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ORIGINAL ARTICLE

Post-operative paralysis and elective ventilation reduces anastomotic complications in esophageal atresia: a systematic review and meta-analysis

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Abstract

Aim of study The repair of esophageal atresia (EA) carries an increased risk of anastomotic leak and stricture formation, especially in patients with anastomotic tension. To minimize this risk, pediatric surgeons perform elective post-operative muscle paralysis, positive-pressure ventilation, and head flexion (PVF) to reduce movement and tension at the anastomosis. We systematically reviewed and analyzed the effect of post-operative PVF on reducing anastomotic complications.

Methods Embase, MEDLINE, Web of Science, and PubMed databases were used to conduct searches. Articles reporting pediatric EA undergoing primary anastomosis, anastomotic complications, and comparisons between patients who received post-operative PVF to those who did not were included. Odds ratios (OR) for all post-operative anastomotic complications were calculated using random effects modelling.

Main results Three of the 2268 papers retrieved met inclusion criteria (all retrospective cohort studies). There were no randomized controlled trials. Post-operative PVF showed a significant reduction in anastomotic leak (OR 0.07; 95% CI 0.01–0.35) when compared to no PVF. Stricture formation was not statistically different between groups. Potential sources of bias include patient allocation.

Conclusions Based on available data, our analysis indicates PVF may reduce anastomotic post-operative leak. To confirm these results, a prospective study with clearer definitions of treatment allocation should be performed.

Keywords Pediatric surgery · Esophageal atresia · Primary anastomosis · Endotracheal intubation · Mechanical ventilation · Muscle paralysis

Introduction

Esophageal atresia (EA), with or without tracheoesophageal fistula (TEF), is a congenital anomaly affecting the continuity of the esophagus with a worldwide incidence of approximately 1 in 2500–4500 births [1]. Since the first successful EA/TEF repair in 1941 [2], many advances have occurred to better treat this disease and recent survival of infants born with EA/TEF has increased to exceed 90% [3]. These advances may include an increased knowledge of the disease and associated anomalies, improved surgical techniques, and advancement in neonatal intensive care and cardiac surgery. The common issue with EA/TEF repair is no longer mortality, but the morbidity and complications that result from attempting primary anastomosis. Surgeons have developed various techniques to help connect the esophageal ends in order to decrease complications: elongating the esophageal pouches through traction and performing a delayed anastomosis under tension [4], creating a circular myotomy to help close the gap between the esophageal pouches [5], performing post-operative muscle paralysis, elective positive-pressure ventilation, and head flexion to reduce tension [6], or esophageal substitution (i.e., gastric transposition or colonic interposition) when primary anastomosis is impossible [7, 8]. Although many techniques exist, replacement of the

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patient's esophagus with other tissues is considered inferior to using the patient's own esophageal tissue [9].

To minimize complications while maintaining the patient's own esophagus, elective post-operative muscle paralysis, positive-pressure ventilation, and head flexion (PVF) are performed to reduce movement and tension across the anastomosis. First performed by MacKinlay et al. [6], PVF requires mechanical ventilation via endotracheal intubation between 2 and 7 post-operative days while sedation and paralysis are performed [6, 10–12].

We systematically reviewed and analyzed the effect of post-operative PVF on reducing anastomotic complications after esophageal atresia repair. Our goal was to determine whether post-operative PVF is beneficial in children undergoing primary anastomosis, and whether it minimizes the occurrence of anastomotic complications such as those observed when the esophageal anastomosis is performed.

