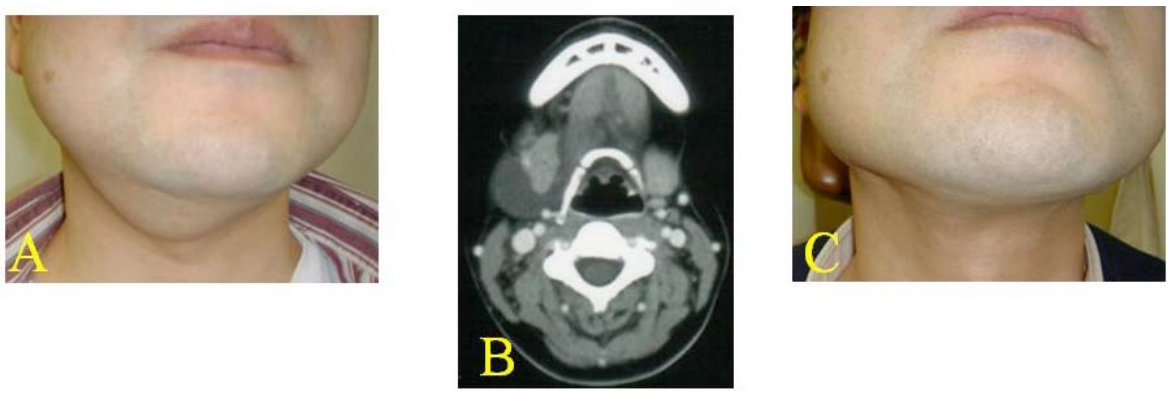

Figure 2: There was total shrinkage after a single OK-432 treatment at a dose of 2 KE in this 28-year old man with right submandibular swelling. (**A**, **B**) Local findings before OK-432 therapy, showing a plunging ranula in the right submandibular region (about 5.6 × 5.6 cm); (**C**) Local findings after OK-432 therapy, showing absence of marked swelling in the right submandibular region (6 weeks after treatment).

Our study is the first showing that ranula can be treated by the use of OK-432 in a larger patient series. Dermouid cyst resembles ranula in that it is a cystic lesion with a thin cyst wall and CT and MRI findings, however, surgical excision is first line treatment modality for dermoind cyst, as shown in Figure **3** and **4**. On CT, dermoid cysts typically appear as low-density, well-circumscribed, thin-walled, unilobular masses. On MRI, dermoid cysts are of low signal intensity on T1-weighted images and of high signal intensity on T2-weighted images, reflecting their fluid content. When located within the sublingual space, these lesions may

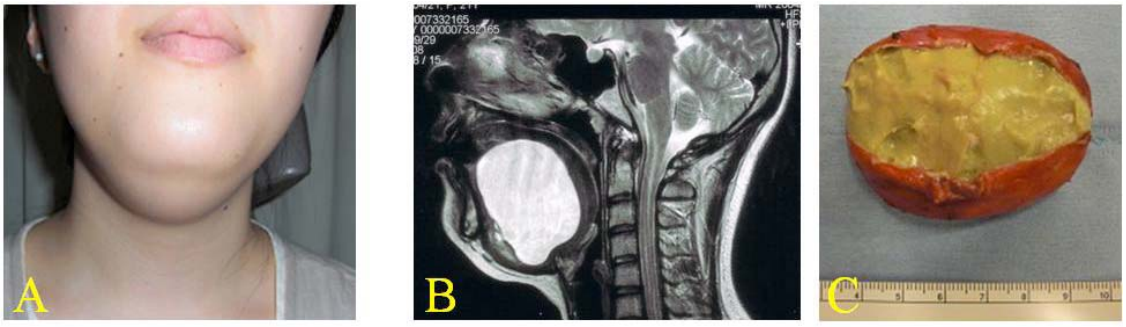

Figure 4: There was total removal after a excisional surgery in this 19-year old woman with submental swelling. (**A**) Local findings before surgery, showing a swelling in the submental region (about 5.5 × 6.5 cm); (**B**) Sagittal-T1 weighted MRI shows an 55 × 65-mm well-circumscribed cystic mass extending from the sublingual area to the mylohyoid muscle. (**C**) Surgical excision was performed orally. Following removal, the specimen measured approximately 5.5 × 5.6 × 4.5 cm and the dissected cyst shows cheesy, solid material. Pathological diagnosis was dermoid cyst.

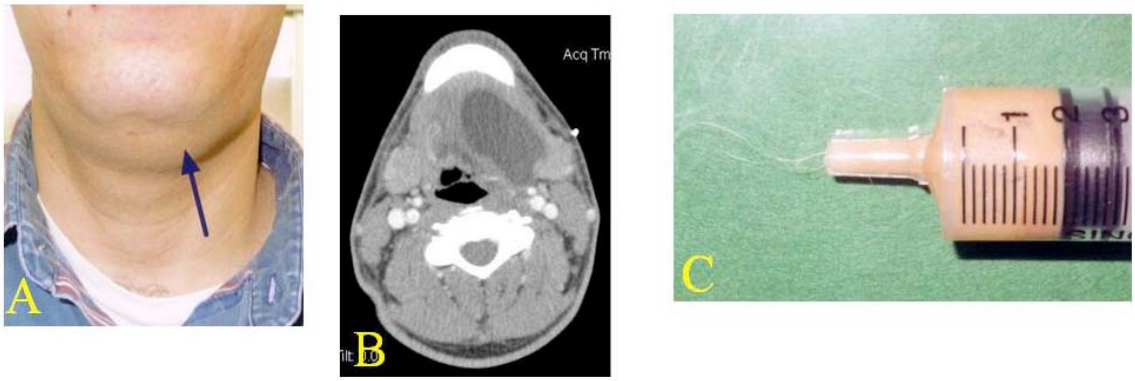

Figure 3: There was total removal after a excisional surgery in this 28-year old man with left submandibular swelling. (**A**) Local findings before surgery, showing a swelling in the left submandibular region (about 6.3 × 4.7 cm); (**B**) Initial axial contrast-enhanced computed tomography scan before treatment, showing a low soft tissue density area in the left submandibular space; (**C**) Initial aspiration cytology before treatment, showing a debris including caseous material and a hair. Pathological diagnosis was dermoid cyst.

be very difficult to distinguish from ranula, on the basis of imaging criteria alone. Dermoid cyst should be always kept in the mind to make precise diagnosis for ranula. The ranula can be primarily treated with OK-432 therapy, several times in needed. Surgery is recommended only for limited cases in which there is a poor, or no, response to OK-432 therapy.

CONCLUSIONS

Our results suggest that the treatment of ranula by OK-432 is simple, easy, safe and effective therapy that results in complete or a significant decrease in the volume of ranula. OK-432 therapy is a potentially curative procedure that may be used as a first choice treatment for ranula before considering surgical procedure.

AUTHOR CONTRIBUTION

Yusuke Suzuki, data analysis, article revision; **Shigeru Fukase**, conception and design, article revision; **Masaru Aoyagi**, conception and design, final approval; **Seiji Kakehata**, data analysis, article revision; **Nobuo Ohta**, conception and data analysis, design, article revision, final approval.

DISCLOSURES

Competing Interests

None.

Sponsorships

Supported by grants from the Ministry of Education, Science, Sports and Culture (Grant in Aids for Scientific Research C).

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Received on 13-02-2013 Accepted on 16-03-2013 Published on 20-06-2013