

Treatment of benign thyroid cysts by intracystic injection of OK-432

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Background. Benign thyroid cysts have been successfully treated with nonoperative sclerotherapy. Although OK-432 is a safe and effective sclerosing agent used to treat benign cystic lesions, little is known about its effectiveness in thyroid cysts. This study tested the efficacy of OK-432 sclerotherapy for thyroid cysts.

Methods. This was a prospective cohort study of 45 consecutive patients with benign thyroid cysts, as assessed by ultrasound (US)-guided biopsy. After evacuation, about 50% of the aspirated fluid volume was replaced with saline solution containing 0.1 to 0.2 mg OK-432. Recurrences were treated by repeat treatments, to a maximum of 3. Outcome was cyst volume on US 6 months after the last treatment.

Results. Median pretreatment cyst volume was 15 mL (range, 3.5–110). Of the 45 patients, 33 (73%) were cured, defined as a residual cyst volume <1 mL; 20 were cured after 1 treatment, 8 after 2 treatments, and 5 after 3 treatments. Of the 12 patients (27%) not cured, 7 had >50% of the original cyst volume and 5 had <50% volume reduction; 3 of these patients underwent hemithyroidectomy. Multivariate analysis showed that the chance of success decreased with the number of previous aspirations and with increased cyst volume ($P < .015$ each). Transient mild local pain and low-grade fever were observed in 26 (58%) and 19 (42%) patients, respectively, but there were no significant treatment-related complications.

Conclusions. Intracystic injection of OK-432 may be a safe and effective treatment for benign thyroid cysts. (Surgery 2008;144:775-9.)

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CYSTIC THYROID NODULE is a common clinical problem, accounting for 15% to 25% of solitary thyroid nodules on ultrasonography (US).¹ These thyroid lesions are frequently benign, although thyroid carcinoma may occasionally present as a purely cystic nodule.¹⁻³ Diagnostic accuracy has been improved by US-guided fine-needle aspiration biopsy (FNAB) of the walls or solid portion of cystic nodules.⁴

Although simple aspiration of benign cystic lesions is a satisfactory nonoperative treatment, these cysts commonly recur, even after repeated

aspiration. The recurrence rate varies from 10% to 80%, depending on the number of previous aspirations and cyst volume.^{5,6} Suppressive therapy with levothyroxine or sclerotherapy with tetracycline have failed to reduce this high recurrence rate^{7,8}; however, ethanol instillation has been found to have a high success rate in thyroid cysts and is considered an effective treatment alternative to surgery.⁹⁻¹¹ Generally, ethanol instillation has only mild and transient side effects, but the escape of ethanol outside the capsule can induce paraglandular fibrosis and subsequent serious respiratory distress.¹²

OK-432 is a lyophilized mixture of low-virulence group A *Streptococcus pyogenes* and penicillin G potassium, which was developed as an immunotherapy agent for cancer.¹³ Recently, OK-432 was reported to be safe and highly effective in the treatment of various cystic lesions, including lymphangiomatosis.^{14,15} Although this sclerosing agent may be used to treat thyroid cysts, only 2 previous retrospective studies have been performed.^{16,17} Prospective studies are required to validate the safety and efficacy of OK-432 sclerotherapy in thyroid cysts as an alternative to surgical excision or other

Supported by a Korea Research Foundation Grant funded by the Korea Government (MOEHRD, Basic Research Promotion Fund) (KRF-2007-331-E00146), and by the Ministry of Health & Welfare, the National R&D Program for Cancer Control (Grant No. 0620160), Seoul, Republic of Korea.

Accepted for publication June 6, 2008.

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0039-6060/\$ - see front matter

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doi:10.1016/j.surg.2008.06.014

sclerotherapies. We therefore prospectively evaluated the effectiveness of OK-432 in the treatment of benign thyroid cysts.

