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Enlarged Tracheoesophageal Puncture after Total Laryngectomy: A Systematic Review and Meta-Analysis

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Abstract

Background—Enlargement of the tracheoesophageal puncture (TEP) is a challenging complication after laryngectomy with TEP. We sought to estimate the rate of enlarged puncture, associated pneumonia rates, potential risk factors, and conservative treatments excluding complete surgical TEP closure.

Methods—A systematic review was conducted (1978–2008). A summary risk estimate was calculated using a random-effects meta-analysis model.

Results—Twenty-seven peer-reviewed manuscripts were included. The rate of enlarged puncture and/or leakage around the prosthesis was reported in 23 articles (range, 1% to 29%; summary risk estimate, 7.2%; 95% confidence interval [CI], 4.8% to 9.6%). Temporary removal of the prosthesis and TEP- site injections were the most commonly reported conservative treatments. Prosthetic diameter ($p = .076$) and timing of TEP ($p = .297$) were analyzed as risk factors; however, radiotherapy variables were inconsistently reported.

Conclusion—The overall risk of enlarged puncture seems relatively low, but it remains a rehabilitative challenge. Future research should clearly establish risk factors for enlarged puncture and optimal conservative management.

Keywords

tracheoesophageal puncture; total laryngectomy; enlarged tracheoesophageal puncture; complications; leakage

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The gold standard for voice restoration after total laryngectomy is tracheoesophageal puncture (TEP). The TEP is a small surgically created fistula in the tracheoesophageal (TE) wall that may be created at the time of the total laryngectomy (primary TEP) or later after the patient has healed from surgery (secondary TEP). A one-way valved silicone voice prosthesis (VP) is placed into the TEP. The prosthetic valve opens to allow pulmonary air into the vocal tract for vibratory sound production when the tracheostoma is occluded, but remains closed to prevent aspiration of foods/liquids during swallowing.^{1,2}

One of the most difficult complications to manage after TEP is enlargement of the TE fistula that results in aspiration of saliva, liquid, and/or food around the VP into the trachea. Tissue changes associated with radiation, malnourishment, diabetes, smoking, and hypothyroidism may reduce elasticity and integrity of the TEP and have been implicated as potential risk factors for enlarged puncture.³⁻⁶ Development of an enlarged TEP has also been associated with acute infection or tumor recurrence.^{3,7} However, the actual contribution of these potential risk factors is unclear.

An enlarged TEP intuitively increases the risk of pneumonia and respiratory complications due to frequent aspiration around the VP. Reduced tissue elasticity also increases the likelihood of spontaneous dislodgement of the VP and consequently the potential for aspiration of the prosthesis. Various treatments, including surgical closure of the TEP, have been proposed to mitigate the ill-effects of an enlarged TEP. Although surgical closure eliminates problems associated with leakage around the prosthesis, closure of the TEP prevents TE voice production, thus negatively impacting quality of life. Because of this, conservative methods, either surgical or nonsurgical, that aim to eliminate leakage around the VP while preserving functional TE voice, either surgical or nonsurgical but excluding complete TEP closure, are of particular interest. Although a variety of conservative treatments have been proposed, there are no clear guidelines for the conservative management of this complication.

A better understanding of factors associated with enlarged TEP will lead to more uniform assessment and management of this complication, and may guide preventive efforts. For this purpose, a systematic review was conducted with the following objectives: (1) to estimate the rate of enlarged TEP causing leakage around the VP after total laryngectomy with TEP, (2) to estimate the risk of pneumonia in patients with enlarged TEP, (3) to summarize the effect of potential risk factors for enlarged TEP, and (4) to summarize the type and effectiveness of conservative treatments used to prevent leakage around the prosthesis due to enlarged TEP.

MATERIALS AND METHODS

Search Methods

The search for this systematic review was conducted from May through July 2008. The primary search was conducted using the electronic MEDLINE database (data source: OVID). The search was limited to human subject research in peer-reviewed journal articles published between 1978 and June (week 1) 2008. Medical subject heading (MeSH) terms

were used to identify articles pertaining to 3 conceptual groups of references: (1) total laryngectomy, (2) TEP/alaryngeal voice restoration, and (3) complications. Within concept 1 (“total laryngectomy”), the following MeSH terms were ‘exploded’ to include all subject headings under the term: Laryngectomy, Laryngeal Neoplasms/Surgery. A total of 10,417 articles were identified in concept 1. These terminologies also identified extended procedures that included pharyngeal resection and use of flap reconstructions. Within concept 2 (“TEP/alaryngeal voice restoration”), the following MeSH terms and subheadings were exploded: Larynx, Artificial; Speech, Alaryngeal; Tracheoesophageal Fistula/Rehabilitation, Surgery; Laryngeal Neoplasms/Rehabilitation; Prosthesis Implantation/Rehabilitation, Methods; Laryngectomy/Rehabilitation. A total of 15,178 articles were identified in concept 2. Within concept (“complications”), the following MeSH terms and subheadings were exploded: Punctures/Adverse Effects, Classification, Complications; Prostheses and Implants/Adverse Effects, Classification; Laryngectomy/Adverse Effects; Larynx, Artificial/Adverse Effects, Classification; Prosthesis Failure; Treatment Outcome. A total of 394,308 articles were identified in concept 3. The final MEDLINE search identified 303 articles by cross-referencing the 3 conceptual reference groups for common articles. The bibliographies of relevant articles were hand-searched to identify additional manuscripts. Hand-searching identified 7 additional articles for a total of 310.

