How to Reduce Pharyngocutaneous Fistula Incidence?

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Abstract

Objective: To summarize the protection factors for pharyngocutaneous fistula.

Data Sources: Published English-language literature.

Review Methods: PubMed, Ovid, Cochrane, and Web of Science databases were systematically searched using multiple search terms 127 studies were identified.

Study Selection: We included studies about the PCF risk factors (meta analysis articles), Using Vascularized flap in high risk patients, Using Stapler during Pharyngeal repair, Pharyngeal Reconstruction type, using antibiotics, using anti GERD medication, using collagen patch, Early oral feeding and type of manual pharyngeal repair. We also included some under investigated measurements.

Results: 127 studies were included for this study. The results showed that early detection of tumor, Control Co-Morbidities, Avoid Radiotherapy and tracheotomy if that is possible, Local control of tumor during Surgery, Using Vascularized flap such Pectoralis Muscle Flap in high risk patient, Using Stapler during Pharyngeal repair and Using Jejunal Free Flap for laryngeal Reconstruction using antibiotic, anti GERD medication and collagen patch may decrease the incidence of Pharyngocutaneous.

Conclusion: We can decrease the incidence of FCF by taking some measurements preoperatively, during the surgery and postoperatively.

Introduction

Pharyngocutaneous fistula is a common complication of total laryngectomy, since it is a self-limiting disease, its management is based on conservative treatment; however, at some times, surgery is required for this complication. PCF increases the rate of morbidity, hospitalization, and cost of care, in addition it delays starting indicated adjuvant therapy. The incidence of pharyngocutaneous fistula after primary total laryngectomy is 14.3%.1

Material and Method

Literature review was conducted using PubMed (MEDLINE) for English articles, from January 1989 to May 2016. The following keywords were used: of Pharyngocutaneous and Fistula.

Results

4 meta analysis articles about risk factors, 5 articles about the role of antibiotics in decreasing pharyngocutaneous fistula incidence, 3 articles about the role of anti GERD medications in decreasing pharyngocutaneous fistula incidence, 7 articles about the role of Collagen patch and artificial biological material1 in decreasing pharyngocutaneous fistula incidence, 12 articles including one meta analysis article about the role of early oral feeding in pharyngocutaneous fistula incidence, 16 articles including two meta analysis articles about the role of vascularized flap in decreasing...
pharyngocutaneous fistula incidence in highly risk patients, 8 articles including one meta analysis article about the role of Stapler mechanical pharyngeal repair in decreasing pharyngocutaneous fistula incidence in highly risk patients, 5 articles about the role of manual pharyngeal repair in pharyngocutaneous fistula incidence, 7 articles about the role of under investigated procedures used to decrease pharyngocutaneous fistula incidence, 62 articles about the role of different flap types used for pharyngeal reconstruction in pharyngocutaneous fistula incidence Tables 1-6.

### Table 1: PCF risk factors.

| Meta Analysis Article | Articles Number | morbidities | Anemia | Anemia nutritional deficiency | Radiotherapy | Chemotherapy | Supraglottic Tumor site | Stage | Cartilage invasion | Positive Margins | Neck dissection | Surgery’s duration, surgeon’s experience | Local complications of the wound | Previous Tracheostomy |
|-----------------------|----------------|-------------|--------|--------------------------------|--------------|---------------|------------------------|-------|------------------|-----------------|----------------|------------------------------------------|-------------------------------|-------------------|
| Dedivitis, et al. [1]  | 311            | +           | +      | +                              | +            | +             | +                     | +     | +                | +               | +              | +                                       | +                            | +                 |
| Cecatto, et al. [2]    | 39             | +           | +      | +                              | +            | +             | +                     | +     | +                | +               | +              | +                                       | +                            | +                 |
| Paydarfar, et al. [3]  | 65             | +           | +      | +                              | +            | +             | +                     | +     | +                | +               | +              | +                                       | +                            | +                 |
| Liang, et al. [4]      | 21             | +           | +      | +                              | +            | +             | +                     | +     | +                | +               | +              | +                                       | +                            | +                 |

