Treatment of branchial cleft cyst with intracystic injection of OK-432

JONG-LYEL ROH1, MYUNG-WHUN SUNG2, KWANG HYUN KIM2 & CHAN IL PARK1

1Department of Otolaryngology, Asan Medical Center, University of Ulsan College of Medicine, Republic of Korea and
2Department of Otolaryngology-Head and Neck Surgery, Cancer Research Institute, Clinical Research Institute, Seoul
National University College of Medicine, Seoul, Republic of Korea.

Abstract

Conclusions. The data suggest that branchial cleft cyst (BCC) can be primarily treated with OK-432 sclerotherapy and only
the remaining lesions with excision.

Objectives: To evaluate the effectiveness of sclerotherapy using OK-432 in the treatment
of BCC.

Materials and methods. We treated 12 BCC patients (3 males and 9 females; mean age 25 years) with OK-432
sclerotherapy at an outpatient clinic. The cystic fluids were aspirated and diagnosed by cytomorphology and DNA
 cytometric analysis to exclude malignancy. The fluid aspirated from the cyst was replaced with an equal volume of OK-432
solution. The sizes of cysts were measured and compared before and after injection. The remaining cysts were excised and
histopathologically compared with the excised BCCs that had not been treated with OK-432.

Results. Seven of 12 patients (58%) showed a complete response after OK-432 injection, administered one to three times. Three patients (25%) had only
partial response and two (17%) were stationary. Five patients with remaining lesions underwent excision. There was no
difficulty in dissecting around the cysts and no increased morbidity during operation. None of the patients had evidence of
recurrences or malignancies developing during the follow-up period (mean 21 months, range 17–26 months). There were
no major side effects except fever after sclerotherapy.

Keywords: Branchial cleft cyst, sclerotherapy, OK-432

Introduction

A branchial cleft cyst (BCC) is a congenital abnormality usually located in the lateral neck along the
anterior part of the sternocleidomastoid muscle. This is the most common cystic lesion presenting
in the neck and occurs most frequently in the third
decade of life. Most cases of BCC present non-tender
persistent cystic swelling that may become secondarily inflamed or infected, which often brings it to
clinical attention. Computed tomography (CT) or
magnetic resonance imaging typically reveals a uni-
locular cystic mass in the lateral neck. Because the
second BCC is located in the upper neck, the same
area as the jugulodigastric lymph node, this can be
mistaken for an enlarged suppurative, reactive, or
cystic tumor-infiltrated jugulodigastric node [1].

Surgical excision is the treatment of choice in
BCC. It is best performed when the lesion is not
infected or acutely inflamed. It is advisable to
manage an infected cyst with antibiotics, allowing
the inflammation to resolve before excision is
attempted. However, the surgery requires cervical
incision, leaving a postoperative external scar in the
neck, and may include potential operative morbidity.
Meanwhile, nonsurgical modalities with less asso-
ciated morbidity have been used in the treatment of
congenital lesions in the head and neck, including
sclerotherapy with diverse agents such as boiling
water, hypertonic saline, salicylates, ethanol, tetra-
cycline, cyclophosphamide, sodium morrhuate, and
bleomycin [2]. However, these sclerosing agents
have shown limited success and unpredictable scarring
or systemic side effects caused by spreading of
agents beyond the endothelial lining of the cysts. In
the last decade, however, it was reported that about
60% of patients with lymphatic malformation can
be successfully treated by the use of OK-432,
a lyophilized mixture of low-virulence group A
Sclerotherapy has rarely been applied to treatment of BCC. This is probably because there are no significant difficulties in the surgery of the monocystic lesions and because of the potential existence of primary branchiogenic carcinomas or cystic metastases from head and neck primaries [1,5,6]. Fukumoto et al. [7] first successfully applied ethanol injection sclerotherapy to three branchial cleft cysts and two thyroglossal duct cysts. Recently, a case report demonstrated that a neonatal BCC was successfully treated with OK-432 local injection [8]. OK-432 is a safe drug that does not cause damage to the overlying skin and does not lead to scar formation [2–4]. Therefore, we hypothesized that patients with BCC can be primarily treated with sclerotherapy using OK-432 if the cyst does not include cancer cells. Patients with only partial or no response to the sclerotherapy underwent surgical excision. Here, we analyze the outcome of OK-432 sclerotherapy in patients with BCC.