MATERIALS AND METHODS

Subjects. This was a prospective cohort study of patients with benign thyroid cystic nodules who received intracystic injections of OK-432 from March 2003 to December 2006. Eligible subjects included patients who had benign palpable thyroid cysts causing discomfort or cosmetic complaints. Inclusion criteria were US-demonstrated solitary or predominantly anechoic cystic lesions with/without additional nodules <1 cm and with no or <10% solid components; biopsy results confirming that the mass was a benign nodule; euthyroid state; and normal vocal fold mobility. Patients with thyroid malignancies or major concomitant diseases, those who received treatments affecting thyroid function, and those who previously underwent major neck operations or head and neck irradiation were excluded.

All patients underwent US-guided FNAB of the wall and solid portion of the cystic nodule. If the smears were nondiagnostic, FNAB was repeated; if the second smear was also nondiagnostic, the patient was excluded ($n = 4$). Forty-seven eligible patients were included in this study. The study was approved by the Institutional Review Board of our institution, and written informed consent was obtained from each patient.

Treatment and study design. After skin sterilization and local anesthesia using 1% lidocaine hydrochloride, a thyroid cyst was identified by inspection, palpation, or US guidance. To avoid outflow of injected OK-432 solution, a 21-gauge needle was first placed in the skin about 2 to 3 cm from the cyst margin, tunneled into the subcutaneous space, and used to puncture the cyst. As much cystic fluid was aspirated as possible; the syringe was detached with the needle left in situ, and a different syringe used for instillation of OK-432 solution. For each patient, about half the volume of aspirated fluid was replaced with 0.1 to 0.2 mg OK-432 (picibanil; Chungai Pharmaceutical Co., Tokyo, Japan) dissolved in normal saline, with the maximum amount of OK-432 not exceeding 0.2 mg in a single injection. After instillation, a small pressure dressing was applied to the injection site for 2 hours, and patients were observed for 20 minutes. All procedures were performed in the outpatient clinic.

All patients were evaluated before treatment and 1, 3, 6, and 12 months or more after their last treatment. Measurements included serum thyroid hormone, thyroid-stimulating hormone, and

thyroglobulin, as well as US-assessed thyroid cyst volume. The thyroid and cyst volumes were calculated on the basis of an US scanning procedure. Cure after treatment was defined as remaining cyst volume <1 mL on US 6 months after the last treatment.¹¹ In case of recurrence (volume >1 mL), treatment was repeated 1 to 2 months later, with a maximum of 3 treatments per patient. Patients with recurrence after the third treatment were observed or offered hemithyroidectomy.

Statistical analysis. SPSS 12.0 for Windows (SPSS Inc., Chicago, Ill) was used for statistical analyses. The Mann-Whitney test or 1-way analysis of variance followed by Tukey's procedure was used to compare continuous variables. Effects of variables on treatment success were evaluated by odds ratio with confidence intervals obtained from logistic regression. To exclude the possible influence of other variables, multiple logistic regression was performed. Differences were considered significant when $P < .05$.

RESULTS

A total of 47 patients were enrolled. Two patients were excluded because they were lost to follow-up after initial treatment, without proper assessment of the treatment response. The demographic, clinical, and US data of the 45 eligible patients are listed in Table I. Most of the thyroid lesions were solitary pure cysts; 5 patients, the lesions were predominantly cysts, with <10% solid component. The median cyst volume was 15 mL (range, 3.5–110). The cyst fluid was turbid and dark brown in 37 patients and clear yellow in 8.

The median treatment volume (5 mL) was approximately half the median aspiration volume (9 mL; Table II). Of the 45 patients treated, 33 (73%) were cured, 20 after only 1 treatment, 8 after 2 treatments, and 5 after 3 treatments. Failure after 3 treatment sessions was observed in 12 patients (27%); of these, 7 showed marked reduction of the original cyst volume (>50%), whereas 5 had no or minimal changes of the original cyst volume (<50%); 3 of these patients underwent hemithyroidectomy. In these 3 patients, no significant adhesions, fibrosis, or other changes were noted and no malignant tumors were found on permanent pathology. Patients treated successfully had significantly smaller mean pretreatment cyst volumes than did patients not successfully treated (12.0 ± 9.6 vs 21.8 ± 16.6 mL; $P = .024$; Table III). When patients successfully treated were grouped by the total number of treatments, however, there were no between group differences in original cyst volume ($P = .416$).

