

Bleomycin Sclerotherapy Following Doxycycline Lavage in the Treatment of Ranulas: A Retrospective Analysis and Review of the Literature

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Abstract

Objective: A ranula is a mucus-filled salivary pseudocyst that forms in the floor of the mouth, commonly arising from the sublingual or submandibular salivary glands following obstruction or trauma. Complete excision of the injured gland and removal of the cyst content is first-choice therapy, but has the potential for complications related to injury to nearby structures. As such, minimally invasive approaches such as percutaneous sclerotherapy have been investigated. We aim to contribute to the literature by assessing the efficacy and safety of our technique through our experience with 18 patients over the last decade.

Methods: This retrospective study evaluated 18 patients with intraoral and plunging ranulas treated by percutaneous bleomycin ablation. The primary endpoint was treatment result. Secondary endpoints included bleomycin dosage and complications.

Results: The study evaluated 12 males and 6 females with a median age of 23.5 years (range, 13–39 years). At a final follow-up of at least 2 months (6.5 ± 5.5 months), 4 patients demonstrated complete response (22%) and 14 patients demonstrated residual presence, recurrence or regrowth of the lesion (78%). There were no statistically significant associations between outcomes and history of prior treatment, number of treatments, and size or type of ranula. No complications were noted.

Conclusions: Our findings indicate that bleomycin, while safe for use in various head and neck malformations, is of limited utility in ranula therapy when the offending gland is not addressed primarily.

Keywords: Ranula; Sclerotherapy; Marsupialization; Bleomycin; Doxycycline

Level of evidence

Level 4 (Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence guidelines).

Introduction

A ranula is a mucus-filled salivary pseudocyst that forms in the floor of the mouth, commonly arising from the sublingual or less often the submandibular glands as a resulted of obstructed salivary drainage [1]. Clinically, they are separated into two classes – intraoral and plunging. Intraoral ranulas are confined superior to the mylohyoid muscle, while the plunging subtype extends inferiorly along fascial planes into the cervical, submandibular or submental spaces [2]. Though morbidity associated with these lesions are low, associated symptoms such as pain, swelling, and dysphagia can significantly impact a patient's quality of life [3].

Treatment approaches for ranula include: total excision of the ranula along with involved gland, exclusive excision of the ranula or involved gland alone, marsupialization (including the decompressive "stitch-and-stab" technique) of the pseudocyst wall, and, more recently, percutaneous drainage and injection of a sclerosant into the pseudocyst lumen with or without sclerosant injection of the culprit gland [2,4]. Surgical excision of the involved gland with or without the ranula itself reports recurrence rates as low as 1% in some studies and should be considered the first-choice therapy for these lesions [5]. However, open surgical interventions carry risk

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of injury to adjacent structures, infection and bleeding. In a report of 571 patients, the most common surgical complications included damage to the ipsilateral lingual nerve (4.89%) and/or Wharton's duct (1.82%) [6]. It is important to note that, excluding complete salivary gland excision, recurrence rates are high across all modalities (24.2-44.4%) [5].

In an effort to develop less invasive treatments for these lesions, attention has turned towards image-guided percutaneous drainage of the pseudocyst with replacement of pseudocyst content with a sclerosant such as pure ethanol, OK-432, or sodium tetradecyl sulfate. The most well studied of these, ethanol and picibanil (OK-432), have reported eradication rates as high as 88% and 93% respectively in small case series [7,8]. Variations in technique have been explored. Recently, high eradication rates have been achieved when the sclerosant is injected directly into the involved gland, though this can be associated with injury or ablation of adjacent structures such as the lingual artery or nerve [3].

While ethanol and OK-432 have been the most reported sclerosants in the literature, other agents can be considered for use. Bleomycin and doxycycline have been reported as capable sclerosants when employed in the treatment of lymphatic and venous malformations, including in the head and neck [9-11]. The availability and safety profile of bleomycin when compared to OK-432 and ethanol renders it an attractive target of study. In our current technique, an intraluminal doxycycline lavage is implemented in order to clear the highly viscous mucous from the pseudocyst, followed by an intraluminal injection of bleomycin foam as the primary sclerosant. In the present study, this technique is evaluated in order to determine whether or not intraluminal lavage may lead to high eradiation rates by increasing sclerosant penetration into the involved salivary gland without incurring the risks inherent to direct ablation.