Selection Criteria and Data Collection

The abstracts of 310 peer-reviewed journal articles identified by electronic and hand searches were screened. Articles were excluded after screening according to the following exclusion criteria: (1) single case report study design, (2) review article, (3) non-English publication, or (4) no discussion of complications, failures, enlarged puncture, or prosthetic leakage within the abstract. The full-text of 54 articles was reviewed for the following data points: number of patients studied, number of VP replacements, study design, study setting, length of follow-up, proportion of primary and secondary TEP, receipt of pre- or postoperative radiotherapy, sex, age, case definition (eg, enlarged fistula, leakage around the VP), rate of enlarged TEP and/or leakage around the VP, rate of pneumonia, rate of dislodgement/aspiration of VP, potential risk factors (eg, timing of TEP, radiotherapy, flap reconstruction, diabetes, smoking, hypothyroidism, malnutrition, prosthetic diameter), type of VPs used (brand, diameter, indwelling vs non-indwelling), and conservative management techniques for enlarged TEP. Conservative management was defined as any surgical or nonsurgical intervention used to eliminate leakage around the VP but still preserve functional TE voice. These included temporary removal or modification of the prosthesis, TEP-site injection, TEP-site cautery, and purse-string closure. Complete closure of the TEP site was not considered a conservative management technique and was excluded from the analysis of conservative management. A complete listing of conservative methods is provided in Table 1.

The rate of enlarged TEP/leakage around the VP was calculated by dividing the number of patients with enlarged puncture and/or leakage around the VP over the total number of patients studied. Several studies reported the occurrence of this complication by the number of times the VP was replaced. In these studies, multiple replacements may have occurred in a single patient and, therefore, the complication rates were calculated as a percentage of total

number of VP replacements. Rates calculated as a proportion of total number of VP replacements are reported separately from those that were calculated per patient. We included cases that described either enlargement of the TEP and/or leakage around the VP when calculating the rate of the complication because the 2 descriptions are used interchangeably in the literature. Twenty-seven of 54 articles reported sufficient data on enlarged TEP and/or leakage around the VP and were included in the final report; 4 of these studies did not estimate a rate of enlarged TEP/leakage around the VP but only reported on management techniques in a case series design. Therefore, 23 studies reported rates of enlarged TEP/leakage around the VP.

Methodologic Reporting

Consensus guidelines for methodologic reporting in observational studies were established by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement initiative in 2004.⁸ The STROBE statement outlines 9 items that should be transparently reported in the methods section of observational research articles to assess the external validity, strengths, and weaknesses of observational findings. The reporting of these 9 methodologic items was recorded for all studies included in this review: (1) study design, (2) study setting, (3) participants, (4) variables, (5) data sources/measurement, (6) bias, (7) study size, (8) quantitative variables, and (9) statistical methods.

Statistical Methods

A meta-analysis was performed to estimate the rate of enlarged puncture/leakage around the VP after total laryngectomy with TEP. A summary risk estimate was calculated using the random-effects model to account for underlying sources of variation between studies beyond that of random error. Meta-analysis results are displayed in a Forest Plot (Figure 1). Results from both prospective and retrospective cohorts were included in the meta-analysis model due to the similarity of observational study designs. The nonparametric Wilcoxon Rank Sum test was used to compare the proportion of patients with enlarged puncture and/or leakage around the VP in risk stratifications. Additional results are presented in descriptive format. Statistical analyses were performed using the STATA data analysis statistical software, version 10.0 (StataCorp, College Station, TX).

RESULTS

Rate of Enlarged Tracheoesophageal Puncture

Twenty-three studies reported rates of enlarged TEP and/or leakage around the VP T2 (Table 2). Twenty studies reported rates of enlarged TEP and/or leakage around the prosthesis per patient, and 2 by the total number of times the VP was replaced. One study reported rates both by patients and by the number of VP replacements. Overall, an enlarged TEP/leakage around the VP was reported in 1% to 29% of patients ($n = 21$) and in 3% to 11% of VP replacements ($n = 3$). The description of the problem varied across studies and can be conceptualized in 2 categories: (1) studies that described leakage around the TEP attributed to an enlarged puncture, or (2) studies that reported leakage around the VP without clearly attributing this occurrence to an enlarged TEP. Thirteen studies that clearly attributed leakage around the VP to an enlarged TEP reported rates of enlarged puncture

between 1% and 29% of patients and 3% of VP replacements. In contrast, 10 studies did not clearly attribute leakage around the prosthesis to an enlarged fistula; these studies reported rates of leakage around the VP between 2% and 13% of patients and 7% to 11% of VP replacements.

