Platelet-rich Fibrin in Upfront Total Laryngectomy and Pharyngocutaneous Fistula: A Systematic Review and Meta-Analysis

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Abstract

Objective: To examine the efficacy of platelet-rich fibrin (PRF) in reducing postoperative pharyngocutaneous fistula (PCF) for patients undergoing primary total laryngectomy (TL).
Review Methods: A systematic review and meta-analysis was conducted using PubMed, Embase, Scopus, CENTRAL and Web of Science databases from inception to December 2024. Three studies were included.
Results: 155 patients undergoing upfront TL were included. 78 patients were in the PRF arm, and 77 patients were in the control arm (no PRF application). Follow-up time ranged from 5 to 30 days across studies. The incidence of PCF was found to be significantly reduced in the PRF groups (OR = 0.13, 95% CI [0.08; 0.38], I^2 = 0%, p < 0.01). Average length of hospital stay, and postoperative pain and edema were significantly lower in the PRF group. There was an inverse correlation between low albumin and hemoglobin with higher PCF incidence.
Conclusions: PRF shows potential in reducing the incidence of PCF in patients undergoing primary TL. Longer follow-up times are needed to ensure the oncologic safety of PRF application. Exploration of the application of PRF to radiated tissue is necessary in the setting of a salvage laryngectomy due to higher incidence of PCF in irradiated tissue.

Introduction

Pharyngocutaneous fistula (PCF) is a well-known complication following total laryngectomy (TL).[1] It has been shown to increase mortality, morbidity, hospital stay, delay in adjuvant treatment, and length of feeding tube dependence.[2-3] Multiple efforts have been made to decrease the incidence of PCF following TL, such as tension-free closure, multilayer closure, adequate preoperative nutrition and thyroid function to mount a robust healing response.[4-5] PRF has been shown to improve healing in various tissues.[6] It is affordable and easy to procure.[6] In the literature, PCF occurs at a rate of about 10% in primary TL, with reported incidences ranging from 11.7-17.0%, but increases to up to 30% in salvage TL, with reports ranging from 23.4-31.8% in salvage TL.[7-10] Recent studies have proposed the application of PRF to reduce PCF formation following upfront TL.[11-13]

Methods and Materials

Eligibility Criteria:
Inclusion criteria: age > 18 with laryngeal squamous cell carcinoma (SCC) undergoing TL (primary or salvage) with application of PRF to the pharyngeal repair. The primary outcome of interest was the incidence of PCF. Secondary outcomes, such as postoperative hemoglobin, albumin, time to oral feeding, postoperative pain, edema, and hyperemia, are reported when available.
Exclusion criteria: patients with laryngeal tumors extending to the post cricoid region, piriform sinuses, and/or the hypopharynx, or patients who did not undergo TL. Animal studies, case reports, and case series with <10 patients were excluded.
Data Analysis:
A meta-analysis of binary outcomes was conducted on R-Studio using the Mantel-Haenszel model due to low heterogeneity. The Mantel-Haenszel method was used to perform odds ratio meta-analysis. Heterogeneity was assessed via the I^2 statistic. Publication bias was evaluated plotting a funnel plot for visual representation.

Results

Study Characteristics:
Two studies included in the meta-analysis were randomized controlled trials,[12,13] while one was retrospective[11] (***Table 1***). All patients were assigned to the PRF or control arm. Patients had Stage T3 and T4a tumors. All 3 studies **excluded** patients with history of radiation to the head and neck.

Baseline characteristics and PRF methods are in ***Table 2***. In all 3 studies, PCF was identified by swallow study or by administration of sterile water or blue dye. PRF was applied as follows:
- Laid into a T-shape and secured with several sutures (n=2 studies)
- PRF applied directly over the pharyngeal closure line (n=1 study)

All 3 studies performed pharyngeal reconstruction with a two-layer tensionless reconstruction. Evidence of PCF formation was assessed on day 5, day 10, and day 30 for each study respectively.

Meta Analysis:
All three studies reported the incidence of PCF postoperatively as a binary outcome. A meta-analysis of odds ratios demonstrated a significant reduction in the incidence of PCF postoperatively, as shown in ***Figure 2.*** (n=155 patients, OR= 0.13, 95% CI [0.08; 0.38], p<0.001). Additionally, the analysis indicated a lack of interstudy heterogeneity (I^2= 0%, p=0.71).

Secondary Outcomes:
Yilmazer et al:
The time to transition to oral feeding was 10.7 ± 1.1 days for the PRF group and 11.3 ±1.9 days for the control group (p = 0.26). The average hospital stay was 16.9 ± 7.5 and 20.7 ± 14.9 days in the PRF and control groups, respectively (p = 0.09).[11]
Eid et al:
Found correlation between low basal albumin and hemoglobin levels with an increase in the overall incidence of PCF (Correlation coefficient: -0.699, -0.579; p < 0.001). Patients with T4 SCC had an increased incidence of overall PCF with an odds ratio of 4.7 compared to patients with T3 disease.[12]
Reksodiputro et al:
VAS pain scores indicated a statistically significant decrease on postoperative days 2, 5, and 6 in the PRF group compared to the control (p<0.05). A statistically significant reduction in edema was observed on day 6 in the PRF group compared to the control (p < 0.05), with no difference noted on days 2, 3, 4, 5, and 14. There was no significant difference in hyperemia on days 2-14.[13]