Currently, no data on the use of bleomycin sclerotherapy in the treatment of ranula exist in the English literature. We aim to assess the efficacy and safety of our technique through a quantitative and qualitative analysis of our experience across 18 cases over the past decade.

Materials and Methods

This investigation is a retrospective analysis of patients with plunging or intraoral ranula who received treatment with bleomycin sclerotherapy between January 2009 and September 2019. The primary endpoint was treatment outcome (complete resolution at final follow-up). Secondary endpoints included bleomycin dosage and complications. This study was approved by an Institutional Review Board.

All patients presented with neck swelling and/or pain over a span of weeks to months. Diagnosis was made using a combination of clinical and radiologic findings and confirmed via postprocedural fluid analysis (presence of amylase or mucin in fluid or tenuous gelatinous fluid on gross inspection). Initial imaging modality included MRI (72%), CT (17%), and ultrasound (11%).

The reason for referral for sclerotherapy and not open surgical excision was categorized as either surgical failure, patient preference, or equivocal imaging characteristics requiring cyst puncture for definitive diagnosis of ranula vs lymphatic malformation. All patients were referred by board registered Otolaryngologists.

Patient underwent up to 3 separate sclerotherapeutic procedures. Treatment outcomes were categorized as either recurrence (R) or complete resolution (CR). All cases of complete resolution were confirmed via follow-up imaging performed at least 3 month following final treatment. Follow-up imaging was not deemed necessary to confirm treatment failure if clinical evidence of recurrence was present.

Description of technique

All procedures were performed in the interventional radiology suite by one of two board registered attending interventional neuroradiologists with approximately 6 years and 43 years of experience, respectively. Following explanation of the benefits, risks, and alternatives for the procedure, consent was obtained from the patient. Patients were then brought to the angiographic suite and cardiopulmonary monitoring was placed. All patients were treated under general anesthesia. The region to be treated was prepped and draped in the usual sterile fashion.

Treatment proceeded in 4 steps: access, aspiration, lavage, and injection. First, real-time image guided access into the dominant cystic space was gained with a 4-French Yueh Centesis Catheter Needle (Cook Medical, Bloomington, IN, USA). Subsequently, the cyst fluid was aspirated from the lesion and used to estimate the total volume of the ranula. Supplementary access into the cyst was then gained using an identical catheter needle at a second puncture site. A doxycycline/contrast mixture (60:40) was lavaged between

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the two syringes and the ranula lumen in 6 to 10 cycles in order to clear the mucinous components of the lesion. Syringe contents were discarded at the end of each cycle. Lavage was deemed complete once visual and tactile feedback confirm the absence of high viscosity mucous in the lavage mixture.

Finally, up to 5 mL of bleomycin (3 mg/mL) was drawn into a syringe and, if necessary, incorporated into a foam (albumin 25%, contrast, and air in equal amounts) in order to replace the entire cyst volume. If a final volume greater than 10 mL was required, doxycycline was used to prevent over-dilution of the sclerosant. The bleomycin foam was injected into the ranula, the needles were removed, and hemostasis achieved with thrombin foam. Injections were repeated up to 3 times if complete resolution was not achieved at 6-month post-procedural follow-up.

Statistical analysis

For consistency, final outcomes were stratified in a binary fashion into groups, adapted from the case series performed by Kono., *et al.* and Ryu., *et al.* [7,12]. This included: complete resolution (CR) if no visible mass persisted on imaging after a minimum of 4 weeks, and recurrence (R) if there were any signs of residual lesion. We tested for an association between final outcome and history of prior treatment, number of bleomycin sclerotherapy injections, ranula subtypes or lesion size. The Pearson's Chi-Square ($\chi 2$) with Yates' continuity correction and Kruskal-Wallis tests were used for comparison of the factors according to the outcome. A *P* value <.05 was considered statistically significant.