A summary risk estimate was calculated based on 19 studies; 2 studies that solely reported enlarged TEP per number of VP replacements were excluded from the meta-analysis. Two overlapping cohorts were identified in this review^{1,4,9,10}; the latter publications^{4,10} from these cohorts were included in the meta-analysis. The test of homogeneity revealed significant differences in risk of enlarged TEP/leakage around the VP between studies (Q-test; $p < .0001$). Therefore, the summary risk estimate was calculated using a random-effects model; the summary risk estimate for enlarged TEP/leakage around the VP was 7.2% (95% CI, 4.8% to 9.6%). Risk estimates and 95% CIs for each study and the summary estimate are illustrated in Figure 1.

Geographic and Time Trends

We assessed geographic and temporal differences in risk of enlarged TEP/leakage around the VP for 19 studies that reported complications per patients, excluding the earlier publications^{1,9} of 2 overlapping cohorts, and 2 studies that solely reported complications per number of VP replacements. Of the 19 studies, 8 were conducted in North America, 8 in Europe, 2 in Asia, and 1 in Africa. The median rate of enlarged TEP/leakage around the VP reported in North American cohorts was 8.7% (range, 3.7% to 29.2%; interquartile range [IQR], 5.5% to 13.0%), 7.4% (range, 0.8% to 17.9%; IQR, 3.3% to 13.1%) in European cohorts, and 4.0% (range, 1.5% to 5.7%) in the remaining 3 studies conducted in Asia and Africa. By decade of publication, the median rate of enlarged TEP/leakage around the VP reported was 11.8% ($n = 4$; range, 5.8–13.3), 4.5% ($n = 10$; range, 0.08% to 29.2%), and 10.0% ($n = 5$; range, 5.8% to 17.9%) in the 1980s, 1990s, and 2000s, respectively.

Pneumonia

Two studies^{3,10} we reviewed reported rates of hospitalization due to respiratory infection or pneumonia. Acton et al³ found that 4.5% of patients (3 of 66) seen for prosthetic leakage (either through or around the VP) during the study period required hospitalization for upper respiratory infection, whereas Singer et al¹⁰ reported that no patients in their cohort developed aspiration pneumonia. Three studies^{3, 11, 12} cited a potential relationship between leakage around the VP and pneumonia, but did not quantify the association nor did they compare pneumonia rates in patients with and without enlarged puncture/leakage around the VP.

Risk Factors for Enlarged Tracheoesophageal Puncture

Risk factors for enlarged TEP were rarely addressed in the manuscripts reviewed and were not statistically analyzed in any of the studies included in this systematic review. We analyzed the effect of 2 potential risk factors, VP diameter and timing of TEP, by stratifying results of studies that reported rates of enlarged TEP in cohorts with similar characteristics. These 2 potential risk factors were selected for subgroup analysis because they were the only characteristics reported similarly across studies. Enlarged TEP/leakage around the VP

was reported in 2% to 13% (median, 6%) of patients who exclusively used a 16- or 16.5-French diameter prosthesis^{10, 11, 13–18, 24, 27} in comparison to 6% to 21% (median 9%) of patients who exclusively used a 22-French or larger diameter prosthesis^{4, 6, 12, 19} ($p = .076$). Excluding 1 outlier, 20 rates of enlarged TEP/leakage around the VP were similar ($p = .297$) among cohorts exclusively treated with primary TEP (range, 2% to 13%; median, 4%) compared with those exclusively treated with secondary TEP (range, 5% to 13%; median, 11%). No studies reported the influence of radiotherapy on enlarged TEP/leakage around the VP. In addition, we were unable to assess the effect of radiotherapy using a subgroup analysis due to incomplete reporting of radiation history in many studies included in this review. In studies that did report radiation history, complication rates were not stratified by radiotherapy which precluded assessment using meta-regression techniques.

Conservative Management of Enlarged Tracheoesophageal Puncture

Twenty studies reported using conservative treatments for enlarged TEP and/or leakage around the VP (Table 1). Temporary removal of the VP and injections into the TE wall were the most commonly reported treatments; additional methods are listed in Table 1.

