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Review

Comparison of outcomes of treatment for ranula: a proportion meta-analysis

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Abstract

Treatment for ranula is classified into three categories depending on how the leaking saliva is managed: removal of the leaking site by intraoral or transcervical resection of the sublingual gland; formation of a drainage tract through the wall of the pseudocyst by micromarsupialisation or marsupialisation; or sealing of the site of the leak by inducing fibrosis with a sclerosing agent. Resection of the sublingual gland is probably the option most likely to be curative for both oral and plunging ranula considering their pathophysiology. Although alternative treatments have been introduced to avoid the invasiveness of resection of the gland, their outcomes have been inconsistent. The objective of this study therefore was to help decision-making by providing more integrated rates of cure, consistency of treatment, and morbidity, depending on types of treatment used in previous series of cases. We used proportion meta-analysis of 39 such published series, and the most curative treatment for oral ranula was intraoral resection of the sublingual gland. Micromarsupialisation and its modification showed cure rates comparable with those of resection of the gland, but these were moderately inconsistent. In the treatment of plunging ranula, there was no significant difference in cure rate between the intraoral and transcervical approaches, although they both showed higher cure rates than injection of OK-432. Comparisons of morbidity were available for patients who had developed nerve dysfunction and haematoma after the intraoral and transcervical approaches and there was no significant difference between the two, though the morbidity was higher after the transcervical than that after the intraoral approach. In conclusion, intraoral resection of the sublingual gland is sufficient treatment with a tendency to have fewer complications than that in the transcervical approach.

Keywords: Oral ranula; Plunging ranula; proportion meta-analysis

Introduction

Leakage of saliva and its accumulation in surrounding tissues can induce inflammation resulting in a pseudocyst, called a ranula, on the floor of the mouth or neck.[1,2] Ranulas may develop from the duct of the submandibular gland, and the minor salivary or sublingual (SL) gland or duct, the latter being the most common site of salivary leaks as a result of trauma, anatomical variation, or chronic disease of the SL gland.[1–4] Saliva that leaks from the SL gland has a higher viscosity than that from other salivary glands, and is more likely to induce a strong inflammatory reaction.[3] Spontaneous secretory activity of the SL gland is continuous, and can resist inflammatory granulation and fibrosis,[1] which are thought to be why ranulas are associated with the SL gland.

Clinically ranulas are classified as oral or plunging, depending on the expansion of the pseudocysts. Resection

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of the SL gland is thought to be the best treatment for both types of ranula based on their pathogenesis.[1,5] Nevertheless, combined transcervical and intraoral approaches are still used to remove the cystic component completely, because entire exposure of the cyst below the mylohyoid muscle is difficult when using an intraoral approach alone, despite the relatively increased risk of complications.[5]

Resection of the SL gland requires general anaesthesia and, in addition, it is invasive and can lead to complications such as nerve injury, damage to Wharton's duct, or bleeding. For these reasons, several other treatments have been introduced to minimise complications and invasion. These treatments are: formation of a drainage tract through the wall of a pseudocyst by micromarsupialisation or marsupialisation; and sealing of the site of leakage by inducing fibrosis through modified marsupialisation or injection of a sclerotic substance. However, few comparative studies have addressed the outcomes of these two treatments, and compared them with resection of the SL gland for the treatment of either oral or plunging ranulas.

The complication rate after surgical management in one large study has been reported to be 5.78% for recurrence, 4.89% for sensory deficit of the tongue, and 1.82% for damage of Wharton's duct.[6] However, the exact rate has not been established because of difficulties in conducting a well-designed comparable study.

Proportion meta-analysis is a statistical technique for the quantitative synthesis of results of case series, and presents estimations of event rates in the form of a proportion rather than a relative risk or odds ratio.[7,8] Because the certainty of evidence from a meta-analysis is contingent on the design of the studies included, the level of evidence derived from case series is relatively lower than that from conventional meta-analysis.[9] The results derived from proportion meta-analysis have therefore been graded as a weak recommendation in clinical guidelines. However, proportion meta-analysis is still helpful in decision-making in a field that lacks data from comparative studies.[8]

The objective of the present study was to use meta-analysis to help clinicians decide about treatment according to the type of ranula by providing more integrated results of cure rate, consistency in the results of treatment, and morbidity.