Statistical analysis was conducted using SPSS, version 22.0 (IBM Corp., Armonk, NY).

Results

Between January 2009 and September 2019, 29 patients were treated with sclerotherapy for plunging or intraoral ranula. 11 patients were excluded from this study due to the use of other sclerosants (i.e. STS or doxycycline alone); thus, 18 patients were included in the final analysis. Ages ranged from 13 to 39 years (24.6 \pm 7.96 years, median 23.5 years), and 33% of patients were female. 2 patients were treated for separate, bilateral ranulas. The reason for referral for sclerotherapy by otolaryngologist was prior therapeutic failure in 12 cases (67%), patient preference in 5 cases (28%), and presumed lymphatic malformation as underlying diagnosis based on non-invasive imaging (5%). With respect to the 12 patients referred for prior therapeutic failure, 7 (39%) patients had undergone previous surgery, 3 (17%) patients sclerotherapy with another agent or technique, and 2 (11%) a combination of both surgery and sclerotherapy. Patient characteristics and results are presented in table 1.

Patient number	Age	Sex	Ranula subtype	Largest dimension (cm)	Previous surgery/ sclerotherapy	Number of bleomycin treatments	Bleomycin dose per treatment (mg)	Total follow-up (months)	Outcome
1	13	М	Intraoral	2.8	Yes (Sx)	1	14	13	R
2	16	F	Intraoral	NR	no	1	15	4	R
3	17	F	Intraoral	4.3	Yes (Sx)	1	15	4	CR
4	36	М	Plunging	6.3	Yes (Sx x2)	1	15	4	R
5	21	М	Plunging	7.6	Yes (Sx)	1	15	11	CR
6	38	М	Plunging	3	Yes (Sx)	1	12	7	R
7	23	М	Plunging	4.4	no	1	15	5	R
8	24	М	Plunging	1	Yes (Sx)	1	4.5	2	R
9†	24	М	Plunging	6.2; 4.7	no	1	15	21	CR
10	17	F	Intraoral	NR	Yes (Sx)	2	15, 15	4	R
11	22	М	Plunging	3.1	Yes (St x5)	2	15, 15	17	R
12	15	F	Plunging	3	no	2	15, 15	3	R
13	23	М	Plunging	7.7	no	2	15, 15	2	R
14	34	М	Plunging	3.9	Yes (Sx and St)	3	15, 10, 15	2	R
15	29	F	Plunging	4.5	Yes (St)	3	12, 10, 5	4	R
16 [†]	39	М	Plunging	5.1; 4.3	Yes (Sx and St x4)	3	15, 15, 15	5	R
17	24	М	Plunging	NR	Yes (St x 2)	3	15, 10.5, 15	2	R
18	28	F	Plunging	3.6	no	3	15, 15, 10.5	8	CR

Table 1: Characteristics of patients treated with bleomycin sclerotherapy following doxycycline lavage.

CR: Complete Resolution; PR: Partial Resolution; R: Recurrence; Sx: Previous Surgery; St: Previous Sclerotherapy M: Male; F: Female; NR: Lesion Dimensions Not Recorded; [†] Indicates Patient with Separate, Bilateral Ranulas.

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On radiological examination, plunging ranula were observed in 14 patients (78%). The interval between sclerotherapy and final follow-up ranged from 2 to 21 months (6.5 ± 5.5 months), at which point 4 patients demonstrated complete response (22%) (the 4 patients with complete resolution had follow up length of 4, 8, 11 and 21 months respectively), and 14 patients demonstrated residual presence, recurrence or regrowth of the lesion (78%). Selected examples of a complete response and incomplete response are presented in figure 1 and figure 2.



Figure 1: (A, B) Initial T2-weighted magnetic resonance imaging (MRI) shows a 5.8 x 3.0 x 2.4 cm plunging ranula (arrows) in the right submandibular space on coronal and axial imaging, respectively. (C, D) Follow-up T2-weighted MRI obtained 1 year after bleomycin sclerotherapy depicts total shrinkage of the plunging ranula.



