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The effect of postoperative ventilation strategies on postoperative complications and outcomes in patients with esophageal atresia: Results from the Turkish Esophageal Atresia Registry

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Abstract

Objectives: Postoperative ventilatory strategies in patients with esophageal atresia (EA) and tracheoesophageal fistula (TEF) may have an impact on early postoperative complications. Our national Esophageal Atresia Registry was evaluated to define a possible relationship between the type and duration of respiratory support on postoperative complications and outcome.

Study Design: Among the data registered by 31 centers between 2015 and 2021, patients with esophago-esophageal anastomosis (EEA)/tracheoesophageal fistula (TEF) were divided into two groups; invasive ventilatory support (IV) and noninvasive ventilatory support and/or oxygen support (NIV-OS). The demographic findings, gestational age, type of atresia, associated anomalies, and genetic malformations were evaluated. We compared the type of repair, gap length, chest tube insertion, follow-up times, tensioned anastomosis, postoperative complications, esophageal dilatations, respiratory problems requiring treatment after the operation, and mortality rates.

Results: Among 650 registered patients, 502 patients with EEA/TEF repair included the study. Four hundred and seventy of patients require IV and 32 of them had NIV-OS treatment. The IV group had lower mean birth weights and higher incidence of respiratory problems when compared to NIV-OS group. Also, NIV-OS group had significantly higher incidence of associated anomalies than IV groups. The rates of postoperative complications and mortality were not different between the IV and NIV-OS groups.

Conclusion: We demonstrated that patients who required invasive ventilation had a higher incidence of low birth weight and respiratory morbidity. We found no relation between mode of postoperative ventilation and surgical complications. Randomized controlled trials and clinical guidelines are needed to define the best type of ventilation strategy in children with EA/TEF.

KEYWORDS
complication, esophageal atresia, mechanical ventilation, tracheoesophageal fistula

1 | INTRODUCTION

Esophageal atresia (EA)/tracheoesophageal fistula (TEF) is a congenital anomaly with a reported incidence of 1:3000–4500 live births and commonly accompanied by associated anomalies.[1–3] By the use of contemporary postoperative care strategies (postoperative analgesia and ventilation, trans-anastomotic and chest tube management, and prevention, early recognition and treatment of complications), the survival rates increased up to 100% in patients without associated cardiac anomalies and patients with more than 1500 g birth weights.[4]

Prematurity and associated anomalies, especially cardiac pathologies, are among the most important causes affecting the prognosis of infants with EA.[5] One of the most important factors in the postoperative period is the need and duration of mechanical ventilation. The postoperative management of EA/TEF babies varies from "tubeless" meaning that the patient is extubated at the end of the operation to "intubated" for at least

48 h postoperatively with muscle paralysis.[6] This difference is mostly related to the surgeon's own choice and the general condition of the patient including the tension on the anastomosis. Studies have shown that as the duration of mechanical ventilation increased, pneumonia, atelectasis, and other morbidities also increased.[4] On the contrary, it has been shown that endotracheal intubation and mechanical ventilation offers the advantage of decreasing the tension of anastomosis and may prevent aspiration. It may also decrease the risk of re-intubation, and overcome tracheal anomalies inherent with EA/TEF patients such as laryngeal/tracheal anomalies like tracheomalacia, laryngeal cleft, and allowing the tracheal closure to heal.[2] In addition, early extubation should be well planned in patients who may have a chance of needing re-intubation due to various reasons, considering the healing of edematous airway and the trachea that has a fresh anastomosis.[2] Noninvasive ventilation may cause inflation of the esophagus with air resulting in increased pressure and impaired blood supply on the anastomosis.[4] Therefore, the management of mechanical ventilation in the post-operative period of newborn babies with EA may have an important role in the development of postoperative complications and prognosis of these patients. Although the role of ventilatory modality on surgical and respiratory outcomes have been evaluated previously,[2,5] there is no clear information comparing the results of invasive and noninvasive ventilatory strategies in EA patients. Moreover, there are no randomized controlled studies or a clinical guideline about the postoperative ventilation strategies in children with EA. In this study, we aimed to evaluate the data obtained from the Turkish Esophageal Atresia Registry (TEAR) to define whether there is a relationship between the type and duration of respiratory support and oxygen support on complications and outcome especially in patients with and without endotracheal ventilation support, as well as noninvasive ventilation and oxygen support.