Methods

Primary search process

The preferred reporting items for systematic review and meta-analysis (PRISMA) [13] and the Cochrane handbook [14] were followed as a guide for this review. A comprehensive literature search was conducted using the online databases Embase, MEDLINE, Web of Science, and PubMed. These databases were searched for articles and studies that were published until 18 January 2018. No language restrictions were applied. References were identified with the following search terms (alone or in combination with): ("esophageal atresia/complications" OR "oesophageal atresia" OR "congenital esophageal atresia" OR "congenital oesophageal atresia" OR "tracheoesophageal fistula" OR "tracheo-esophageal fistula" OR "tracheooesophageal" OR "tracheo-oesophageal") AND ("elective ventilation" OR "elective ventilatory support" OR "ventilatory" OR "ventilation" OR "post-operative" OR "postoperative" OR "post-operative support" OR "post-operative support" OR "repair" OR "primary repair" OR "primary anastomosis" OR "anastomosis" OR "anastomotic" OR "anastomotic leak" OR "anastomotic failure" OR "anastomotic tension"). In addition, a manual search of the references within retrieved full-text articles was performed.

Study selection criteria

After removing duplicate articles, two independent reviewers (JSO and MJL) screened titles and abstracts using the following inclusion criteria: (1) children less than 1 year old; (2) children undergoing EA primary anastomosis (with/without TEF), either delayed or immediate; (3) studies comparing children who received elective post-operative PVF to children who did not; and (4) studies reporting the incidence of post-operative complications including anastomotic leak (major and minor) and esophageal stricture (major and minor). Randomized-controlled trials (RCTs) and observational studies in all languages were included for the primary search. Full-text manuscripts were retrieved for articles meeting the inclusion criteria. Exclusion criteria included: (1) children not undergoing primary esophageal anastomosis (i.e., those who had gastric transposition, colonic or jejunum interposition, or gastric tube performed); and/or (2) letters to the editor, conference abstracts, case reports, and review articles. Disagreements in study selection were resolved through a discussion between the reviewers until consensus was reached.

Data collection process

All accepted articles and studies underwent an independent full-text review. Information collected from each article included: first author, year of publication, study design, country of origin, total sample size, total control sample, total experimental sample, male percentage, age at surgery, average weight, EA gross classification, details of PVF, and post-operative outcomes. All information included in these studies was reported.

Quality assessment

The Newcastle-Ottawa Scale (NOS) quality assessment tool was used for all studies included in this meta-analysis [15]. Three independent reviewers (JSO, MJL, HM) read all included studies and assessed using the NOS tool. Cumulative scores of the included studies were discussed and agreed upon. Disagreements in study scores were resolved through a discussion between the reviewers until consensus was reached.

Statistical analyses

To analyze the effect of post-operative PVF on the occurrence of post-operative complications, pooled estimates of odds ratios (OR) and their 95% confidence intervals (CI) were calculated using Review Manager (RevMan) 5.3 [16]. Random effects modelling was calculated for all outcomes according to the Mantel–Haenszel method [17]. This was calculated for the individual outcomes of anastomotic leak and stricture formation. The composite outcomes of total complications (leaks and strictures combined) was attempted but none of the included studies specified which patients had both anastomotic leak and stricture. Inter-study heterogeneity was assessed using the Tau square, Chi square, inconsistency (I^2) score, and the test for overall effect (Z and p-value).

The I^2 score was considered substantial if above or equal to 50% [14].

Main results

Study selection

We identified 4382 references with six additional articles identified from our review of other articles and their reference lists. After removing duplicates, our primary search yielded 2268 unique references. There were no previous meta-analyses addressing our research question among the search results. Of the 2268 articles, two reviewers (JSO and MJL) independently selected 156 potentially relevant articles based on abstract and title assessment. These were converted into full-text articles, independently assessed, and six articles were selected as meeting the inclusion criteria. Spitz et al. and Chittmittrapap et al. [18, 19] were studies from the same institution and cohort of patients used in another paper by Spitz et al. [20] and were excluded to avoid the risk of double counting. In addition, Spitz et al. [20] was included in the analysis as it provided further details on patient characteristics and complications compared to the previous two studies [18, 19]. An article by Al-Salem et al. [21] was excluded as they only had one patient as control following accidental extubation at the end of the operation. After excluding those three articles, the three remaining articles were accepted and subjected to data extraction by JSO [6, 12, 20]. Disagreements in extracted data or in quality assessment of the studies were discussed among three independent reviewers (JSO, MJL, HM) and consensus was reached in all cases. For details on study selection, see the PRISMA flowchart in Fig. 1.