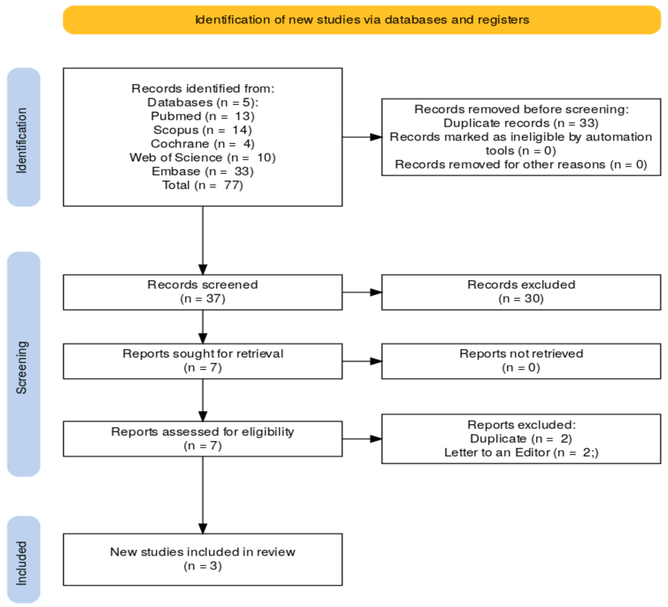

Figure 1. PRISMA flow diagram of study selection

Author	Study Design	Country	Study Duration	Sample Size	Population	Stage of laryngeal SCC	Outcomes
Reksodiputro et al. (2021)	RCT	Indonesia	June 2019-December 2019	n = 20	TL with or without Neck Dissection	T1-T2	Edema, hyperemia, pain, and PCF incidence
Eid et al. (2020)	RCT	Egypt	June 2018–June 2020	n = 67	TL with bilateral or unilateral neck dissection	T3-T4	PCF incidence
Yilmazer et al. (2024)	Retrospective	Turkey	2017-2022	n = 68	TL with bilateral neck dissection	T4a	Hemoglobin and albumin levels, hospital stay duration, and PCF incidence

Table 1. Descriptive summary of the included studies.

Author	Group	Age (Mean, SD)	Sex (Male, Female)	Follow up	Neck Dissection	Pharyngeal Reconstruction
Reksodiputro et al. (2021)	PRF	60	10, 0	5 days	With or without Neck Dissection	Two-layer reconstruction with T-shaped sutures
	Control	60	10, 0			
Eid et al. (2020)	PRF	60.29 ± 8.61	34, 1	10 days	Bilateral or unilateral neck dissection	Two-layer closure with inverted sutures
	Control	59.91 ± 9.24	31, 1			
Yilmazer et al. (2024)	PRF	62.4 ± 7.2	29, 4	Within 30 days	Bilateral neck dissection	Two-layer closure with T-shaped sutures
	Control	64.1 ± 9.3	30, 5			

Table 2. Baseline characteristics of the included studies

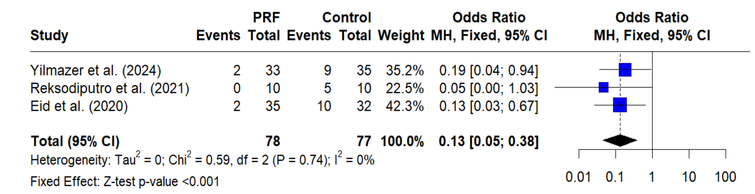

Figure 2. Forest plot of odds ratio meta-analysis of pharyngocutaneous fistula formation following primary total laryngectomy

Discussion

This systematic review and meta-analysis examined the efficacy of PRF in reducing the formation of PCF in patients undergoing primary TL for laryngeal SCC with 2 RCTs and one retrospective cohort study. PCF occurred at a rate of 5.1% versus 31.2% in the PRF and control group, respectively. A meta-analysis by Sayles et al. reported a pooled incidence rate of 14.3% and 27.6% following primary TL and salvage TL, respectively. The control arms had a PCF incidence of 25.%, 31.3%, and 50% for Yilmazer et al. Eid et al. and Reksodiputro et al., respectively. Secondary outcomes, including albumin levels, hemoglobin levels, and time to oral feeding, need further investigation due to possible reduction in hospital stay and pain scores, which would help improve expenditure and patient satisfaction.
Future direction and suggestions for further research:
Future studies should examine PRF application with larger sample sizes and longer follow-up time to better evaluate its oncologic safety. Further studies are needed to examine PRF in salvage TL, as irradiated patients are at higher risk for poor wound healing.

Conclusions

This systematic review and meta-analysis evaluated the efficacy of PRF application in reducing PCF following primary TL for patients with laryngeal SCC. Our meta-analysis showed a statistically significant decrease in PCF. However, due to the substantial disparity between the control arms' average PCF incidence and the literature standard, more studies are needed to ensure the lack of bias within the studies. Additionally, more studies are needed to focus on the efficacy of PRF following salvage TL. Overall, PRF provides a compelling, cost-effective adjunct for reducing PCF; more research is needed on secondary outcomes such as complications, long-term recurrence, time to feeding, discharge, and hospital expenses.

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References