Materials and methods

This was a prospective clinical study of patients with BCC receiving intracystic injection of OK-432 from March 2003 to December 2003. Thirteen patients were clinically diagnosed as having BCC during the study period. One patient was excluded because a solitary cyst in the left upper neck was confirmed as a metastatic lesion by fine needle aspiration cytology. A total of 12 consecutive patients (3 males and 9 females) were enrolled into this study (Table I). The age of patients ranged from 13 to 35 years with a mean of 25 years. The location and size of the cysts were identified and measured by palpation, ultrasonography, or CT. The site of lesions was the upper neck in 10 patients, the mid neck in 2, and right in 6, left in 6. The greatest diameter of cysts was 2.5 to 10 cm (mean 5.5 cm). None of the patients had a metastastic lesion by fine needle aspiration cytology. A total of 12 consecutive patients (3 males and 9 females) were enrolled into this study (Table I).

All procedures were performed at an outpatient clinic without hospital admission. This study was approved by the hospital research ethics committee and informed consent was obtained from all patients.

All patients were regularly observed for a mean of 21 months (range 17–26 months) after the last injection. The sizes of cysts were measured and compared before and after injection. The “complete” absence of prior cyst was defined as negative on palpation and follow-up imaging studies. “Marked” and “partial” were defined as a decrease of more than and less than one half compared with pretreatment size, respectively. In addition, we examined the pathology slides of the excised BCC after receiving OK-432 to look for histologic changes. The histopathology of the cysts remaining after the patients had undergone OK-432 sclerotherapy was compared with the excised BCCs that had not been treated with OK-432.

Results

In total, 7 of 12 patients (58%) showed a complete response after injection of OK-432 solution, administered one to three times (Table I and Figure 1). Three patients (25%) had only a partial response and two (17%) were stationary even after receiving the maximum of six injections (case no. 10). All five patients with partial or stationary response underwent complete excision via a cervical or retroauricular approach. There was no difficulty in dissecting around the cysts and no increased morbidity during operation. After the surgery, the patients had no recurrence of their cysts. One patient had a small fibrotic nodule at the site of a previous lesion after two injections of OK-432 (case no. 6). The outcome of OK-432 sclerotherapy in BCC seemed not to depend on the size and location of the cyst, or the patient’s age. There were no serious complications, although patients experienced fever (37.5°C to 38.5°C) for a few days after injection, usually
controlled by antipyretics. No infection or abscesses developed after injections. None of the patients had evidence of recurrences or malignancies developing during the follow-up period.

On histopathologic examination, the excised BCC had no evidence of co-existing malignancy. Nonkeratinizing stratified squamous epithelium and lymphocyte aggregates with or without reactive germinal centers beneath the lining epithelium were found in the BCC that had not been treated with OK-432 (Figure 2A). However, in the excised BCC that had received prior OK-432 sclerotherapy, the lining squamous epithelium was thin or absent and abundant collagen deposition was found beneath the epithelium or around the lymphoid stroma (Figure 2B).