Material and methods

Search strategy and selection of studies

On 2 July 2017 two reviewers searched the databases of the US National Library of Medicine (MEDLINE) and Excerpta Medica (EMBASE) for papers published in English that used the term "ranula", and then screened the abstracts and titles. Studies were included in a database for detailed review if they met the following criteria: published in the English language; included all types of treatments for oral or plunging ranulas; contained descriptions of cures or complication rate for treatments; and included at least five consecutive patients (to exclude small case series and case reports).[10] If the pools of patients overlapped among the studies, only the largest study was included. Studies that failed to meet these inclusion criteria were excluded. Published abstracts not accompanied by full manuscripts or comments; editorials; and letters to editors were also excluded.

Collection of data and assessment of quality

Name and country of origin of first author, year of publication, study design (prospective or retrospective), number of patients included, type of ranula, primary treatment, recurrence, and complications, were recorded. In addition, we categorised treatments according to the classification described or presented by the authors of the included study as: intraoral resection of SL gland, excision of ranula alone, marsupialisation and its modifications, micromarsupialisation and its modifications, and injection of sclerosant. Micromarsupialisation and its modifications included all types of suture-based techniques that did not remove the overlying mucosa of the ranula. Removal of the overlying mucosa of the ranula with or without supplementary treatment was classified as marsupialisation and its modifications. Sclerosing injection included all techniques that used drugs to promote inflammation and sclerosis. Cure for injection of OK-432 was defined as "nearly complete response with shrinkage of >90%" to account for possible fibrosis of tissue after injection. Complications were classified as transient or permanent nerve injuries, formation of a haematoma, infection or sialadenitis, or injury to Wharton's duct. Data were collected by two reviewers. An effort was made to minimise variability by using identical data forms and achieving consensus by discussion if there was any disagreement about the data with reviewers.

All papers studied were case series (level IV evidence).[11] Although there is no formally accepted quality assessment tool for these, the one for studies of case series from the National Institutes of Health (NIH),[12] composed of nine questions that were allocated scores (**Supplemental Table 1**), was used to assist understanding of the quality of case series included by the two reviewers, and to achieve consensus by discussion about the quality of the assessment.

Statistical analysis

We used proportion meta-analyses to evaluate and compare cure rates and morbidity of treatments using a random-effects model because variables in the studies included were not controlled.[13] Results of proportion meta-analyses are presented as forest plots, in which the length of the horizontal line corresponded to the 95% CI of the effect estimates for each study. When we compared cure rates and complications of surgical treatments, the overlap of 95% CI between treatments was defined as failure to reject the null hypothesis, or no difference between treatments.[13] The Cochran Q and the

I^2 tests were used to assess and describe the heterogeneity of each study, because I^2 does not inherently depend on the number of studies in the meta-analysis. It is more correct for meta-analysis than for the Cochran Q test.[14] The I^2 statistic illustrates the percentage of variability in effect estimates that result from heterogeneity, rather than the sampling error.[13] I^2 lies between 0 and 100%, with the larger value indicating better heterogeneity. In addition, I^2 assigned the adjectives "low", "moderate", and "high" to I^2 values of 25%, 50%, and 75%, respectively.[14]

The Cochran Q test was also used to support the heterogeneity of the results. This measurement is computed by summing squared deviations of the estimate of each study from the overall meta-analytic estimate, weighting each study's contribution in the same manner as in meta-analysis. Probabilities were obtained by comparing the statistic with the chi squared distribution and $k-1$ degrees of freedom (df; where k was the number of studies). A Cochrane Q probability of <0.10 was used to define the heterogeneity of the study.[14,15] MedCalc statistical software was used for statistical analysis, and forest plots were redrawn using Excel for convenience.[16]

Results

Assessment of quality

A total of 4970 abstracts and titles describing the results of treatment of ranula from November 1950 – 2 June 2017 were identified during the initial search. Sixty-seven studies were fully reviewed, and 39 (evidence level of clinical study = IV) were finally included in the analysis (Fig. 1).[3,5,6,17–52] No randomised clinical trials or case-control studies were identi-

Table 1
A brief summary of included studies.