Figure 2: (A, B) Initial T2-weighted magnetic resonance imaging (MRI) shows a 2.2 x 3.9 x 3.1 (arrows) in the right submandibular space on sagittal and axial imaging, respectively. (C, D) Follow-up T2-weighted MRI obtained 3 months after bleomycin sclerotherapy depicts recurrence of the ranula.

Ranula size as measured on CT or MRI revealed an average maximal diameter of 4.43 cm \pm 1.9 cm (range: 1 to 7.7 cm). Nine patients (50%) received one treatment, 4 patients received two treatments (22%) and 5 patients (28%) received three treatments. The average number of treatments was 1.7. The mean dose of bleomycin used was 13.5 mg (range 4.5 to 15, SD=2.85). Doxycycline lavage was not performed in two of the cases.

Treatment results did not differ significantly by history of prior treatment (χ 2 test, p=0.84), number of bleomycin sclerotherapy injections (χ 2 test, p=0.41), ranula subtypes (χ 2 test, p=1), or lesion size (Kruskal-Wallis test, p=.36).

In our cohort, all patients experienced a degree of expected post-sclerotherapy pain and swelling in the injection site. There were no significant complications such as bleeding, infection, pulmonary fibrosis, skin necrosis or nerve injury.

Discussion

In the present study, bleomycin sclerotherapy directed solely at the ranula cyst among 18 patients resulted in a complete response rate of 22% (4 patients) and a recurrence rate of 78% (14 patients) at final follow-up. There were no statistically significant associations between prior treatment, number of treatments, lesion size and type of ranula though this may be a factor of the relatively small number of cases.

For a preliminary comparison of our technique with those using different sclerosants, a review of the literature was conducted (Table 2). We performed a comprehensive electronic search of PubMed/MEDLINE, Scopus, Web of Science and Cochrane Library (Central Register of Controlled Trials and the Database of Systematic Review) during September 2019. Search queries were database-specific. 195 articles were screened, and 15 studies were included in the final analysis. Due to variability in reporting, the proportion of patients with prior surgical history was not collated, and outcomes were recorded in a binary fashion as either complete or incomplete resolution. Incomplete resolution included all cases reported as partial resolution, recurrence, or regrowth.

Thirteen studies have previously evaluated OK-432 as a sclerosant (5 case reports, 8 case series) [7,8,13-20]. Combined, these studies included 177 patients with a mean age of 22 years. One hundred and eleven patients (62%) presented with plunging ranula. Average reported maximal diameter of ranulas were 2.96 cm (79 sizes reported). Complete resolution was noted in 119 patients (66%). Complications included transient swelling, mild odynophagia, and one report of severe difficulty swallowing requiring hospitalization [18]. Interestingly, individual case series reported complete eradication rates that ranged widely from 33% (21 patient sample) to 93% (32 patient sample).

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Author(s)	Year	Sclerosant	Gland ablation?	Total patients	Mean follow-up after last treatment (months)	Complete Eradication Rate [†]
Ikarashi., <i>et al</i> .	1994	OK-432	No	1	16	-
Watanabe., <i>et al</i> .	2002	OK-432	No	1	12	-
Woo., et al	2003	OK-432	No	1	12	-
Kinoshita., <i>et al</i> .	2012	OK-432	No	1	10	-
Yoshizawa., et al.	2016	OK-432	No	1	30	-
Ohta., <i>et al</i> .	2014	OK-432	No	6	21.5	83%
Roh., <i>et al</i> .	2008	OK-432	No	9	26	66%
Lee., <i>et al</i> .	2006	OK-432	No	13	24.3	69%
Rho., <i>et al</i> .	2006	OK-432	No	21	14.3	33.30%
Kono., <i>et al</i> .	2017	OK-432	No	23	5.4	78.20%
Roh JL	2006	OK-432	No	26	12	77%
Fukase., <i>et al</i> .	2003	OK-432	No	32	1	93%
Kim., <i>et al</i> .	2008	OK-432	No	42	14.4	45.20%
Nguyen., et al	2017	Ethanol	No	1	2	-
Ryu., et al.	2017	Ethanol	No	23	20	43%
Brannen., <i>et al</i> .	2019	Ethanol	Yes	24	13.9	87.50%

Table 2: Summary of studies investigating sclerotherapy for ranula.