2 | MATERIALS AND METHODS

The TEAR is a registry system for EA patients which were founded by the Turkish Association of Pediatric Surgeons in 2015. Thirty-one centers have registered 650 patients at the time of this study. The study was approved by the Local Noninvasive Clinical Research Ethics Committee (Approval number: 2021/28). All collected information was recorded in a digital database consisting of two separate forms. The first form includes demographic features and early outcomes of patients within the first month of age and the second one collects data about developmental and long-term outcomes at the end of the year of life.

2.1 | Study design

Patients diagnosed with TEF/EA between March 1, 2015, and March 31, 2021 were enrolled in the study. Among 650 registered patients, the missing and/or incomplete data of 30 patients and three patients died from various causes before surgery were excluded. Totally 617 of the data met for the inclusion criteria and evaluated for further analysis. In 502 of patients, esophago-esophageal anastomosis with tracheoesophageal fistula (EEA/TEF) repair were performed during neonatal period (before 1 month of age) and 115 patients had delayed esophageal repair (after 1 month of age) and/or other surgical techniques such as cervical esophagostomy and/or gastric tube for long-gap EA. Since, patients with delayed anastomosis and/or other procedures for long gap EA constitutes wide variation in postoperative outcome, patients with EEA/TEF repair in the newborn period ($n = 502$) were included in the study. Patients were evaluated for age, birth weight, gender, type of EA, associated anomalies, gap length, placement of chest tube, tensioned anastomosis, postoperative complications, number of esophageal dilatations, respiratory problems (respiratory problems refer to gastroesophageal reflux and aspiration, pneumonia and atelectasis secondary to reflux) requiring treatment after the operation (those who need prokinetic, inhaler or antisecretory therapy after repair), and the mortality rates.

To define the role of postoperative ventilatory strategy on the outcomes of the patients, patients with EEA/TEF repair were divided into two groups: patients who were treated by postoperative invasive ventilation (IV) and those who were followed up by noninvasive ventilation and/or oxygen support (NIV-OS). We defined IV group as patients followed up intubated after surgery and the patients who were extubated from the surgery, and did not need any intubation while the postoperative period with or without oxygen support composed the NIV-OS group. The mean intubation and follow-up days of both groups were also investigated. The above mentioned parameters were compared for IV and NIV-OS groups.

2.2 | Definitions

There is no standardized protocol for gap measurement. The gaps were recorded as number of vertebral bodies and, cases of EA with greater and equal distance to three vertebrae were considered "long-gap" EA. Since there is no clear definition for a tensioned anastomosis, it was defined by consulting surgeons and recorded accordingly. The postoperative complications were based on clinical findings, saliva drainage from chest tubes, upper gastrointestinal (GI) contrast studies, and endoscopic interventions. Data about balloon or rigid dilatations for anastomotic strictures were also recorded. Although no detailed information collected regarding the respiratory problems in our registry, at the end of first evaluation (end of first month or discharge before 1 months of age), medical treatment for respiratory problems were recorded (necessitating inhalers, broncho-dilators, and/or O_2 support). Therefore, the patients with respiratory problems requiring treatment is defined as patients requiring any kind of medical treatment for any respiratory problem during the first month of life.

2.3 | Statistical analysis

The χ^2 or Fisher exact test was applied for categorical variables, the Student t-test for continuous variables with normal distribution, and

the Mann–Whitney U test for nonparametric variables. Data are presented with a mean (±) standard deviation, number, and %. The statistical significance limit was taken as $p < 0.05$.

The power analysis of the study was calculated as 96% by Power-End-Precision program.