Year, first author, and reference	Country	Outcomes	Quality assessment									
			Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total
2017 Nguyen[17]	US	C	Yes	Yes	NR	NA	Yes	No	NR	NA	Yes	Fair
2017 Kokong[19]	Nigeria	PR, C	Yes	No	NR	NA	Yes	No	Yes	NA	Yes	Fair
2017 Aluko-Olokun[20]	Nigeria	OR	Yes	No	Yes	NA	Yes	Yes	No	NA	No	Fair
2017 Kono[18]	Japan	OR	Yes	Yes	NR	NA	Yes	Yes	No	NA	No	Fair
2016 Hills[22]	UK	OR, PR, C	Yes	Yes	Yes	NA	Yes	Yes	Yes	NA	Yes	Good
2016 Liu[21]	China	OR, C	Yes	No	Yes	NA	Yes	No	Yes	NA	No	Fair
2015 Woo[23]	Korea	OR	Yes	Yes	Yes	NA	Yes	Yes	Yes	NA	Yes	Good
2015 Lee[24]	Korea	OR, C	Yes	Yes	NR	NA	Yes	No	Yes	NA	Yes	Fair
2014 Yang[25]	Korea	PR, C	Yes	Yes	NR	MA	Yes	Yes	Yes	NA	Yes	Fair
2014 Garofalo[26]	Italy	OR	Yes	Yes	NR	NA	Yes	Yes	Yes	NA	Yes	Fair
2014 Ohta[50]	Japan	PR	Yes	Yes	NR	NA	Yes	Yes	Yes	NA	Yes	Fair
2012 Amaral[27]	Brazil	OR	Yes	Yes	Yes	NA	Yes	Yes	Yes	NA	Yes	Good
2012 Amaral[28]	Brazil	OR	Yes	Yes	Yes	NA	Yes	Yes	Yes	NA	Yes	Good
2011 Bonet-Coloma[29]	Spain	OR	Yes	Yes	NR	NA	Yes	Yes	No	NA	Yes	Fair
2011 Samant[30]	New Zealand	PR, C	Yes	Yes	NR	NA	Yes	Yes	No	NA	No	Fair
2010 Seo[31]	Korea	OR, C	Yes	Yes	NR	NA	Yes	Yes	Yes	NA	Yes	Fair
2010 Huang[32]	Taiwan	PR, C	Yes	Yes	NR	NA	Yes	Yes	NR	NA	Yes	Fair
2010 Ohta[51]	Japan	PR	Yes	Yes	NR	NA	Yes	Yes	Yes	NA	Yes	Fair
2009 Zhi[33]	China	PR, C	Yes	Yes	NR	NA	Yes	Yes	Yes	NA	Yes	Fair
2009 Patel[5]	US	OR, PR, C	Yes	Yes	NR	NA	Yes	Yes	NR	NA	Yes	Fair
2008 Roh[34]	Korea	PR	Yes	Yes	Yes	NA	Yes	Yes	Yes	NA	Yes	Good
2008 Mortellaro[35]	Italy	OR, C	Yes	Yes	NR	NA	Yes	Yes	Yes	NA	Yes	Fair
2007 Chidzonga[36]	Zimbabwe	C	Yes	Yes	NR	NA	Yes	No	Yes	NA	Yes	Fair
2006 Lee[39]	Korea	OR	Yes	Yes	No	NA	Yes	Yes	Yes	NA	Yes	Fair
2006 Roh[37]	Korea	OR, PR	Yes	Yes	Yes	NA	Yes	Yes	Yes	NA	Yes	Good
2006 Rho[52]	Korea	PR	Yes	Yes	No	NA	Yes	Yes	No	NA	Yes	Fair
2006 Mahadevan[38]	New Zealand	C	Yes	Yes	Yes	NA	Yes	Yes	Yes	NA	Yes	Good
2005 Yuca[40]	Turkey	OR	Yes	Yes	Yes	NA	Yes	Yes	NR	NA	Yes	Fair
2005 Zhao[6]	China	C	Yes	Yes	NR	Yes	Yes	Yes	NR	Yes	Yes	Good
2004 Haberal[41]	Turkey	C	Yes	Yes	NR	NA	Yes	Yes	No	NA	No	Fair
2003 Choi[45]	Korea	OR	Yes	No	NR	NA	Yes	Yes	No	NA	Yes	Fair
2003 Fukase[44]	Japan	OR, PR	Yes	Yes	NR	NA	Yes	Yes	Yes	NA	Yes	Fair
2003 Kobayashi[43]	Japan	PR	Yes	Yes	NR	NA	Yes	Yes	Yes	NA	Yes	Fair
2003 Morita[42]	Japan	OR	Yes	Yes	NR	NA	Yes	Yes	No	NA	Yes	Fair
1998 Davison[3]	New Zealand	PR, C	Yes	Yes	NR	NA	Yes	Yes	No	NA	Yes	Fair
1996 Ichimura[46]	Japan	PR, C	Yes	Yes	No	NA	Yes	Yes	No	NA	No	Fair
1994 Mintz[47]	Israel	OR	Yes	No	NR	NA	Yes	Yes	Yes	NA	No	Fair
1988 Crysdale[48]	Canada	OR	Yes	Yes	NR	NA	Yes	Yes	NR	NA	Yes	Fair
1984 McClatchey[49]	US	PR	Yes	Yes	NR	NA	Yes	Yes	NR	NA	No	Fair