† Complete eradication rate reported for series only. All single case reports were successful.

Two studies have reported outcomes of ethanol sclerotherapy (1 case report, 1 case series.) [1,12]. This cohort included 24 patients with a mean age of 23 years. 20 patients presented with plunging ranula (83%), and 11 patients (45.8%) demonstrated complete resolution, with no serious complications noted.

These results suggest that bleomycin sclerotherapy following doxycycline lavage is not an effective treatment method for ranula eradication when compared to ethanol or OK-432. However, response rates reported by different series studying the same sclerosant have also varied widely. One potential explanation for this is that the technique of sclerotherapy delivery, as opposed to the sclerosant alone, plays a major role in determining efficacy.

A recent series reported by Brannan., *et al.* helps to elucidate this point. In that study, mucous was aspirated from the pseudocyst, and the salivary gland was chemically ablated by ethanol injection [3]. The complete response rate was 87.5% (sample n = 24)— more than 2-fold higher than the rate reported by Ryu., *et al.* using intra-pseudocyst ethanol injections only [12]. These findings are in line with the general observation, as reported in a large metanalysis by Patel., *et al.* that recurrence rates decrease as more aggressive surgical treatment is targeted towards the involved gland, dropping from 44% in cases of simple cyst excision to between 0 and 1% when the cyst and gland are excised together [21].

Intraluminal sclerotherapy is exceptionally effective at obliterating lymphatic malformations, which are filled by the passage of interstitial fluid directly through the lumen wall, the mucous responsible for ranula recurrence is produced remotely from the cyst. By inducing fibrosis around the entry point of the pseudocyst, intraluminal sclerotherapy redirects salivary products along pathways of less resistance. However, if resistance along anatomically normal drainage pathways is prohibitively high due to trauma other pathology, this may nonetheless result in luminal re-expansion or novel ranula formation at a new location. For this reason, sclerotherapeutic success is determined by both the degree of fibrosis induced by the agent, and the degree of penetration into the involved gland.

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The wide variability in success rates reported using OK-432 may be in part attributable to this second factor. Procedural technique, sclerosant volume, ranula architecture, and other unrecorded factors may all play a role in affecting the amount of sclerosant reaching the gland, and thus the degrees of success achieved. It is also probable that the poor complete resolution rates observed in the current study are due in part to the use of sclerosive foam, which likely inhibits egression towards the gland.

Our study has limitations inherent to a small volume retrospective analysis. As such, causal relationships between groups, the impact of ranula complexity on treatment outcomes, and the evaluation of uncommon complications are beyond the scope and power of our analysis. While the average follow-up time was a little over half a year, a number of individual follow up times were as short as 2 months, which may be insufficient in the monitoring of final outcome. However, for the 4 patients with complete resolution, follow up length was 4, 8, 11 and 21 months respectively. Finally, 67% of patients in this cohort had underwent previous surgical or sclerotherapeutic therapy. It is reasonable to assume that prior treatment can confound our results due to fibrosis or incomplete removal leading to retained cystic structures that may be more difficult to treat. However, statistical analysis demonstrated no difference in outcome with respect to previous treatment.

Conclusions

In our analysis, ranula treatment using bleomycin sclerotherapy following doxycycline lavage achieved poor rates of complete resolution and cannot be recommended as therapy. A review of the literature indicates higher success rates are achieved utilizing ethanol and OK-432, however outcomes between individual case series are highly variable and should also be viewed critically. Direct chemical ablation of the offending gland and pseudocyst drainage offer higher rates of cure, though this needs to be balanced against the risk of unintended local tissue injury that may be associated with agents such as pure ethanol.

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