3 | RESULTS

The distribution of patients in our national registry is shown in Figure 1. Among 650 patients, 502 of patients with EEA/TEF repair were included. In EEA/TEF repair group 470 (93.6%) of patients require IV and 32 (6.4%) of them had NIV-OS treatment (Table 1). The patients in both EEA/TEF repair and other surgical treatment groups significantly require higher incidence of IV than NIV-OS treatment ($p = 0.001$).

The demographic features of patients with EEA/TEF repair in IV and NIV-OS groups are summarized in Table 2. The mean birth weight is significantly lower IV group when compared to NIV-OS group ($p = 0.0046$). On the other hand, NIV-OS group had significantly higher incidence of associated anomalies than IV groups ($p = 0.0038$). Other parameters including mean age, gender, birth height, and gestational age did not show any statistical difference ($p > 0.05$). When we compare the results of IV and NIV-OS groups according to presence and absence of associated anomalies and normal (>2500 g) versus low birth weights (less than 2500 g), there was no significant difference between groups in terms of birth weights and presence of associated anomalies ($p > 0.05$) (Table 3).

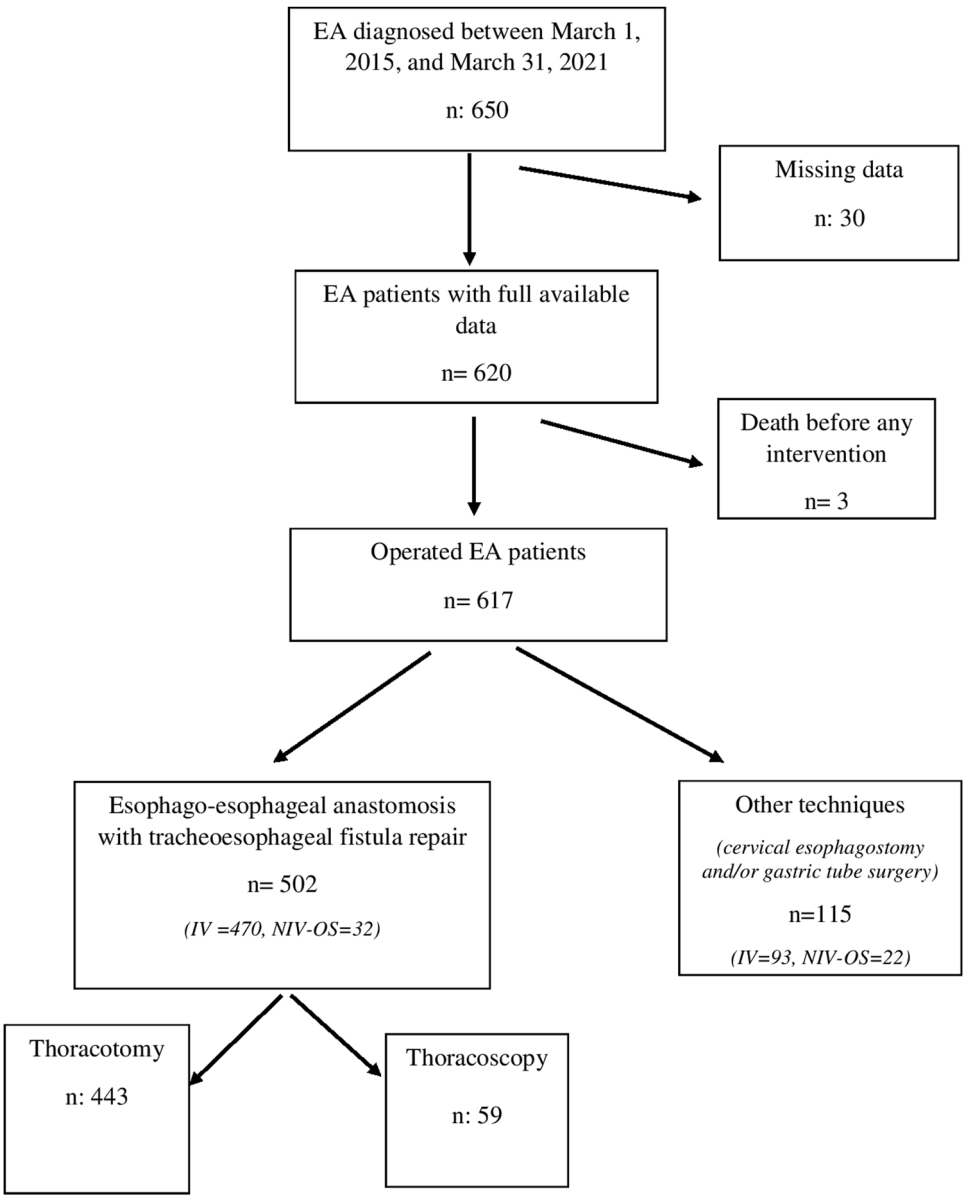

FIGURE 1 Flow diagram of the study selection

TABLE 1 The ventilation modes (IV and NIV-OS) in patients with esophago-esophageal anastomosis with tracheoesophageal fistula repair (EEA/TEF) and other surgical options

Parameters	Invasive ventilated (IV) group (*n* = 563)	Noninvasive ventilated and oxygen supported (NIV-OS) group (*n* = 54)	*p* Value
EEA/TEF *n* (%)	470 (93.6)	32 (6.4)	**0.001***
