

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 material I 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.

Meta Analysis Article	Articles Number	morbidities Anemia nutritional deficiency	Radiotherapy Chemotherapy	Supraglottic Tumor site	Stage	Cartilage invasion	Positive Margies	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 1: PCF risk factors.

Prophylactic antibiotics		Prophylactic anti GERD Medications		Collagen patch and artificial biological material	
Article	influence	Article	Influence	Article	influence
Li, et al. [5]	Decrease	Stephenson, et al. [10]	Decrease	Wang, et al. [13]	Decrease
Stathas, et al. [6]	Decrease	Seikaly, et al. [11]	Decrease	Weiss, et al. [14]	Decrease
Harris, et al. [7]	Decrease	Sarria, et al. [12]	Decrease	Zhang, et al. [15]	Decrease
Violaris, et al. [8]	Decrease			He, et al. [16]	Decrease
Johansen, et al. [9]	Decrease			Yang, et al. [17]	Decrease
				Lee, et al. [18]	Decrease
				Yin, et al. [19]	Decrease

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
Aswani, et al. [20]	Do not increase	Paleri, et al. [32]	Decrease	Calli, 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

Saydam, et al. [25]	Do not increase	Mizrachi, et al. [37]	Decrease	Babu, et al. [53]	Decrease		
Eustaquio, et al. [26]	Do not increase	Powell, et al. [38]	Decrease	Manola, et al. [54]	Decrease		
Rodríguez-Cuevas, et al. [27]	Do not increase Do not increase	Kadota, et al. [39]	Decrease	Ahsan, et al. [55]	Decrease		
Boyce, et al. [28]	Do not increase	Iida, et al. [40]	Decrease				
Song, et al. [29]	Do not increase	Patel, et al. [41]	Decrease				
Lau, et al. [30]	Do not increase	Cömert, et al. [42]	Do not Decrease				
Sousa, et al. [31]	Do not increase	Albirmawy, et al. [43]	Decrease				
		Oosthuizen, et al. [44]	Decrease				
		Higgins, et al. [45]	Decrease				
		Mebeed, et al. [46]	Decrease				
		Righini, et al. [47]	Decrease				

Table 3: Strong evidence prophylactic measurements.

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.

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

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. [121]	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			
Zelken, et al. [77]	12	2	Ko, et al. [97]	6	3	Perez-Smith D, et al. [109]	368	30	Katzenell, et al. [126]	59	2			
Chao, et al. [78]	9	2	Burke, et al. [98]	11	3	Ferahkose, 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%	

Table 5: Rate of PCF in Different Flap Used in Pharyngeal Reconstruction.

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 tracheostomy it is possible.	3-Using Collagen patch and artificial biological material during pharyngeal reconstruction.		
4-Local control of tumor during Surgery		3-botulinum toxin-A injection inside salivary gland to decrease Saliva production.	
5- Using Vascularized flap such Pectoralis Muscle Flap in Salvage laryngectomy		4-Using salivary bypass tubes.	
6- Using Stapler during Pharyngeal repair		5-Using hyperbaric oxygen therapy.	
7-Using Jejunal Free Flap for laryngeal Reconstruction			

Table 6: PCF Protective Measurements.

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 bacterially 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

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
Tracheostomy	Contamination ,fibrosis and higher T stage	Avoid tracheostomy if it is possible
Supraglottic 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, - <i>increased plasma oxygen content and microvascular blood flow</i>
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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