Abbreviations: OR = oral ranula; PR = plunging ranula; C = complication; NA = not applicable; NR = not reported.

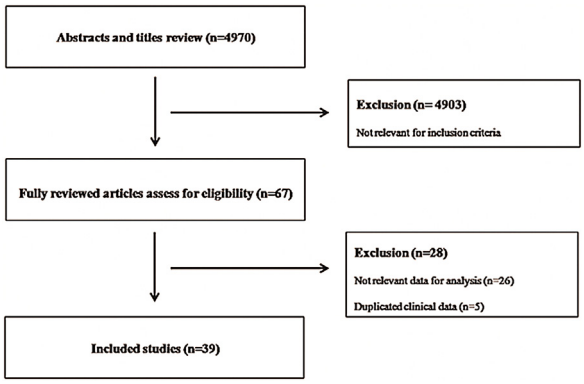

Fig. 1. Flow chart of the review showing the 39 case series that were finally included for proportion meta-analysis from 4970 abstracts and titles.

fied. The studies chosen included intraoral resection of the SL gland; excision of the ranula alone, marsupialisation and its modifications, micromarsupialisation and its modifications, and injection of OK-432 as treatments for oral ranulas. For plunging ranulas they included intraoral resection of the SL gland; transcervical resection of the SL gland; and injection of OK-432. Because only one study used alcohol to treat the ranula, alcohol-based sclerosing treatment was excluded from analysis and the only sclerosing treatment included was injection of OK-432. All the studies included had fair or good assessment ratings (4 to 7 points) (Table 1).

Cure rate

Among treatments for oral ranulas, intraoral resection of the SL gland had the highest cure rate (98.84%, 95% CI 96.74 to 99.98%, $I^2 = 0\%$), and was significantly better than excision alone (89.12%, 95% CI 78.49 to 96.43%, $I^2 = 0\%$). Intraoral resection of the SL gland also had a better cure rate than the other treatments except micromarsupialisation and its modifications (93.85%, 95% CI 84.18 to 99.15%, $I^2 = 45.97\%$). The cure rate of micromarsupialisation and its modification was comparable to that of intraoral resection of the SL gland. However, its heterogeneity was moderate: $I^2 = 45.97\%$. For alternative treatments of oral ranulas, the cure rate of marsupialisation and its modifications was 78.72% (95% CI 63.49 to 90.69%, $I^2 = 73.16\%$), and that of injection of OK-432 was 76.44% (95% CI 64.90 to 86.27%, $I^2 = 24.02\%$). These results did not differ significantly from the cure rate of 93.85% with micromarsupialisation and its modifications. In addition, cure rate heterogeneity of included studies was high for marsupialisation and its modifications ($I^2 = 73.16\%$) but low for injection of OK-432 ($I^2 = 24.02\%$).

Treatments for plunging ranulas were categorised into three groups: intraoral resection of the SL gland, transcervical resection of the SL gland, and injection of OK-432. No significant differences were seen among these treatments between the cure rates of intraoral (98.95%, 95%CI 97.36 to 99.82%, $I^2 = 0\%$) and transcervical resection of the SL gland (91.51%; 95%CI: 80.00 to 98.38%, $I^2 = 0\%$), which showed no inconsistency of results. However, intraoral resection of the SL gland had the highest cure rate, and this was significantly better than that of injection of OK-432 (65.60%, 95%CI 39.02 to 87.77%, $I^2 = 67.49\%$) (Fig. 2). In addition, the cure rate of injection of OK-432 showed good heterogeneity of results ($I^2 = 67.49\%$) (Fig. 3).