Other surgical options *n* (%)	93 (80.9)	22 (19.1)	
Total	563	54	617

Note: *$p < 0.05$ are considered as significant.

TABLE 2 Demographic features, type of repair and the gap records of the IV and NIV-OS groups in esophago-esophageal anastomosis and tracheoesophageal fistula repair (EEA/TEF, *n* = 502)

Parameters	Invasive ventilated (IV) group (*n* = 470)	Noninvasive ventilated and oxygen supported (NIV-OS) group (*n* = 32)	*p* Value
Gender (male/female) (*n*, %)	247(52.6)/223(47.4)	18 (56.3)/14 (43.8)	0.824
Birth weight (g) (mean ± SD)	2486.3 ± 651.2	2724.1 ± 657.6	**0.046***
Birth height (cm) (mean ± SD)	46.2 ± 4.8	46.5 ± 3.9	0.968
Gestational age (week)	36.5 ± 3.0	37.2 ± 2.2	0.276
Type of esophageal atresia *n* (%)			-
A	25 (5,3)	3 (9.4)	
B	13 (2,8)	1 (3.1)	
C	416 (88,5)	28 (87.5)	
D	14 (3,0)	0	
E	2 (0,4)	0	
Associated anomalies *n* (%)	119 (25.3)	14 (43.8)	**0.038***
Neurologic	31 (96.9)	1 (3.1)	-
Renal	60 (92.3)	5 (7.7)	-
Cardiovascular	292 (95.4)	14 (4.6)	-
Extremity	42 (100)	0	-
Anorectal	46 (95.8)	2 (4.2)	-
Genitourinary	30 (100)	0	-
Costovertebral	13 (90.9)	1 (7.1)	-
Genetic anomalies/vacterl/charge	52 (96.3)	2 (3.7)	0.560
Type of repairn (%)			0.781
Thoracotomy	415 (93.7)	28 (6.3)	
Thoracoscopy	55 (93.2)	4 (6.8)	
Mean gap (vertebral body numbers, mean ± SD)	2.06 ± 1.1	1.9 ± 1.1	0.306
Mean follow-up time (day, mean ± SD)	5.72 ± 7.3	4.6 ± 3.8	-

Note: *$p < 0.05$ are considered as significant.

Thoracotomy was performed in 443 of the patients who underwent primary anastomosis, and thoracoscopy was performed in 59 patients. The mean intubated times of IV group was 5.72 ± 7.3 days, the follow-up times of NIV-OS group was 4.6 ± 3.8 days.