### Table 2: Medium evidence prophylactic measurements.

| Early Oral Feeding | Vascularized flap such pectoris flap | Stapler Using | Manual Pharyngeal suturing Repair Type |
|--------------------|--------------------------------------|---------------|--------------------------------------|
| Article            | Influence                            | Article       | Influence                            | Article       | Influence | Article       | Influence | Article       | Influence | Article       | Influence | Article       | Influence | Article       | Influence |
| Aswani, et al. [20] | Do not increase                      | Paleri, et al. [32] | Decrease                            | Cali, et al. [48] | Decrease | Aydin, et al. [56] | Non       |
| Timmermans, et al. [21] | Do not increase                      | Merdad, et al. [33] Meta analysis | Decrease | Dedivitis, et al. [49] | Decrease | Deniz, et al. [57] | Non       |
| Aires, et al. [22] Meta analysis | Do not increase                      | Guimarães, et al. [34] Meta analysis | Decrease | Zhang, et al. [50] | Decrease | Shukla, et al. [58] | Significant |
| Kishikova, et al. [23] | Do not increase                      | Gendreau-Lefèvre, et al. [35] | Decrease | Aires, et al. [51] Meta analysis | Decrease | Haksever, et al. [59] | Non       |
| Medina, et al. [24] | Do not increase                      | Sharma, et al. [36] | Decrease | Liu, et al. [52] | Decrease | Wang, et al. [60] | Non       |
The incidence of pharyngocutaneous fistula can be decreased by various prophylactic measures. Table 3 summarizes these measures:

| Study Authors | Measure Description | Reduction |
|---------------|---------------------|-----------|
| Saydam et al. [25] | Do not increase |  |
| Eustaqui et al. [26] | Do not increase |  |
| López-Cuevas et al. [27] | Do not increase |  |
| Boyd et al. [28] | Do not increase |  |
| Song et al. [29] | Do not increase |  |
| Lau et al. [30] | Do not increase |  |
| Sousa et al. [31] | Do not increase |  |
| Eryilmaz et al. [61] | Using tissue adhesives and platelet-rich plasma | Decrease |
| Asher et al. [62] | Using Intraluminal negative pressure wound therapy | Decrease |
| Marchese et al. [63] | Botulinum toxin-A injection inside salivary gland to decrease saliva production | Decrease |
| Punthakee et al. [64] | Using salivary bypass tubes | Decrease |
| Cordova et al. [65] | Using and hyperbaric oxygen therapy | Decrease |

Table 4: Protective procedures under investigation.

| Flap Type | Article Authors | Article Ref. | PN | FN |
|-----------|----------------|-------------|----|----|
| Fasciocutaneous Free Flap | Liu et al. [66] | [66] | 22 | 3 |
| | Huang et al. [67] | [67] | 45 | 8 |
| | Chen Salvage et al. [68] | [68] | 33 | 14 |
| | Tan et al. [69] | [69] | 5 | 0 |
| Pectoralis Muscle Flap | Chao et al. [78] | [78] | 9 | 1 |
| | Montemario et al. [87] | [87] | 45 | 2 |
| | Espitalier et al. [88] | [88] | 41 | 9 |
| | Zhang et al. [89] | [89] | 22 | 2 |
| Jejunal Free Flap | Nakatsuka et al. [84] | [84] | 70 | 3 |
| | Li et al. [99] | [99] | 14 | 0 |
| | Mizukami et al. [100] | [100] | 2 | 0 |
| | Yan et al. [101] | [101] | 112 | 10 |
| Gastric Pull Up | Marion et al. [115] | [115] | 38 | 1 |
| | Liu et al. [116] | [116] | 24 | 9 |
| | Sreehari Prasa et al. [117] | [117] | 42 | 2 |
| | Shuangba et al. [118] | [118] | 17 | 1 |
| Hemilaryngeal Flap | Mc Combe et al. [127] Meta analysis | [127] | 86 | 16 |