Table I. Clinical characteristics of patients with thyroid cysts

Characteristic	No. of patients	% of total
Gender (male/female)	13/32	29/71
Median age, years (range)	48 (10–71)	
Ultrasound findings		
Pure cystic	34	76
Predominantly cystic	11	24
Solitary lesion	31	69
Additional small nodules	14	31
Pretreatment size of the cyst		
Median volume, mL (range)*	15 (3.5–109.8)	
Median diameter, cm (range)*	3.6 (2.0–7.2)	
Median total thyroid volume, mL (range)*	36 (18.4–152.6)	
Cystic fluid appearance		
Yellow/clear	8	18
Brownish/bloody	37	82
Median follow-up, months (range)	30 (12–52)	

*Calculated by ultrasound measurements.

Table II. Treatment characteristics and outcomes

Characteristic	Results
Treatment	
Median aspiration volume, mL (range)*	9 (1.9–42.5)
Injected OK-432 solution	
Median volume, mL (range)	5 (1–20)
Median dose, mg (range)	0.1 (0.1–0.2)
No. of treatments, median (range)	2 (1–3)
Response, no. (%)	
Cure	33 (73)
Failure	12 (27)
Marked volume reduction > 50%†	8 (18)
Minimal volume reduction < 50%†	4 (9)
Recurrence after cure	0
Side effects	
Low-grade fever	19 (42)
Tolerable pain and local tenderness	26 (58)

*At the time of initial treatment with OK-432.

†Of original cyst volume.

On multivariate analysis, OK-432 treatment success was inversely associated with a history of previous aspirations ($P = .012$) and original cyst volume ($P = .005$; Table IV). Treatment success, however, was not significantly associated with patient gender, age, or with other cyst variables.

No significant complications were observed after treatment. No spillage of OK-432 solution was detected in any patient during or immediately

Table III. Relationship of treatment response and original cyst volume

Response	Initial cyst volume, mL mean $\pm$ SD (range)	No. of patients (%)
Cure after		
1 treatment	10.4 $\pm$ 8.4 (3.5–42.5)*	20 (44)
2 treatments	13.2 $\pm$ 10.6 (3.8–64.4)*	8 (18)
3 treatments	16.5 $\pm$ 12.2 (4.5–66.6)*	5 (11)
Failure	21.8 $\pm$ 16.6 (6.5–109.8)†	12 (27)

* $P = .416$ among the 3 groups with different number of treatments.

† $P = .024$ versus the 33 cured patients (Mann-Whitney test).

Table IV. Multivariate effects of variables on treatment success

Variable	OR	95% CI	P
Gender	1.294	0.062–19.364	.526
Age	1.478	0.168–1.694	.429
Previous aspirations	0.101	0.009–0.569	.012
Cystic vs complex	2.761	0.153–6.329	.283
Additional nodules	2.353	0.678–38.461	.156
Thyroid volume	0.973	0.029–10.276	.257
Initial cyst volume	0.019	0.005–0.429	.005
Clear versus bloody cyst fluid	3.698	0.264–25.683	.147

OR, Odds ratio; CI, confidence interval.

after treatment. Low-grade fever and mild local pain were observed in 19 (42%) and 26 (58%) patients, respectively, for 2 to 6 days after treatment, and these symptoms subsided after symptomatic treatments (Table II). Serum concentrations of free thyroxine, thyroid-stimulating hormone, and thyroglobulin were not changed after treatment (data not shown). No patient successfully treated showed cyst recurrence during the median follow-up period of 30 months.