Morbidity

The comparison of complication rates was available only between intraoral and transcervical resection of the SL

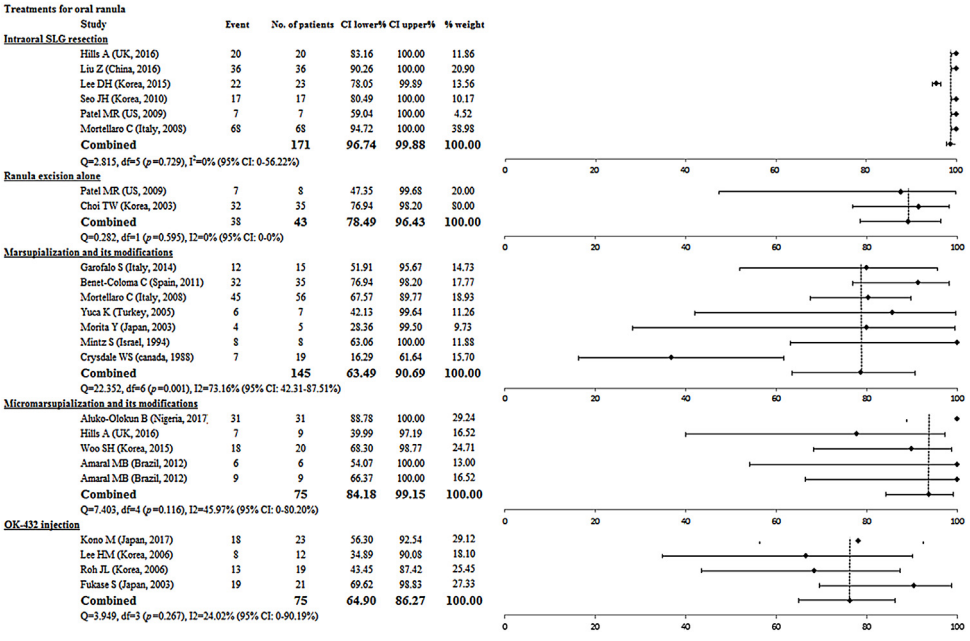

Fig. 2. Proportion meta-analysis results of cure rates for oral ranula in the case series.

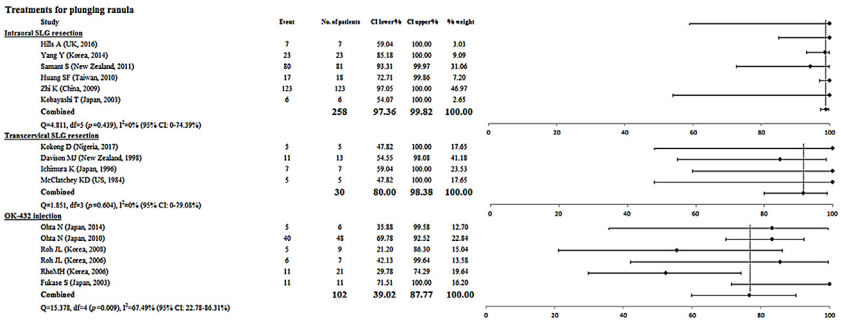

Fig. 3. Proportion meta-analysis results of cure rates for plunging ranula in the case series.

gland. Data about major complications for alternative treatments were not available, and only nerve dysfunction and haematoma after resection of the SL gland were eligible for proportion meta-analysis because infection, sialadenitis, and injury to Wharton's duct showed inconsistent descriptions or lack of data depending on the studies. Nerve dysfunction and haematoma were less common after intraoral resection of the SL gland than after transcervical resection, although these differences did not differ significantly between the two resection groups (**Supplemental Fig. 1**). In addition, nerve dysfunction for intraoral ($I^2 = 60.45\%$) and transcervical ($I^2 = 64.65\%$) resection of the SL gland showed good heterogeneity of results.