Temporary removal of the prosthesis with or without catheter placement was used to encourage spontaneous narrowing of the TEP. Authors reported temporary removal of the prosthesis from a “few hours or days”¹¹ up to 30 days.⁹ Nasogastric tubes were sometimes placed, and 1 institution¹² routinely hospitalized patients for monitoring during temporary removal of the VP. Eight studies reported using more than 1 conservative treatment method to manage leakage around the VP. Among those, several authors^{4, 13} advocated that temporary removal of the VP should be attempted as the first method of treatment. Additional treatments were attempted in these studies only when leakage persisted after temporary removal of the VP.

Eight studies reported injecting a foreign material into the TE wall to shrink the diameter of the TE puncture. The types of injectable materials applied are shown in Table 1. Two reported injecting around the VP in situ,^{21, 22} 1 reported injecting both into an open TE tract and with the VP in situ,²³ and the remaining 5 authors did not specify.^{4, 13, 24–26} Most patients had between 1 and 3 injections^{21–23, 25, 26} regardless of the injectable material used.

Ten studies reported the effectiveness of conservative treatments (excluding complete surgical closure of the TEP) for leakage around the VP (Table 3). Outcomes were highly variable; however, none of the conservative treatments reportedly worsened the problem. The assessment methods, outcome measures, and length of follow-up varied substantially across studies. Ten additional studies reported the use of conservative treatment methods including placing an anterior collar, downsizing the TEP with catheter placement, collagen injection, and thickening liquids, but did not describe the effectiveness of these treatments. Complete surgical closure of the TEP site was reported in 14% to 50% of cases in the cohorts we reviewed, and most reported surgical closure in less than 20% of cases.^{1, 4, 6, 9, 10, 21, 27} No comparative prospective trials were identified.

Methodologic Reporting

Methodologic reporting was assessed based on the STROBE statement guidelines for observational studies.⁸ Methodologic reporting was incomplete (at least 1 item was not reported) in all studies, and at least 2 methodologic items were not reported in 96% (22 of 23) of the studies. Specifically, the majority of publications did not report length and method of follow-up (65%), diagnostic criteria for enlarged TEP/leakage around the prosthesis (78%), methods for assessing enlarged TEP (61%), exclusion criteria (78%), and efforts to address potential biases in the study (91%).

DISCUSSION

Enlarged TEP is clinically recognized as a significant complication of TE voice restoration; yet the literature provides no consensus regarding the frequency of its occurrence, risk factors, or management. Studies included in this review identified enlarged TEP or leakage around the VP in 1% to 29% of the patients studied. Small sample sizes yielding imprecise estimates along with methodologic differences between studies likely contributed to the wide range of results. Our meta-analysis found a summary risk estimate of 7.2% (95% CI, 4.8% to 9.6%) for enlarged TEP/leakage around the VP. The 95% CI indicates that the risk of an enlarged TEP may be as low as 5% or as high as 10%, suggesting a relatively low overall risk of this complication after TEP. Risk of enlarged puncture is likely elevated in certain groups of patients; unfortunately, incomplete reporting precluded our ability to assess potential risk factors using meta-regression techniques.

We considered differences in the rate of enlarged puncture/leakage around the VP by geographic region and decade of publication. Substantial differences were not observed between European and North American cohorts. Interestingly, the median rate of enlarged puncture/leakage around the VP did fluctuate by decade of publication. The differences observed may be due in part to the small number of studies published in each decade; however, higher median rates reported in the 1980s and 2000s may also reflect a learning curve in the development period of alaryngeal voice restoration (1980s) and more recently the use of TEP in medically complex salvage laryngectomy cases after chemoradiation failure (2000s). In contrast, the lower median rate observed in the 1990s may be reflective of fewer complications seen with routine application of this procedure in standard, frontline laryngectomy.

Another objective of this systematic review was to estimate the risk of pneumonia in patients with enlarged TEP. Aspiration related to enlarged puncture is a potentially life-threatening complication, as evidenced by 1 study that reported death in a patient who developed severe aspiration pneumonia after progressive enlargement of the TEP.¹² Few authors^{3, 11, 12}, however, acknowledged a relationship between leakage around the VP/enlarged TEP and pneumonia. Enlargement of the TEP should also increase the likelihood of spontaneous dislodgement of the VP. Dislodgement of the prosthesis poses risk for severe aspiration through the open, unstented TE tract and consequently increases the potential for aspiration pneumonia. In addition, frequent dislodgement of the VP increases the chance of aspiration of the prosthesis. None of the studies included in this review, however, reported

the frequency of prosthetic dislodgement or aspiration of the VP in patients with enlarged TEP.