Table 3: Strong evidence prophylactic measurements.
### Table 5: Rate of PCF in Different Flab Used in Pharyngeal Reconstruction.

| Scaglioni, et al. [70] | 13 | 3 | Leite, et al. [90] | 84 | 31 | Pesko, et al. [102] | 5 | 0 | Homma, et al. [119] | 208 | 39 |
|------------------------|----|---|-------------------|----|----|-------------------|---|---|-------------------|-----|----|
| Kim, et al. [71]       | 6  | 1 | Rudes, et al. [91] | 10 | 3 | Oestreicher-Kedem, et al. [103] | 5 | 0 | Huscher, et al. [120] | 10  | 2 |
| Revenaugh, et al. [72] | 21 | 1 | Spriano, et al. [92] | 37 | 5 | Zhao, et al. [104] | 7 | 1 | Ni, et al. [111] | 10  | 1 |
| López, et al. [73]     | 55 | 5 | Xu, et al. [93] | 30 | 4 | Chevalier, et al. [105] | 56 | 2 | Watanabe, et al. [122] | 120 | 12 |
| Spyropoulou, et al. [74] | 55 | 10 | Saussez, et al. [94] | 12 | 4 | Zhu, et al. [106] | 58 | 11 | De Paula, et al. [123] | 14  | 2 |
| Sagar, et al. [75]     | 20 | 5 | Morshed, et al. [95] | 11 | 5 | Tizian, et al. [107] | 48 | 3 | Shenoy, et al. [124] | 120 | 10 |
| Wu, et al. [76]        | 2  | 0 | Jegoux, et al. [96] | 18 | 4 | Takooda, et al. [108] | 44 | 4 | Cahow, et al. [125] | 105 | 15 |
| Zeiken, et al. [77]    | 12 | 2 | Ko, et al. [97] | 6  | 3 | Perez-Smith D, et al. [109] | 368 | 30 | Katsenell, et al. [126] | 59  | 2 |
| Chao, et al. [78]      | 9  | 2 | Burke, et al. [98] | 11 | 3 | Ferakhose, et al. [110] | 14 | 1 | Denewer, et al. [86] | 34  | 5 |
| Zhang, et al. [79]     | 11 | 3 |                      |    |    | Julieron, et al. [111] | 73 | 11 |
| Joo, et al. [80]       | 48 | 5 |                      |    |    | Chang, et al. [112] | 168 | 23 |
| Hong, et al. [81]      | 12 | 1 |                      |    |    | Benazzo, et al. [113] | 29 | 1 |
| Amin, et al. [82]      | 16 | 5 |                      |    |    | Walker, et al. [114] | 104 | 11 |
| Scharpf, et al. [83]   | 25 | 2 |                      |    |    | Denewer, et al. [86] | 25  | 2 |
| Nakatsuka, et al. [84] | 39 | 15 |                      |    |    |                      |    |    |
| Ho, et al. [85]        | 15 | 1 |                      |    |    |                      |    |    |
| Denewer, et al. [86]   | 50 | 12 |                      |    |    |                      |    |    |

| Total                   | 514| 98 | 328 | 76 | 113 | 801 | 86 | 16 |
| Percentage              | 19%| 23,1% | 9,9%| 12,6%| 19% |
Discussion