Study characteristics

All three studies included in this review were observational retrospective cohort studies [6, 12, 20]. Age at surgery varied between the first 24 h and 12 weeks post-natal (Table 1).

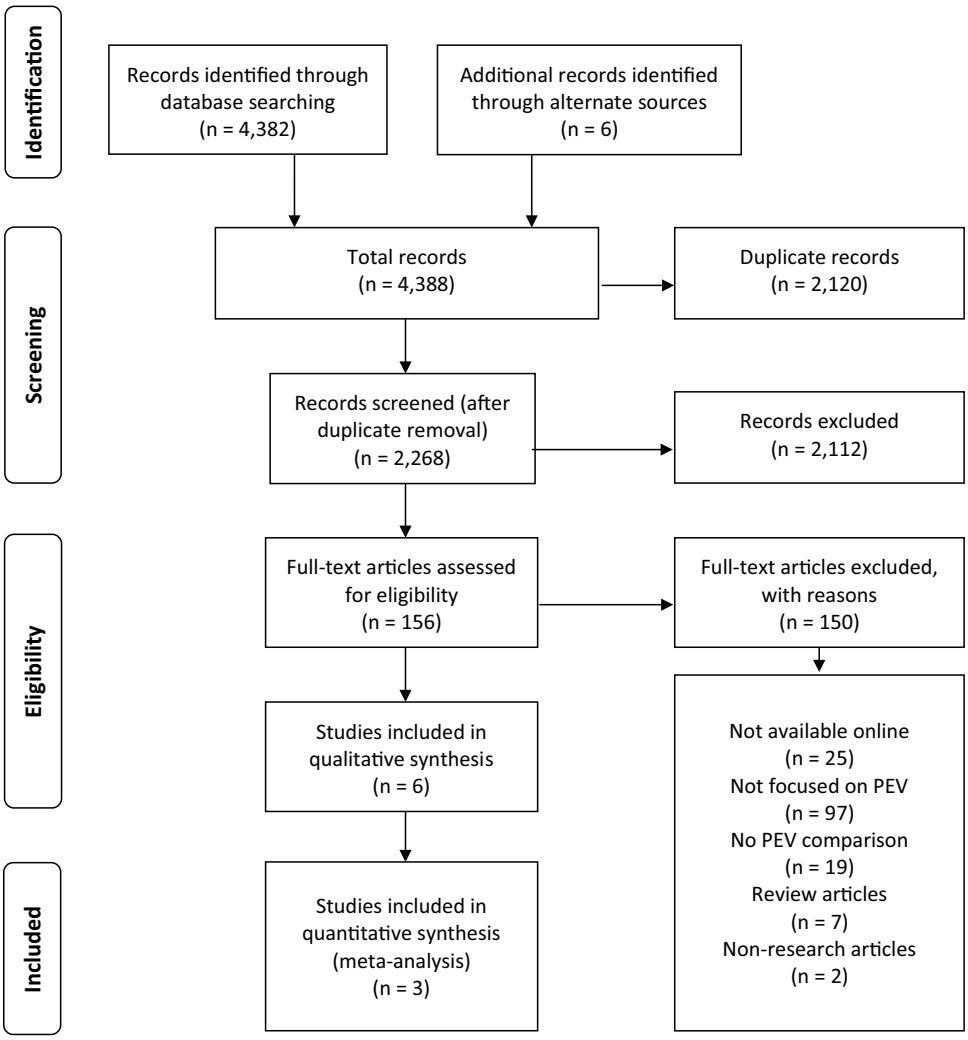


Fig. 1 PRISMA flowchart. Breakdown of the inclusion and exclusion process; from primary search to the final included articles