This review also sought to summarize the effect of potential risk factors for enlarged TEP. The risk of enlarged TEP may increase over time as a late complication of treatment. Four studies reviewed^{1, 6, 21, 26} documented TEP enlargement between 1 and 115 months post-TEP with mean time to enlargement between 20 and 40 months. Tissue damage associated with radiation therapy may contribute to the development of enlarged TEP and often manifests months or years after treatment has ended. Thus, the length of follow-up becomes a critical consideration when estimating the risk of this complication, but was not specified in more than half of the studies reviewed. In addition, none of the studies included in this review statistically analyzed the effect of radiation therapy on enlarged TEP nor was radiation history reported consistently across studies, which precluded our assessment of this risk factor by meta-regression methods or subgroup analysis.

The use of a large diameter VP has gained recent interest as another potential risk factor for enlarged TEP.^{3, 28, 29} Our subgroup analysis did not identify a statistically significant difference in the risk of enlarged TEP/leakage around the VP based on prosthetic diameter in studies that exclusively used a single diameter VP; however, there was a tendency toward higher rates in cohorts that used a 22-French or larger diameter prosthesis. Alternatively, 2 studies compared leakage patterns between prostheses of different diameters. Acton et al³ concluded that leakage around the VP could be minimized by avoiding large diameter (20-French) prostheses based on their finding that 76% of cases of leakage around the VP occurred in patients wearing a 20-French VP. However, the majority (61%) of all prosthetic changes in their sample occurred using a 20-French VP. Thus, it is unclear whether their findings reflect an unequal sample distribution of prosthetic diameters as they did not statistically analyze this association. We calculated a nonsignificant elevated relative risk (RR, 2.05; 95% CI, 0.78–5.36; $p = .13$) based on their data. In addition, Issing et al²⁹ reported salivary leakage exclusively in patients who wore a 22.5-French diameter VP compared to no cases of leakage in patients who wore a 16.5-French prosthesis. It is difficult to interpret the relevance of these findings to the risk of enlarged TEP as the case definition for salivary leakage was unclear and reported data were inconsistent. Therefore, it cannot be concluded based on current evidence that a large diameter VP increases the risk of enlarged TEP. Nevertheless, current data do not exclude the possibility of an association, and prosthetic diameter may be an important consideration, particularly in the management of patients who are at greater risk of complications after TEP.

Other risk factors for enlarged TEP may include variable practice patterns associated with primary versus secondary TEP, flap reconstruction, esophageal stricture, smoking history, thyroid function, reflux, and diabetes. Although none of these variables were analyzed as independent risk factors for enlarged puncture, 2 studies^{16, 30} statistically assessed a variety of potential risk factors for aggregated TEP-related complications that included enlarged puncture. Primary TEP,³⁰ diabetes,¹⁶ and esophageal stricture¹⁶ were found to be significantly associated with TEP complications. In addition, smoking status at diagnosis has been shown to increase the risk of postoperative wound complications after major head and neck surgeries³¹; however, none of the studies reviewed assessed smoking history as a risk

factor for enlarged puncture. Although a number of risk factors likely contribute to the development of an enlarged puncture, further analysis is clearly needed to clarify the multifactorial relationship of these variables on the risk of an enlarged TEP.

A summary of the use and effectiveness of conservative treatments for leakage around the VP found that the 2 most commonly reported methods were injections into the TE wall and temporary removal of the VP. However, most authors reported using a variety of conservative treatments. In our experience, a single approach is not successful for all patients. Unfortunately, current data lack sufficient information to determine a formal evidence-based algorithmic model of management. However, any clinician who has managed the enlarged TEP appreciates the substantial variation in the severity and presentation of this complication. As such, careful assessment to rule out an insidious medical etiology before embarking on prosthetic management is always prudent. We agree with those authors who advocate assessment and resizing of the TEP as the initial step in the hierarchic process of managing leakage around the VP.^{4, 6, 22}

Customization by adding an enlarged silicone collar to the esophageal and/or tracheal end of the prosthesis has been reported elsewhere as a conservative method for controlling leakage around the VP.^{7, 32} Interestingly, none of the studies included in this review described this technique. Custom prostheses provide nonsurgical, symptomatic relief of leakage around the VP, but the primary criticism of this method is that the custom prosthesis does not treat the underlying pathology. That is, the custom prosthesis does not stenose the enlarged TEP. Despite this criticism, customization has gained popularity in recent years because it provides a simple method to eliminate aspiration and avoids further surgical intervention in an already at risk field.

The most effective treatment for enlarged puncture remains unclear as no comparative studies were identified. In fact, many treatment studies were small ($n < 10$) case series whose results are difficult to generalize. Furthermore, inconsistent case definitions and assessment methods make treatment comparisons challenging. Although it is difficult to compare the effectiveness of treatments, it seems clear that the success of conservative treatment methods is often temporary, as many studies reported the need for repeated treatments. Temporary VP removal,⁹ electrocautery,¹⁰ TEP site injections,^{22, 23, 26} and purse-string sutures around the TEP⁶ were repeated for recurrent leakage after the initial treatment in 30% to 67% of the patients studied.