### Table I. Outcomes of OK-432 intracystic injection for treatment of patients with branchial cleft cyst.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Site</th>
<th>Side</th>
<th>Size* (cm)</th>
<th>Number of injections</th>
<th>Outcome</th>
<th>Size* of remaining cyst</th>
<th>Follow-up (months)</th>
<th>Further surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>22</td>
<td>Upper neck</td>
<td>R</td>
<td>4</td>
<td>2</td>
<td>Complete</td>
<td>–</td>
<td>26</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>34</td>
<td>Upper neck</td>
<td>L</td>
<td>9</td>
<td>1</td>
<td>Complete</td>
<td>–</td>
<td>25</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>33</td>
<td>Upper neck</td>
<td>R</td>
<td>5</td>
<td>2</td>
<td>Complete</td>
<td>–</td>
<td>22</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>18</td>
<td>Mid neck</td>
<td>R</td>
<td>3</td>
<td>3</td>
<td>Complete</td>
<td>–</td>
<td>21</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>29</td>
<td>Upper neck</td>
<td>L</td>
<td>5</td>
<td>1</td>
<td>Complete</td>
<td>–</td>
<td>21</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>27</td>
<td>Upper neck</td>
<td>L</td>
<td>5</td>
<td>2</td>
<td>Complete</td>
<td>–</td>
<td>19</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>35</td>
<td>Upper neck</td>
<td>R</td>
<td>5</td>
<td>2</td>
<td>Complete</td>
<td>–</td>
<td>17</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>25</td>
<td>Mid neck</td>
<td>R</td>
<td>2.5</td>
<td>2</td>
<td>Partial</td>
<td>1.5</td>
<td>21</td>
<td>Excision</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>22</td>
<td>Upper neck</td>
<td>R</td>
<td>8</td>
<td>3</td>
<td>Partial</td>
<td>5</td>
<td>19</td>
<td>Excision</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>19</td>
<td>Upper neck</td>
<td>L</td>
<td>6</td>
<td>6</td>
<td>Partial</td>
<td>4</td>
<td>17</td>
<td>Excision</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>13</td>
<td>Upper neck</td>
<td>L</td>
<td>10</td>
<td>2</td>
<td>Stationary</td>
<td>10</td>
<td>22</td>
<td>Excision</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>28</td>
<td>Upper neck</td>
<td>L</td>
<td>4</td>
<td>2</td>
<td>Stationary</td>
<td>4</td>
<td>21</td>
<td>Excision</td>
</tr>
</tbody>
</table>

*The greatest diameter of cyst (cm).

---

**Discussion**

Surgery has been considered to be the treatment of choice for most congenital cystic lesions of the head and neck. A number of reports, however, have suggested that sclerotherapy can become the first-line treatment modality of the lesions because it has the advantages of no external scarring, little morbidity, and few complications in comparison with surgery [2–4]. It is better to apply the sclerotherapy before surgery [4], especially in the treatment of vascular malformations that often infiltrate surrounding tissues or adjacent vital structures of the head and neck, leading to high surgical morbidity, recurrence, and ongoing difficulties with subsequent treatments [2]. Meanwhile, surgery is usually preferred in the treatment of unilocular congenital cysts.

---

![Figure 1](image-url)  
**Figure 1.** Axial CT scans of the neck before (A) and after (B) intracystic injection with OK-432 in BCC (case no. 5). A cystic lesion in the left upper neck (arrow) completely disappeared on follow-up CT (B) 6 months after only one intracystic injection of OK-432.
such as BCC or thyroglossal duct cyst because excision can be performed with no significant morbidity or recurrence compared with multilocular lymphatic malformation or other vascular lesions. However, the external scar in the visible area of the head and neck is unavoidable after excision via a conventional surgical approach. In addition, general anesthesia and hospital admission are usually required for the surgery. In contrast, sclerotherapy is well known to be safe and cost-effective because the procedure can be performed at an outpatient clinic without requiring hospital admission. This can also be inferred from the fact that sclerotherapy is increasingly being applied to even benign thyroid cysts that can be simply removed [11]. The present study also suggests that BCC can be primarily treated with sclerotherapy and the persistent or remaining lesions excised secondarily.