Low hemoglobin increase the frequency of PCF due to decrease the oxygen carriage to surgical site by the hemoglobin, thus inducing poor wound healing [128]. The frequency of malnutrition is about 30-50% in patient with head and neck cancers. Patients who lose more than 10% of their weight prior to surgery are at risk to have higher incidence of fistula, so controlling malnutrition at head and neck cancer patients preoperatively may decrease the incidence of fistula [129]. Skin incision heals in a water tight fashion within 24-48h after surgery, so early oral feeding do not increase the fistula incidence, but it increase the granulation tissue formation along surgical site and help more the closure of wound [130]. Tracheotomy is frequently done in advanced tumors due to the airway obstruction at presentation. It is done in emergency situation in a bacteriaily contaminated field; and this may lead to increase post total laryngectomy PCF fistula formation [131]. Large tumor, Supraglottic tumor need more mucosal resection and these make stitches under tension and increase the fistula incidences, so early detection of small tumors and early treatment may decrease the fistula incidence [132]. Irradiated tissue lacks good circulation and more friable and must be handled more gently. Radiations also produce mucositis at early phase and in chronic phase it produce endarteritis, fibrosis, decrease cellular replication and impaired angiogenesis. All above increase the fistula formation, so avoid preoperative radiation may decrease the incidence of fistula formation [130]. Positive surgical margins induce deficient healing process at surgical wound increasing the frequency of fistula formation, so insuring that surgical margins are free by frozen section may decrease the number of fistula formation [133]. The use of PMF in salvage laryngeal surgery can minimize pharyngocutaneous fistulas formation and it help primary skin wound healing. This flap will help the patient to start early oral feeding, it also give good tracheotomy care, short hospital stay and protection from vascular blow out complication [134]. Pharyngeal reconstruction type is almost dependent on pharyngeal defect , but the rate of fistula formation when we use jejunum flap is much less than when we use tube pectoralis muscle, also the rate of spontaneous closure is higher, this is due to better healing of muco-mucous anastomosis in free jejunum flap. Aydin, et al. [56] Deniz et al. [57] & Wang, et al. [60] found that there is no association between PCF formation with pharyngeal repair time, mucosal suture count, and suture frequency after total laryngectomy. Pharyngeal repair using linear staplers during total laryngectomy has been reported to reduce the rate of PCF the last Manual stitches

**Table 6: PCF Protective Measurements.**

| Protective Measurements (strong Evidence) There is meta analysis Articles | Protective Measurements (medium Evidence) Multiple Articles | Protective Measurements (low under investigated Evidence) Few Articles | Non-Significant Measurements (do not increase or decrease risk of fistula) |
|---|---|---|---|
| 1-Early Detection Of tumor. | 1-Antibiotics | 1-using tissue adhesives and platelet-rich plasma | 1-Early Oral Intake. |
| 2-Control Co-Morbidities like anemia, COPD, nutritional deficiency, hypoalbuminemia | 2-Anti GERD Medication | 2-Using Intraluminal negative pressure wound therapy. | 2-Type of pharyngeal manual Suturing. |
| 3-Avoid Radiotherapy, chemotherapy and tracheotomy it is possible. | 3-Using Collagen patch and artificial biological material during pharyngeal reconstruction. | 3-botulinum toxin-A injection inside salivary gland to decrease Saliva production. | |
| 4-Locak control of tumor during Surgery | | 4-Using salivary bypass tubes. | |
| 5- Using Vascularized flap such Pectoralis Musle Flap in Salvage laryngectomy | | | |
| 6- Using Stapler during Pharyngeal repair | | 5-Using hyperbaric oxygen therapy. | |
| 7-Using Jejunal Free Flap for laryngeal Reconstruction | | | |
take longer, increase the risk of necrosis of the pharyngeal mucosa, and saliva contamination of the surgery site. Additionally, a weak spot in manual laryngeal closure is noticed at junction point in the T-shaped stitches. This weak spot is not seen when a stapler is used [51]. GERD has important role in multiple inflammatory and neoplastic disorders of the upper aerodigestive tract. 70%. Patients of laryngeal carcinoma have abnormal 24-hour pH studies using the double pH probe monitoring system. Also many laryngectomy patients have gastro esophageal reflux. Gastric acid is known to cause severe laryngopharyngeal injury and poor mucosal healing. So applying routine postoperatively Anti GERD Medications may decrease the rate of PCF development [130]. Antibiotic help to decrease the incidence of fistula by decreasing contamination at surgical site 5-6-7-8. A collagen patch integrated with activated thrombin and fibrinogen was reported in multiple articles to decrease the postoperative fistula formation by applying them on sites with a high risk site of salivary leakage [13]. Eryilmaz, et al. [61] found that using platelet-rich plasma tissue may prevent fistula, he found higher inflammatory cells and higher fibroblastic activity at surgical site when using such tissue [62].