The primary limitation we encountered during this systematic review was inconsistent and incomplete methodologic reporting. The description of the complication varied across the studies and the etiology of leakage around the VP was not clearly specified in 10 studies we reviewed. It is important to acknowledge that leakage around the VP may occur as the result of an enlarged TEP but also as the result of improper length of the VP in the absence of TEP enlargement. Only 1 study⁴ we reviewed differentiated the etiology of leakage and found that improper prosthetic length was the cause of leakage around the VP in 57% of the cases. We sought to determine the effect of these 10 studies on our results by performing a sensitivity analysis. Exclusion of studies that did not describe the etiology of leakage around the VP from the meta-analysis and subgroup analyses had little effect on the summary risk

estimate or statistical outcomes for VP diameter and timing of TEP. It is imperative, however, that future studies differentiate the etiology of leakage around the VP to avoid overestimation of a potentially serious complication, enlarged TEP, because leakage around the prosthesis due to improper sizing is easily remedied by replacing an appropriately sized prosthesis.

Incomplete reporting limited our ability to compare results and assess heterogeneous observational findings across the studies. The risk estimates were statistically heterogeneous (Q-test; $p < .001$) among the 19 studies included in the meta-analysis. A sensitivity analysis was conducted to determine whether outliers were the primary source of variability. The test of homogeneity remained statistically significant after exclusion of 4 outliers^{15, 20, 27, 33} (risk estimate $<2\%$ or $>25\%$) from the meta-analysis; however, the fixed-effect and random-effect estimates became approximately equal indicating improved homogeneity after exclusion of the outliers. The results of this sensitivity analysis suggest that the extreme outcomes of these 4 studies contributed to the heterogeneity, but other unknown factors within the remaining studies also contributed to the variability. These results further support the need for clear methodologic reporting and description of population characteristics to ensure appropriate interpretation of findings and generalizable results across studies.

CONCLUSION

Our meta-analysis suggests that the overall risk of enlarged puncture after total laryngectomy with TEP is relatively low ($<10\%$); however, this complication presents a significant challenge for patients and clinicians to manage. We identified a number of conservative treatment methods that have been proposed to eliminate leakage around the prosthesis while maintaining functional TE voice; however, an effective long-term solution has not yet been reported. Current data suggest that, in most cases, conservative management techniques provide only transient relief of this complication. Incomplete reporting and methodologic discrepancies limit the ability to compare conservative treatment methods further or develop an evidenced-based algorithm for management. In addition, this review did not find clear evidence for any single risk factor for enlarged TEP. Our findings suggest that the role of prosthetic diameter remains controversial, and no study provided quantifiable evidence for the association between enlarged puncture and the effects of radiotherapy. It should be emphasized that the development of an enlarged puncture is a multifactorial event. Further investigation is needed to identify individual risk factors and multivariable interactions to achieve prevention of the enlarged TEP. Directions for future research should also include correlation of enlarged puncture with pneumonia, and prospective comparative assessments of conservative treatment methods. We are currently reviewing our experience with enlarged puncture guided by the findings of this systematic review and meta-analysis.

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Figure 1.
Forest plot for rate of enlarged TEP/leakage around the voice prosthesis (VP; $n = 19$).

Table 1Use of conservative treatments for enlarged TEP/leakage around the VP ($n = 20$)*

Treatment	No. of studies
Decrease length of VP ^{4, 24}	2
Increase diameter of VP ²⁷	1
Place anterior collar ²⁵	1
Temporary removal of the VP ^{4-9, 11-13, 19}	6
Downsizing around catheter ^{11, 16-18}	4
Injection	8
Collagen ^{4, 13, 25}	3
Bioplastique ²⁶	1
GM-CSF ²³	1
Autologous fat ²¹	1
Cymetra ²²	1
Other ²⁴	1
Purse-string suture ^{4, 6, 12}	3
Cautery ^{1, 8, 10, 11}	4
Thickening liquid ⁵	1
Multiple conservative treatments reported ^{14, 11-13, 20, 24, 25, 27}	8

Abbreviations: TEP, tracheoesophageal puncture; VP, voice prosthesis; GM-CSF, granulocyte-macrophage colony-stimulating factor

* Number of studies.

NOTE: Treatments are not mutually exclusive, 8 studies reported the use of a variety of treatments. Conservative treatments exclude complete surgical closure of the TEP.