Discussion

Accumulated evidence showed that salivary leakage from a SL gland is the predominant cause of formation of a pseudocyst, so only intraoral resection of a SL gland without excision of the ranula is generally considered sufficient from the perspective of cure, even for plunging ranulas.[24,53] However, evidence to support these results is insufficient because well-designed clinical trials on the treatment of ranulas have various constraints that make it difficult and sometimes impossible to do a controlled study to validate many invasive treatments.[54] For this reason, it is difficult to predict the outcomes of alternative treatments because of inconsistency of results, although the treatments have the same concepts. We therefore conducted a proportion meta-analysis. We think that these results could improve counselling and treatment for ranula. In addition, because clinical trials of an invasive practice should be conducted with the best possible ethical and scientific evidence,[54] these results might be used when well-designed prospective and controlled studies were done to evaluate various treatments of ranula.

In the present study, intraoral resection of the SL gland had the highest cure rate for the treatment of oral ranulas (98.84%, 95% CI 96.74 to 99.98%, $I^2 = 0\%$), and it was significantly higher than that of excision of the ranula alone. Considering this result, excision alone is not proper surgical practice for treatment of ranulas. Micromarsupialisation and its modifications showed a cure rate comparable (93.85%, 95% CI 84.18 to 99.15%, $I^2 = 45.97\%$) to that of intraoral resection of the SL gland. They had no major complications. However, there was moderate inconsistency in the cure rates that might be the result of limitations and modifications of the procedure. In other words, micromarsupialisation and its modifications are more unreliable options for treatment of oral ranulas than intraoral resection of the SL gland.

Among alternative treatments for oral ranulas, marsupialisation and micromarsupialisation are well-known for generating a drainage tract into the oral cavity. Their modifications include an additional technique with formation of a drainage tract by promoting fibrosis or adding a suture technique.[26,35,42,44,49] However, there were no significant differences in cure rate among alternative treatments for oral ranulas, so all alternative treatments might be optional. However, efforts should be made to provide an appropriate technique when choosing marsupialisation (high, $I^2 = 73.16\%$), micromarsupialisation (moderate, $I^2 = 45.97\%$), and injection of OK-432 (low, $I^2 = 24.02\%$) by considering the heterogeneities of the cure rates.

We found no significant differences in the cure rates between the intraoral and transcervical approaches, so it seemed logical to include the cure rate for the treatment of plunging ranulas as well. This is consistent with the findings of a previous study that reported the outcome of intraoral resection of the SL gland for plunging ranulas.[53] In addition, although the transcervical approach tended to have a higher complication rate, rates of complications such as nerve dysfuction and haematoma did not differ significantly between these two approaches (intraoral and transcervical). This implies that intraoral resection of the SL gland is sufficient for treatment of a plunging ranulas if the resection is wide enough. Our results suggest that the intraoral approach should be considered in patients who are reluctant to have an incision scar in the neck. However, heterogeneities of nerve dysfunction rates are high, so we need to pay attention to the identification and preservation of the lingual nerve in both intraoral and transcervical resections of the SL gland. Injection of OK-432 into a plunging ranula was found to have a worse therapeutic effect than intraoral resection of the SL gland. However, it is considered the only alternative treat-

ment for those who fear major complications of resection, as injection of OK-432 has no major complications other than fever or local pain.[22,36,39,41,46]

This proportion meta-analysis has several limitations. First, proportion meta-analyses are known to have a lower level of evidence than randomised clinical trials because of the limitations of the method. Detailed interpretation, including heterogeneity of results, is therefore important to understand proportion meta-analysis. Secondly, the cause of the lack of data about complications of alternative treatments was not apparent – whether it was absence of data or reporting bias is not known. Thirdly, because alternative treatments were probably used by experts, the experience of the physician or surgeon might have influenced rates of cure and complications, considering the heterogeneity of the results. Caution is therefore needed when alternative treatments are considered. Fourthly, recent techniques such as robotic surgery, injections of botulinum toxin, and sclerosing injection with alcohol were not included. The present study, therefore, did not provide information on all options for treatment.

Conclusions

Resection of the SL gland is the best and most reliable surgical treatment for oral and plunging ranulas with no heterogeneity of results. In addition, intraoral resection of the SL gland is sufficient treatment, with a tendency to lower morbidity than that after the transcervical approach. In addition, there is only one alternative treatment for plunging ranula, which is injection of OK-432. We measured its efficacy in this analysis. Finally, when we use an alternative treatment for ranula, care should be taken to use the proper technique to ensure the best results, particularly if marsupialisation, micromarsupialisation, and injection of OK-432 are chosen as alternative treatments.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

Neither ethics approval nor patients' permission was required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjoms.2019.06.005.

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