Table 4 shows the rate of postoperative complications and outcome of patients in the IV and the NIV-OS groups. The rate of tensioned anastomosis and of chest tube placements were similar between the two groups ($p > 0.05$). There was no significant difference between the IV and the NIV-OS groups for the rates of anastomotic leaks, fistula

TABLE 3 The comparison of IV and NIV-OS groups according to presence of associated anomalies and birth weights

Parameters	Invasive ventilated (IV) group ($n = 470$)	Noninvasive ventilated and oxygen supported (NIV-OS) group ($n = 32$)	p Value
Birth weight ≤2500 g and presence of associated anomalies *n* (%)	43 (19.6)	4 (36.4)	0.242
Birth weight ≤2500 g and absence of associated anomalies *n* (%)	176 (80.4)	7 (63.6)	
Birth weight >2500 g and presence of associated anomalies *n* (%)	75 (30)	10 (47.6)	0.154
Birth weight >2500 g and absence of associated anomalies *n* (%)	176 (70)	11 (52.4)	

TABLE 4 The postoperative complications and outcome of patients in the IV and the NIV-OS groups

Parameters	Invasive ventilated (IV) group ($n = 470$)	Noninvasive ventilated and oxygen supported (NIV-OS) group ($n = 32$)	p Value
Tensioned anastomosis *n* (%)	149 (34.6)	6 (20.7)	0.184
Placement of chest tube *n* (%)	463 (98.5)	0	1.000
Postoperative complications *n* (%)			
Anastomotic leak *n* (%)	24 (5.1)	0	0.389
Fistula recanalization *n* (%)	10 (2.1)	1 (3.1)	0.519
Symptomatic anastomosis stricturen (%)	95 (20.1)	6 (5.9)	1.000
Esophageal dilatation n (%)	108 (36.6)	9 (28,1)	0.653
Number of esophageal dilatations (mean ± SD)	3.2 ± 3.0	2.5 ± 1.3	0.975
Respiratory problems requiring treatment	211 (44.9)	7 (21.9)	**0.018***
Mortality (1st month)	73 (16.0)	4 (9.4)	0.450
Mortality (1st year)	11 (2.3)	1 (31)	0.550

Note: *$p < 0.05$ are considered as significant.

recanalization, symptomatic anastomotic strictures or the need for esophageal dilatations ($p > 0.05$). The mean number esophageal dilatations were 3.2 ± 3.0 in IV group and 2.5 ± 1.3 in the NIV-OS group and no significant difference between the groups. The rate of presence of respiratory problems requiring treatment was significantly higher in the IV group when compared with the NIV-OS ($p < 0.05$). The mortality rate at the end of the first month and at the end of the first year was similar in both groups ($p > 0.05$). The most common causes of death were severe cardiac anomalies and sepsis.

In the regression analysis model, neither birth weight nor tensioned anastomosis showed statistical significance for necessitating IV mode in the postoperative care (Table 5, p > 0.05).

TABLE 5 The regression analysis evaluating the factors necessitating the IV mode in the postoperative care

	OR	95 % CI		p
Associated anomalies	0.49	0.22	1.06	0.071
Tensioned anastomosis	0.55	0.22	1.41	0.217

Abbreviations: CI, confidence interval; IV, invasive ventilated; OR, odds ratio.

4 | DISCUSSION

There have been an increasing number of publications about the surgical outcomes of EA/TEF patients. The survival of these patients has prominently improved with the developments in surgical methods as well as preoperative and postoperative management protocols.[7] However, a limited number of articles have addressed the use of noninvasive ventilation techniques including Continuous Positive Pressure Ventilation (CPAP), Noninvasive Positive Pressure Ventilation, High Flow Nasal Cannula, and oxygen support.[2,4] Mechanical ventilation has a known risk of bronchopulmonary dysplasia and adverse neurodevelopmental outcomes.[8] Moreover, it has been reported that noninvasive ventilation decreases post-extubation failures.[8] The benefits of noninvasive ventilation for neonates are decreasing intrapulmonary shunting, increasing

compliance and functional residual capacity and prevention of atelectasis, improving oxygenation, decreasing thoracoabdominal asynchrony and obstructive and mixed apnea (splints the airways and diaphragm and stabilizes chest wall), and improving lung growth.[9] On the other hand, there are some contraindications for noninvasive ventilation methods including respiratory failure, congenital malformations of the upper airway, congenital diaphragmatic hernia, bowel obstruction, omphalocele, gastroschisis, severe cardiovascular instability, and poor respiratory drive.[9] In patients with pure EA, there is no clear postoperative ventilation strategy that has been defined and none of the ventilation modes have been recommended as superior to another.