Table 2

Rates of enlarged TEP and/or leakage around the VP (n=23) *

Primary Author	Year	No. Pts (No. VPs)	Design	Definition	Ratio (%) Enlarged TEP	Sample characteristics(timing of TEP, RT, VP type)
<i>Denominator: Patients</i>						
Singer ¹	1980	60	Retrospective	"Leakage around the voice prosthesis"	6/60 (10%)	Timing: 100% Secondary RT: 63% RT VP Type: 16 Fr BS Duckbill (no flange)
Singer ¹⁰	1981	129	Retrospective	"Leakage/aspiration around the voice prosthesis"	14/129 (11%)	Timing: 100% Secondary RT: Unspecified VP Type: 16 Fr BS Duckbill (no flange)
Silver ¹⁶	1985	47	Retrospective	"Leakage around the prosthesis"	6/47 (13%)	Timing: 100% Secondary RT: 57% RT VP Type: 16 Fr non-indwelling (brand unspecified)
Juarbe ¹⁷	1986	15	Retrospective	"Leaks around the prosthesis"	2/15 (13%)	Timing: 100% Primary RT: 20% Preop, 33% Postop, 47% None VP Type: 16 fr BS & BV Duckbill
Andrews ¹¹	1987	104	Retrospective	"Progressive expansion of the TE fistula"	6/104 (6%)	Timing: 7% Primary, 93% Secondary RT: 80% RT VP Type: 16 Fr BS Duckbill (w/flange)
Manni ²³	1990	132	Retrospective	"Too-large fistula"	1/132 (1%)	Timing: 94% Primary, 6% Secondary RT: 73% Preop, 9% Postop, 18% None VP Type: 21 Fr Groningen indwelling
Recher ²⁴	1991	102	Retrospective	"Fistula incontinence with salivary leakage around the prosthesis"	5/102 (5%)	Timing: 100% Secondary RT: 51% RT VP Type: 16 Fr BS Duckbill & Low Pressure & BV Colorado
Gart ²⁷	1991	119	Retrospective	"Enlarged fistula"	2/119 (2%)	Timing: 45% Primary, 55% Secondary RT: 87% RT VP Type: 16 FR BS Duckbill, Low Pressure, & BV Colorado
Hilgers ⁹	1993	132 (732)	Retrospective	"Widening of the fistula causing leakage around the prosthesis"	27/132 (21%)	Timing: 45% Primary, 55% Secondary RT: 46% Preop, 38% Postop, 16% None VP Type: 22.5 Fr Provox indwelling
Fukutake ¹⁸	1993	52	Retrospective	"Leakage of liquid...[requiring] reduction in diameter of the fistula"	1/25 (4%)	Timing: 100% Primary RT: 56% RT VP Type: 16 Fr BS Low-Pressure
Gerwin ²⁰	1993	24	Retrospective	"Leakage and/or gradually enlarging fistula"	7/24 (29%)	Timing: 100% Secondary RT: Unspecified VP Type: 16 & 20 Fr BS Duckbill and Low-Pressure
Silverman ¹⁴	1994	46	Retrospective	"Leakage around prosthesis...that compromised TE voice rehab or self-care"	3/46 (7%)	Timing: Unspecified RT: Unspecified VP Type: 16 Fr BS Low-Pressure
Izdebski ⁵	1994	95	Retrospective	"Leakage around the VP...result[ing] from fistula enlargement, epithelialization, or both"	5/95 (5%)	Timing: Unspecified RT: Unspecified

Primary Author	Year	No. Pts (No. VPs)	Design	Definition	Ratio (%) Enlarged TEP	Sample characteristics(timing of TEP, RT, VP type)
Mehta ¹⁵	1995	64	Prospective	"Salivary leak around valve"	1/64 (2%)	VP Type: 16 Fr BS Duckbill & 21 Fr Groningen indwelling Timing: 100% Primary RT: 16% Preop, 80% Postop, 4% None VP Type: 16 Fr BS Duckbill
de Carpentier ¹⁹	1996	39 (81)	Retrospective	"Leakage around the valve (necessitating hospitalization)"	3/39 (8%)	Timing: 55% Primary, 45% Secondary RT: 42% Preop VP Type: 22.5 Fr Provox indwelling
Leder ³⁴	1997	81 (206)	Prospective	"Leakage around the prosthesis"	3/81 (4%)	Timing: 43% Primary, 57% Secondary RT: 100% RT VP Type: 20 Fr BS Indwelling
Op de Coul ⁴	2000	318 (2396)	Retrospective	"Leakage around the prosthesis...not solved by simple downsizing"	57/318 (18%)	Timing: 87% Primary, 13% Secondary RT: 45% Preop, 43% Postop, 12% None VP Type: 22.5 Fr Provox & Provox 2 indwelling
Ferrer Ramirez ¹³	2001	350	Retrospective	"Enlargement of the TEP"	25/350 (7%)	Timing: 95% Primary, 5% Secondary RT: unspecified VP Type: 16.5 Fr Hermann Eska non-indwelling
Cornu ¹²	2003	128 (63)	Prospective	"Enlarged or oversized fistula...[or]...leak next to the prosthesis"	6/104 (6%)	Timing: 81% Primary, 19% Secondary RT: unspecified VP Type: 22.5 Fr Provox & Provox 2 indwelling
Calder ³⁰	2006	99	Retrospective	"Fistula too large"	16/99 (16%)	Timing: 91% Primary, 9% Secondary RT: 29% Preop, 51% Postop, 20% None VP Type: 16 Fr BS Low-Pressure, 22.5 Fr Provox & Provox2
Jacobs ⁶	2008	20	Prospective	"Peripheral leakage intractable to downsizing"	21/211 (10%)	Timing: 85% Primary, 15% Secondary RT: 40% Preop, 60% Postop VP Type: 22.5 Fr Provox & Provox 2 indwelling
<i>Denominator: VP Replacements</i>						
Op de Coul ⁽⁴⁾	2000	318 (2,396)	Retrospective	"Leakage around the prosthesis...not solved by simple downsizing"	81/2,396 (3%)	Timing: 87% Primary, 13% Secondary RT: 45% Preop, 43% Postop, 12% None VP Type: 22.5 Fr Provox & Provox 2 indwelling
Trussart ⁽²⁵⁾	2003	35 (178)	Retrospective	"Periprosthetic leakage"	12/178 (7%)	Timing: 100% Primary RT: 20% Preop, 43% Postop VP Type: 20 Fr BS Indwelling, 22.5 Fr Provox & Provox2 indwelling
Acton ⁽³⁾	2008	66 (200)	Prospective	"Leakage around the voice prosthesis"	21/200 (11%)	Timing: 11% Primary, 89% Secondary RT: 95% RT VP Type: 16 & 20 Fr BS Indwelling and non-indwelling