The preference for surgery in the treatment of BCC or thyroglossal duct cyst is also probably due to the possible existence of primary bronchiogenic/papillary carcinomas or cystic metastases of squamous cell carcinomas [5,6,9,10,12]. Solitary cystic metastases from head and neck primaries can mimic benign branchial cleft cysts or primary bronchiogenic carcinomas [6,13]. However, much evidence has suggested that the cystic malignancy can be diagnosed by endoscopic and imaging studies of the upper aerodigestive tract, cytology, and DNA cytometric analysis [9,10]. Nordemar et al [10] reported that aneuploidy was highly specific for malignancy and all benign cysts were diploid in image cytometry DNA analysis. In our study, both cytology and DNA cytometric analysis revealed that there was no evidence of cancer cells in any of the cysts and the permanent biopsy of five excision cases confirmed the benign pathology. All findings suggest that the potential malignancies of BCC can be excluded before sclerotherapy or surgery. However, close follow-up may be needed in patients receiving sclerotherapy for treatment of BCC.

In our study, a complete response after OK-432 injection was found in more than half the patients (58%). This suggests that a proportion of BCC patients may be primarily treated by intralesional injection of OK-432 solution. The sclerosing effect of OK-432 in BCC can be inferred from a report [14] that OK-432 injection induced and activated cellular and humoral responses, such as intracystic change of white blood cells or cytokines, increased the endothelial permeability, and thus the accelerated drainage and increased fluid flow led to shrinkage of the cystic spaces in lymphangiomas. Our study showed that the epithelium was thin or absent and abundant collagen deposition was found beneath the epithelium or around the lymphoid stroma. Although the excised BCC are actually failures as regards sclerotherapy, this possibly suggests a mechanism of action for OK-432, i.e. an inflammatory reaction occurs in cyst walls and seems to cause subsequent fluid drainage, shrinkage, and finally, fibrotic adhesion of cysts.

OK-432 also seems to be more safe and effective than other sclerosing agents such as tetracycline, sodium morrhuate, and bleomycin [2]. No major side effects of OK-432 were found in our study and only transient fever developed after injection. An additional advantage of sclerotherapy may be that extensive scarring was not found around residual lesions after sclerotherapy, thus allowing subsequent surgery to proceed without difficulty [2]. Moreover, small contracted lesions after OK-432 sclerotherapy may allow more convenient excision than the same lesions before the therapy. The potential surgical
complications or incision scar from excision can also be avoided by primary treatment with OK-432 sclerotherapy in BCC. Additionally, the cost benefits of sclerotherapy in the treatment of BCC are significant compared with excision. In Korea, with a nationwide medical insurance system, the total cost of one OK-432 injection is about $75 when provided at an outpatient clinic, which is significantly low compared with the cost of excision, which is at least $2000, including surgery under general anesthesia and hospitalization for 2 days.

Only three reports stated that BCC was treated with sclerotherapy [2,7,8]. One included only one case of BCC showing a marked response after two injections of OK-432 [2], and the second report had three cases of BCC showing a complete remission after injection of absolute ethanol [7]. A recent report demonstrated that a huge BCC in the neck of a neonate almost completely disappeared after local injection of OK-432 was administered four times. In our study, most lateral cysts treated by sclerotherapy were in teenagers and young adults, i.e. an older population than in the previously reported cases. Our study is the first showing that BCC can be treated by the use of OK-432 in a larger patient series; therefore, a guideline as to how to manage BCC can be suggested from our experience. If the cyst is probably a non-malignant, solitary cyst in the lateral neck, especially in a young patient, the cyst can be primarily treated with intracystic injection of OK-432 solution, several times if needed. Excision is only recommended for residual cyst after the sclerotherapy. Any recurrent cyst after remission produced by the injection may be re-treated with OK-432 sclerotherapy. Cytologic or DNA cytometric analysis needs to be performed prior to injection to exclude potential cystic malignancies. Long-term follow-up is also required to detect potential development of malignancy in the remnants of the injected cyst.

In conclusion, our results suggest that benign cystic lesions may be primarily treated with OK-432 sclerotherapy. If the traditional worry about co-existing malignancy of the cysts is excluded, sclerotherapy can be used before surgery. From our case series, it is proposed that a proportion of patients with BCC may be treated primarily with intracystic injection of OK-432 and the remainder secondarily with surgery.

References