Spitz et al. recommended that patients with tensioned anastomosis should be electively paralyzed in the postoperative period and not extubated for 5 days.[10] Hunt et al. mentioned that some surgeons request that the patient be kept muscle relaxed for a variable time postoperatively for the sake of the anastomosis and suggested elective postoperative ventilation.[11] On the contrary, Beasley et al. suggested that there was no evidence for routine use of mechanical ventilation to protect the anastomosis.[12] Therefore, although postoperative mechanical ventilation management is indispensable in some selected patients, its routine use is questioned by some authors. The duration of intubated period after the operation varies according to the characteristics of each patient. Among these are the type of the atresia, accompanying anomalies, the weight and maturity of the baby and the surgical technique employed. The noninvasive ventilation methods chosen after the extubation also varied according to the patient characteristics and the clinical findings. As expected, patients with primary anastomosis require more IV support than patients with other surgical options (such as gastrostomy).

In our database, when we compared the patients in terms of use of invasive or noninvasive ventilation, gender, mean birth height, and gestational week were found to be similar. As expected, the number of low birth infants was significantly higher in the IV group. On contrary, patients require NIV-OS treatment had higher incidence of associated anomalies. These results suggest that patients with low birth weight are expected to have increased need for postoperative IV support in children with EA. However, when we compared the IV and NIV-OS groups according to presence of associated anomalies and normal versus low birth weights, we found that there was no difference between two ventilation modalities. Therefore, we suggest that higher respiratory problems in IV group may relate with ventilation strategy and may not affected by these parameters. The issue of chest tube placement after the operation is also a controversial issue, and our results showed that the majority of patients in both groups had chest tubes inserted.[13]

After EA repair, patients may receive elective respiratory support to eliminate probable anastomotic complications by decreasing the tension on esophageal anastomosis. In addition, concomitant patient-related risk factors such as prematurity and lung-related respiratory tract problems may result in a respiratory support requirement. Although, it has been suggested that patients who had tensioned anastomosis, low birth weight or major accompanying anomalies were more likely to develop complications, we found no significant risk factor for necessitating IV mode in regression analysis.[14] Moreover, no clear relationship has been reported between anastomotic complications and respiratory support. It has been suggested that postoperative invasive and noninvasive respiratory support may either have a positive or negative effect on anastomosis.