DISCUSSION

We found that the overall cure rate of OK-432 sclerotherapy for thyroid cysts was 73% and that 89% of patients showed cystic volume reduction of >50%. Moreover, patients successfully treated did not show cyst recurrence after a follow-up of 12 to 52 months. These results were similar to those observed in patients treated with percutaneous ethanol or tetracycline injections.^{9–11,18,19} Since ethanol instillation was introduced in 1989,²⁰ its success rate, defined as near disappearance or marked size reduction (>50%), has been reported to vary from 72% to 95%.¹¹ Moreover, in a randomized controlled study, the success rate of ethanol injection (80%–82%) was significantly higher than that of simple aspiration (30%) or saline injection (48%).^{10,11} However, initial favorable

results with tetracycline^{18,19} have not been substantiated in a prospective randomized study, in that there was no difference between tetracycline and isotonic saline injection.⁸ In a retrospective study in which OK-432 was used to treat thyroid cysts,¹⁶ 32 of 48 patients (67%) showed cyst disappearance (<0.5 cm in diameter) and 12 (25%) showed a >50% reduction of original cyst size. In another OK-432 study,¹⁷ 11 of 15 patients (73%) showed cyst disappearance (<1.0 cm in diameter) and 4 showed poor response (>50% reduction of original cyst size). Although our prospective study consisted only of a single treatment group without controls, the success rate observed was similar to these seen earlier using ethanol.⁹⁻¹¹

When we assessed the effect of clinical and demographic variables on treatment response, we found that the chance of success decreased with the number of previous aspirations and increased cyst volume. These results were similar to those of a randomized controlled trial, in which recurrent thyroid cysts were treated with ethanol or saline injections.¹¹ In contrast, of 98 patients treated with percutaneous ethanol injections, 92 showed >50% reductions in cyst volume, including one third of the cysts >40 mL, and only 6 of the 92 responsive patients relapsed after a mean follow-up of 9 years, demonstrating that percutaneous ethanol injection is effective in the treatment of large cysts.²¹ The differences in these results, however, may be due to different definitions of treatment success in these and our studies.¹¹ Moreover, although an increased risk of recurrence has been associated with bloody or thick brown fluid and cyst diameter >4 cm,^{1,3,9} we found that fluid character had no prognostic significance.

Instillation of both OK-432 and ethanol generally seems to have only mild and transient side effects, such as local pain and tenderness. In contrast, severe pain and vocal cord paralysis have been reported after intracystic injection of tetracycline.^{22,23} Although ethanol instillation is safer than tetracycline, 1 case of respiratory distress and emergency surgical treatment after ethanol instillation has been reported.¹² These serious complications, which include paraglandular fibrosis, are associated with the escape of injected drugs outside the capsule. To avoid drug leakage from the cyst, submaximal aspiration precedes ethanol injection, with the amount of the latter being <50% of the cyst volume; in addition, the ethanol is left in place for several minutes and then completely evacuated.¹¹ OK-432 seems to be safer than other sclerosing agents, including tetracycline and ethanol,^{14-16,24} with no major side effects

and only temporary pain and fever after OK-432 injection. An additional advantage of OK-432 sclerotherapy may be the absence of extensive scarring around residual lesions, which can increase the morbidity of subsequent operation.²⁵ OK-432 seems to act by inducing inflammatory reactions in cyst walls, resulting in subsequent fluid drainage, shrinkage, and fibrotic adhesion of cysts.²⁵ In our experience in treating other benign cystic lesions, we found that a small leak of injected OK-432 solution did not cause severe adhesion to surrounding tissues or serious complications. However, the evacuation of injected OK-432 solution is not necessary to prevent leakage.

This study had several limitations, including the absence of a control group. A comparison with simple aspiration, saline injection, or ethanol instillation may be warranted. However, our results may be compared with historical control groups of simple aspiration or ethanol instillation previously reported.⁵⁻¹¹ This prospective study utilized a uniform treatment protocol, allowing us to assess the efficacy of OK-432 for thyroid cysts. It remains to be determined whether OK-432 injection may be an alternative treatment for patients unresponsive to ethanol instillation, or vice versa. Prospective, randomized, controlled trials comparing OK-432 and ethanol instillation will also be valuable in comparing the efficacy and side effects of both drugs in the treatment of benign thyroid cysts.

In conclusion, our results suggest that intracystic injection of OK-432 may be a safe and effective nonoperative treatment of benign thyroid cysts. This technique is simple, rapid, safe, and can be performed on an outpatient basis. Intracystic injection of OK-432 may be an alternative to ethanol instillation.

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