Abbreviations: TEP, tracheoesophageal puncture; VP, voice prosthesis; RT, radiation therapy; Fr, French; BS, Blom-Singer; BV, Bivona; TE, tracheoesophageal

* Number of studies. One study, Op de Coul et al (2000), reported rates both by patients and by number of VP replacements and is referenced in both sections of this table. Note: Listed chronologically

Table 3Results of conservative treatments for enlarged TEP/leakage around the voice prosthesis ($n = 10$)*

Treatment	Primary author (y)	Study design (n)	Case definition	Results
Decrease length of VP	Op de Coul ⁴ (2000)	Retrospective (n = 318)	“Leakage around the voice prosthesis”	Eliminated leakage around in 76/133 (57%)
Increase diameter of VP	Garth ²⁷ (1991)	Retrospective (n=119)	“Enlarged fistula”	Successful in 0/2 (0%)
Temporary removal of the VP	Hilgers ⁹ (1993)	Retrospective (n = 132)	“Widening of the fistula causing leakage around the prosthesis”	Single removal successful in 15/27 (56%), 2 removals in 7/27 (26%), 3 removals in 1/27 (4%), and 4/27 (15%) unsuccessful, required surgical closure of the TEP
Injection				
Bioplastique	Lorincz ²⁶ (2005)	Case Series (n = 7)	“Periprosthetic fistula”	Single injection eliminated or minimized leakage in 4/7 (57%), 2 injections in 2/7 (29%), and 3 injections in 1/7 (14%)
GM-CSF	Margolin ²³ (2001)	Case Series (n = 3)	“Fistula too large ...leakage around the VP”	Single injection eliminated leakage in 1/3 (33%) and 2 injections in 2/3 (67%)
Autologous fat	Perie ²¹ (2002)	Prospective (n=10)	“Leakage around the TEP ... previously untreated”	Leak eliminated in 6/10 (60%), minimized to intermittent, slight pooling 2/10 (20%), and marked persistent leak in 2/10 (20%). 10–61 month follow-up
Cymetra	Seshamani ²² (2006)	Case Series (n = 6)	“Leakage around the TEP refractory to downsizing and/or cautery”	Single injection eliminated leak in 2/4 (50%), 3 injections eliminated leak in 1/4 (25%) and minimized leak in 1/4 (25%)
Purse-string suture	Jacobs ⁶ (2008)	Prospective (n = 20)	“Peripheral leakage intractable to downsizing”	Single suture eliminated leakage in 5/20 (25%), multiple in 11/20 (55%), and 4/20 (20%) unsuccessful
Cautery	Singer ¹⁰ (1981)	Retrospective (n=129)	“Leakage around the VP”	Single cauterization successful in 9/14 (64%), multiple in 3/14 (21%), 2/14 (14%) unsuccessful, required surgical closure
	Singer ¹ (1980)	Retrospective (n = 60)	“Leakage/aspiration around the VP”	Successful in 5/6 (83%)

Abbreviations: TEP, tracheoesophageal puncture; VP, voice prosthesis; GM-CSF, granulocyte-macrophage colony-stimulating factor

* Number of studies.