Table 1 General demographic data collected based upon the three included articles

Author (Pub. Yr.)	Study design	Country of origin	Total sample	Total control accepted	Total experimental accepted	Male percentage	Age at surgery	Average weight	Esophageal atresia gross classification	Details of PVF (paralytic, sedative, ventilation, neck flexion, duration)	Outcomes measured
MacKinlay (1987)	Retrospective cohort	Edinburgh, Scotland	34	5	5	N/A	< 24 h	N/A	Type *A* = 8% Type *B* = 0% Type *C* = 92% Type *D* = 0% Type *E* = 0%	Pancuronium Diazepam 25–30% O_2 Neck flexion 6–7 days total	Anastomotic leak (major and minor) and stricture (major and minor), Death
Spitz (1996)	Retrospective cohort	London, England	89	6	39	N/A	2 d to 12 wk	N/A	Type *A* = 30% Type *B* = 7% Type *C* = 63% Type *D* = 0% Type *E* = 0%	Unknown paralytic Unknown sedative IMV O_2 Neck flexion 5 days total	Anastomotic leak (major and minor) and stricture, GER, Death
Uchida (2006)	Retrospective cohort	Japan	42	28	14	50%	< 24 h	Exp (kg) 2.628 ± 0.464 Con (kg) 2.231 ± 0.594	Type *A* = 10% Type *B* = 0% Type *C* = 90% Type *D* = 0% Type *E* = 0%	Vecuronium bromide fentanyl citrate 25–30% O_2 Neck flexion 5 days total	Anastomotic leak and stricture, Atelectasis, Duration of ventilatory support, GER, Death

Pub.Yr. publication year, *N/A* not applicable, *h* hour, *d* day, *wk* week, *kg* kilogram, *IMV* intermittent mandatory ventilation

Study characteristics such as male percentage, average weight, and definition of "long gap" or "marked tension" were not consistently provided by all studies (Table 1). There was a total of 165 patients across all studies, and 97 were included for analysis (58 received PVF, 39 did not receive PVF; Table 1). Details of PVF for each study were varied (Table 1). For further information regarding individual study characteristics, refer to Table 1.

Elective muscle paralysis, positive-pressure ventilation, and head flexion (PVF)

MacKinlay et al. [6] (Table 1) attained complete paralysis using pancuronium, endotracheal intubation with mechanical ventilation, and neck flexion. This regimen, along with decreased diaphragmatic activity, was thought to reduce the risk of anastomotic complications. PVF was performed for a total of 7 post-operative days. After post-operative day 5, the child's head and neck were given gradual mobility. After post-operative day 7, the child recovered completely from muscle paralysis over a period of 12–18 h.

Spitz et al. [20] (Table 1) adopted PVF in children who underwent primary or delayed anastomosis "under tension" (based upon the surgeon's expertise and judgement). Patients receiving PVF would be paralysed and sedated for a period of 5 days. No further information could be elicted from this study.

Uchida et al. [12] (Table 1) utilised PVF in the post-operative treatment of all infants with repaired EA/TEF, whether the anastomosis was under tension or not. Patients received intermittent positive-pressure ventilation while also in neck flexion. Paralysis was induced with vecuronium bromide (0.04–0.08 mg/kg per hour) and sedation was induced with fentanyl citrate (2.5–5 lg/kg per hour) for a period of 5 days.

Post-operative anastomotic leak

The purpose of this analysis was to look at all anastomotic leaks (major and minor) and compare between studies. In some of the included studies, anastomotic leak was separated into major and minor leaks. MacKinlay et al. [6] described major leaks as requiring re-operation, while they did not describe how minor leaks were diagnosed. Similarly, Spitz et al. [20] did not describe the details of the management and diagnosis of major versus minor leak. Uchida et al. [12] described diagnosing anastomotic leak as "… a symptomatic leak, verified by a routine radiological water-soluble contrast study, or as symptomatic discharge of saliva into the drainage fluid". Due to MacKinlay et al. and Spitz et al. [6, 20] being the only studies to mention major and minor anastomotic leaks, it was decided that this sub-analysis was not an option.