Despite advances in neonatal intensive care conditions and surgical techniques, complications such as anastomotic stenosis (5%–20%) and anastomotic leakage (2%–8%) and fistula recanalization (5%–14%)can be encountered in the postoperative period.[4,9,15] The mean number of patients who developed anastomotic strictures was not significantly different in both groups (20.1% in the IV group, 6.9% in the NIV-OS group).[10,12] In our patient cohort, no anastomotic leakage was observed in the NIV-OS group. This is probably because the reported incidence of tensioned anastomosis in the NIV-OS group was less than the IV group. The rate of anastomotic leaks that developed in the IV group was similar to previous studies (5.1%).[4] Our data showed less fistula recanalization rate than the previously published literature data (2.1% in the IV group, 3.1% in the NIV-OS group).[10] This may be due to the fact that our recorded follow-up was ended at the end of the first year of life in our registry. Also, we could not find any statistical difference between the IV and the NIV-OS groups in terms of fistula recanalization rates. Since postoperative complications cannot only be attributed to postoperative ventilatory support and are multifactorial, other reasons that may play role in the occurrence of those complications should be considered as underlying causes. O'Connell et al. analyzed the effect of postoperative muscle paralysis, positive-pressure ventilation and head flexion on reducing anastomotic complications and found these measures were potentially beneficial in infants undergoing EA repair and they significantly lower the risk of developing an anastomotic leak.[16] Al-Salem et al. suggested that especially elective withdrawal from ventilation was beneficial when the anastomosis is under tension.[17] Our data showed that the number of patients with tensioned anastomosis was lower than the patients without tensioned anastomosis and it was reported in 34.6% and 20.7% of cases in the IV and the NIV-OS groups, respectively. These findings suggest that centers in our registry also prefer invasive ventilation in patients with tensioned anastomosis. It has been suggested that postoperative complications can be explained by the position of the patient, including the position given during the surgery with single lung ventilation. This might be causing a decreased blood supply in the collapsed lung with resultant deterioration of oxygenation, and consequently altering the perfusion in the anastomosis. Ferrand et al. suggest that noninvasive ventilation methods may be associated with a higher rate of postoperative complications especially for anastomotic strictures following EA/TEF repair.[2] The need for esophageal dilatations for postoperative esophageal strictures was previously reported to be between 22% and 89% [18] which is similar to our stricture rate of (20.1%). However, our study did not show a relation between use of either invasive or noninvasive ventilation and oxygen support after EA/TEF repair or other commonly observed

complications such as an anastomotic leak, fistula recanalization and symptomatic anastomosis stricture.

Noninvasive ventilation methods in the postoperative period might result in an increased distension of the esophagus leading to an anastomotic leak. However, Shah et al. suggests that use of CPAP after extubation in EA/TEF patients was safe and did not find any correlation with the anastomotic leak, fistula recanalization, anastomotic stricture or mortality.[4] They also stated that a prolonged mechanical ventilatory support is a risk for development of pneumonia, atelectasis. They also observed atelectasis and tracheomalacia development after extubation may require reintubation.[4] Our results were similar with their results in terms of mean mechanical ventilation times. The consensus statement reported by the American Pediatric Association suggest that aspiration pneumonitis caused by secretion pooling above the edematous anastomosis remains a major source of morbiditiy in patients with EA/TEF due to their incompetent gastroesophageal junction and relatively small stomach.[19] Our national registry did not include data regarding the prevalence of aspiration pneumonitis in the early postoperative period. Therefore, it is not possible to comment on which ventilation modality is superior to another for preventing aspiration pneumonitis. In our study, a majority of patients developed respiratory problems requiring treatment at the end of the first year. We found that IV group statistically higher incidence of respiratory morbidity than NIV-OS group. When we compare the mortality rates, both groups show similar results at the end of the first month and first year of life. Our mortality rates slightly more than the other single center experiences in the literature. We suggest that this can be explained by the characteristics of centers which are almost reference centers and manage high-risk and more complicated patients.

Our study had some limitations. Because the data was taken from a registry which recorded input of different centers on preformed survey forms, the selection of the patients was not standard and there were variations in the postoperative follow-up of the patients. Similar to all registry studies, the most important limitation is the lack of a standardized ventilation protocol for the patients registered in our national database. Second, postoperative complications cannot be solely attributed to ventilatory support strategies. Other factors that may affect postoperative complications should also be considered while evaluating the results of these strategies. Finally, since, our registry does not include detailed information about the duration, or success of the ventilatory treatments and the incidence of aspiration pneumonitis. Therefore, we cannot comment on the best ventilation mode with less complication rates. However, herein we present the results of a large cohort of patients and have found no significant relationship between invasive versus noninvasive ventilatory support and postoperative complications or final outcome.

In conclusion, our national database demonstrates that patients with EEA/TEF repair who require invasive ventilation had higher incidence of low birth weight. Although, the patients with IV had higher incidence of respiratory morbidity, no relation has been found between ventilation mode and surgical complications in children with EA/TEF. Therefore, randomized controlled trials and clinical guidelines are needed to define the best type of ventilation strategy in children with EA/TEF.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available upon request.

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