Using Intraluminal negative pressure wound therapy May Help primary closure and accelerate healing process, and protect suture lines from saliva by acting like a stent so it decrease the incidence of the fistula . [62]. There is also a little evidence that botulinum toxin-A injection inside salivary gland may prevent fistula formation as it decrease Saliva production and contamination at surgical site [63]. Some authors reported that using salivary by pass may decrease contamination in surgical site and protect surgical site from the fistula so it may help decreasing fistula formation [64]. There is a few articles suggest that hyperbaric oxygen therapy may decrease the fistula formation as it Induce angiogenesis, fibroblast proliferation, leukocyte oxidative killing, toxin inhibition and antibiotic synergy. It also reduces post-traumatic tissue oedema, and increase plasma oxygen content and microvascular blood flow [65] (Tables 7 & 8).

| Risk factor                  | Pathophysiology                                                                 | Protection                        |
|-----------------------------|---------------------------------------------------------------------------------|-----------------------------------|
| Radiotherapy                | Vasculitis which develops post radiotherapy and increase the risk of infection. | Avoid Radiotherapy if it is possible |
| Tracheastomy                | Contamination Fibrosis and higher T stage                                       | Avoid tracheastomy if it is possible |
| Supraglotic tumor site      | Large amount of mucosal pharyngeal resection leading to closure under tension   |                                    |
| Co-Morbidities              | Poor healing Process                                                            | Control Co-Morbidities            |
| Positive Margins            | Tumor recurrence and need for chemoradiotherapy                                 | Frozen section for margins        |
| Advanced T tumor            | large amount of mucosal pharyngeal resection leading to closure under tension    | Early tumor detection             |

Table 7: Pathophysiology of PCF risk factors.

| Protection measurement      | Mechanism |                                                                 |
|-----------------------------|-----------|-----------------------------------------------------------------|
| Anti GERD medications.      | Decrease pharyngeal injury caused by Gastric acid.               |                     |
| Antibiotics                 | Decrease surgical site contamination                             |                     |
| Vascularized Flap           | Increase blood supply, cover and reinforce surgical site        |                     |
| Collagen patch and artificial | -reinforcement of damaged soft tissues.  
- help the recovery at the site of soft tissue repair.  
-local delivery of bone marrow derived stem cells, growth factors, and other bioactive compounds to further augment repair. |                     |
Stapler

- Decrease the risk of necrosis of the pharyngeal mucosa
- Decrease saliva contamination of the surgery site.
- No weak spot is noticed at junction point in the T-shaped stitches

Using Intraluminal negative pressure wound therapy.

- Help primary closure
- Accelerated healing process
- Reduce salivary exposure of the suture lines; - act as a stent to decrease positive pressure from swallowing along the closure site

Using salivary bypass tubes.

- Decrease contamination in surgical site

Hyperbaric oxygen therapy.

- Induce angiogenesis, fibroblast proliferation, leukocyte oxidative killing, toxin inhibition and antibiotic synergy.
- Reduces post-traumatic tissue oedema.
- Increased plasma oxygen content and microvascular blood flow

Botulinum toxin-A injection inside salivary gland to decrease saliva production

- Decrease saliva production and decrease contamination in surgical site

Table 8: PCF Protection measurements mechanism.

Conclusion

There is strong evidence that. There is medium evident the using antibiotic, anti GERD medication and collagen patch may decrease the incidence of Pharyngocutaneous fistula. Early oral feeding and type of manual pharyngeal repair do not effect on Pharyngocutaneous fistula incidence. There are multiple approaches that should be investigated more about its role in decreasing Pharyngocutaneous fistula incidence such tissue adhesives and platelet-rich plasma, Intraluminal negative pressure wound therapy, botulinum toxin-A injection inside salivary gland, salivary bypass tubes and hyperbaric oxygen therapy.

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