All three studies [6, 12, 20] reported total anastomotic leaks; 12% (7/58) of children in the PVF group and 36% (14/39) in the non-PVF group were identified as having an anastomotic leak (OR 0.07 95% CI 0.01–0.35; Fig. 2a). Coupled with an I^2 score of 0% and test of overall effect of $Z = 3.26$ ($p = 0.001$), this shows a significant reduction in all anastomotic leaks for patients receiving PVF versus those that did not (Fig. 2a).

Post-operative stricture

Only MacKinlay et al. [6] differentiated between major and minor anastomotic strictures, meaning we were unable to run individual analyses of major or minor strictures. MacKinlay et al. [6] also reported a minor stricture in the PVF group, however this was only reported 6 months after the anastomotic operation. The authors felt there were confounding factors to the cause of this stricture and was not counted in the analysis. All three studies [6, 12, 20] included total anastomotic strictures; 53% (31/58) of the patients from the PVF group and 38% (15/39) of the non-PVF group reported anastomotic strictures (OR 0.42 95% CI 0.11–1.59; Fig. 2b). Coupled with an I^2 score of 0% and test for overall effect ($Z = 1.28$; $p = 0.20$), this shows no significant difference in anastomotic strictures for patients receiving PVF versus those that did not (Fig. 2b).

Total post-operative complications

After cross-referencing the data, we wanted to combine the associated complications (anastomotic leaks and strictures) of all three included studies [6, 12, 20]. None of these studies provided details on which children had both leaks and strictures, therefore not allowing this meta-analysis for total complications to occur.

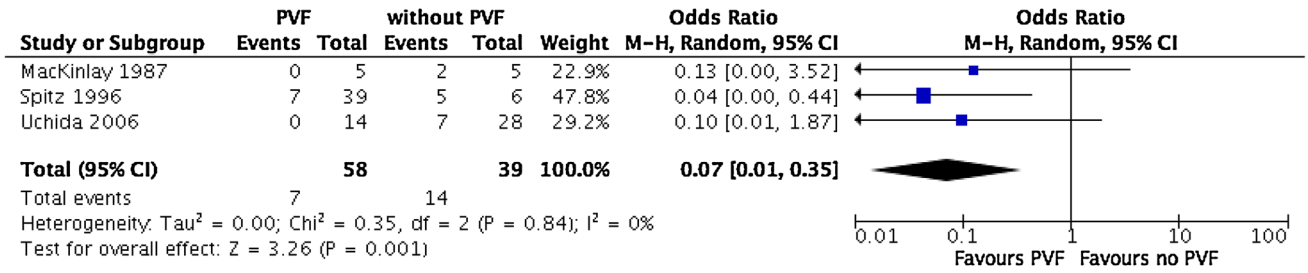
Quality assessment of included studies

We assessed the quality of studies using the Newcastle–Ottawa Scale (NOS) [15]. Overall outcomes of all included studies [6, 12, 20] had a "low" risk of bias as they received a score of 7 or greater (Table 2). Detailed information can be found in Table 2.

Discussion

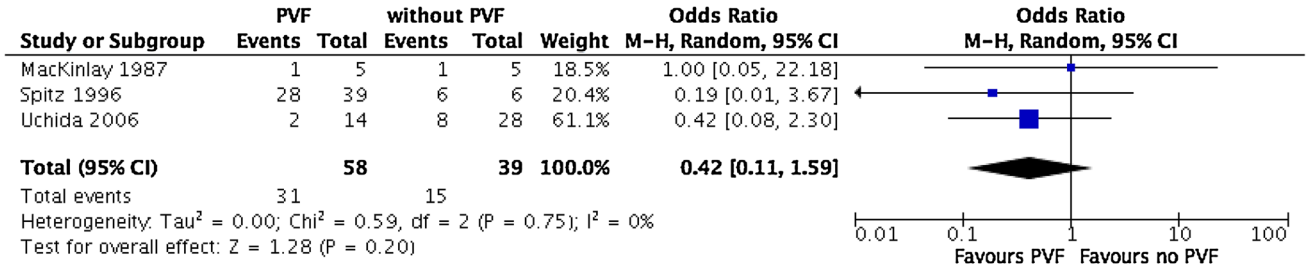
The repair of EA, with or without TEF, is associated with an excellent survival rate, but also associated with high incidence of both short- and long-term morbidities. These include anastomotic leak, stricture formation, gastroesophageal reflux, and recurrence of TEF. To our knowledge, this is the first systematic review and meta-analysis evaluating the

A **Association of PVF with the occurrence of "anastomotic leak"**



Abbreviations: PVF = elective post-operative muscle paralysis, positive-pressure ventilation, and head flexion.

B **Association of PVF with the occurrence of "anastomotic stricture"**



Abbreviations: PVF = elective post-operative muscle paralysis, positive-pressure ventilation, and head flexion.

Fig. 2 Meta-analysis of anastomotic complications for children receiving and not receiving PVF. "Events" refer to "anastomotic leaks" in **a** and "anastomotic strictures" in **b**. Odds ratios (OR) with 95% confidence intervals (CI) for each study are denoted by boxes (lines and arrows). Pooled OR estimates for all studies (using random effects modelling) are represented by the diamonds (M–H = Montel-Haenszel test). Tau-square (Tau^2) > 1, Cochrane Q (Chi^2) $P < 0.1$, and inconsistency (I^2) ≥ 50% suggests substantial statistical heterogeneity. Z score with $P < 0.05$ indicates test for overall effect was statistically significant.

effectiveness of post-operative PVF on anastomotic complications. This study indicates that PVF may reduce the risk of developing anastomotic leak post-operatively. However, all included studies were retrospective and the need for a prospective evaluation is warranted. The indications for the use of PVF after EA repair and its duration remain controversial.

There is no consistency in the duration of PVF between surgeons and studies. Most physicians agree that the minimum duration of PVF is two days [3], however median duration varies across studies. The reason for this is vague and not easily understood or researched, leaving many physicians to weigh the benefits of PVF versus its risks alone. Since the introduction of post-operative PVF [6], physicians have discussed how and why this technique may work. Previous studies have shown that neck flexion allows mobilization of the proximal esophageal pouch 2.5–3cm towards the distal pouch in pig models [22] and in humans [6]. With greater mobilization, and therefore reduced tension, primary repair can be attempted and PVF may lead to a reduction of anastomotic leak post-operatively. Many surgeons are opting to use post-operative PVF in all cases of primary anastomosis where there is some degree of tension. Zani et al. [23] found that more than half of surgeons surveyed use post-operative PVF to reduce esophageal tension and its complications. However, it is difficult to determine clinically the degree of tension of the anastomosis. This is particularly difficult if EA repair is done thoracoscopically, leading to many surgeons using their best judgment on a case by case basis.

Although we discuss PVF and its positive effects, there are also inherent negatives attributed to its use. Unfortunately, we were unable to assess these factors with the included studies. MacKinlay et al. and Spitz et al. [6, 20] did not report pulmonary complications in children receiving PVF. Uchida et al. [12] was the only study included that reported ventilatory and pulmonary complications. They found no significant differences in atelectasis rates between patients receiving PVF and those that did not. Although, those not receiving PVF did show an increase in days on ventilation (non-significant). Beyond these complications discussed by the included studies, there are many others that arise with use of PVF.

One of the possible complications of PVF after EA repair is the development of a lung infection or other iatrogenic factors. Endotracheal intubation (causing trauma

Table 2 The Newcastle–Ottawa Scale (NOS) breakdown of the selection criteria, comparability, outcome measurments, and totals for all included articles

Author (Pub.Yr.)	Selection				Comparability	Outcome				Total
	Exposed representative of population	Non-exposed representative of population	Ascertaining of exposure	Demonstrating outcome of interest not present at start of the study	Comparability of cohorts in the design or analysis	Outcome of interest	Assessment of outcome	Was follow-up long enough for outcomes to occur ?	Adequacy of follow-up for cohorts	
MacKinlay (1987)	*	*	*	*	*	Leak	*	*	*	8/9
						Stricture	*	*	*	
Spitz (1996)	*	*	*	*		Leak	*	*	*	7/9
						Stricture	*	*	*	
Uchida (2006)	*	*	*	*	**	Leak	*	*	*	9/9
						Stricture	*	*	*	

Pub.Yr. publication year

to the nasopharynx, impairing swallowing, increasing bacterial adherence and colonization among others), as well as duration of muscle paralysis and positive-pressure ventilation, increases the likelihood of infectious organisms infiltrating the pulmonary system [24]. The use of paralytics also reduces the recruitment of alveoli, leading to atelectasis and potential long-term lung damage [25]. Sistonen et al. [26] noted that after EA repair, subjects continued to have lung morbidity and bronchial hyperresponsiveness well into adulthood. The use of post-operative PVF should be carefully managed with intermittent vital capacity maneuvers to avoid atelectasis [25], and measures to better treat lung infections and morbidities through identification of pathogens and proper antimicrobial treatment [27]. It is not unusual that after completing the course of elective post-operative PVF is still needed for multiple days afterwards; this may also increase the risk of developing a lung infection.

Another common problem seen after EA repair is vocal cord paresis or paralysis, and PVF may theoretically exacerbate this complication. Lal et al. [1] found paralysis of the vocal cords to be relatively common with 7% affected. Paralysis of the vocal cords was seen more often in patients with a larger esophageal gap (and therefore greater tension) than those with a smaller gap. As the recurrent laryngeal nerve runs down the lateral sides of the trachea and esophagus, it becomes increasingly likely to be damaged during primary anastomosis in EA repair. Although the literature on PVF exacerbating vocal cord paresis or paralysis is limited, it is reported that endotracheal intubation (required for PVF) can cause laryngeal complications including vocal cord paralysis [28].

Interestingly, none of the analyzed studies reported the occurrence of lung infection, vocal cord paralysis, or other PVF complications compared to those undergoing standard post-operative management. It is likely that this is due to either a lack of reporting or the absence of randomized controlled trials. The absence of these side effects can also be due to the short duration of PVF (5 ± 2 days), but there is a need for prospective evaluation of PVF in the post-operative management of EA.

Our study revealed limitations in the current evidence regarding the use of PVF after EA repair. The main risk of bias in all included studies was due to the lack of being prospective or randomized, and therefore not properly controlling for confounders or biases. The number of patients and studies analyzed was also not large enough to discount confounding factors. In addition, there was no consistent protocol for PVF that was adopted in the analyzed studies. These limitations may have contributed to the differing rates of post-operative complications.

Conclusions

On the basis of the existing evidence and our analysis, elective post-operative PVF is potentially beneficial in infants undergoing EA repair and significantly lowers the risk of developing anastomotic leak. This is particularly important in infants with a large esophageal gap where chances of performing a safe esophageal anastomosis are maximized. However, various factors remain unclear: (1) should PVF be reserved to selected infants undergoing esophageal anastomosis under tension; (2) how long should post-operative PVF be planned for; and (3) is the benefit offered by PVF superior to its potential side effects? The low number of studies available to this systematic review, the risk of bias, and the lack of prospective analyses leads to our recommendation of performing a prospective study to test and validate these results.

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Compliance with ethical standards

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