Predictors of mortality in newborns with esophageal atresia: a 6-year study in a single institution

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Abstract
Background Esophageal atresia, with or without fistula, is a congenital defect that causes high morbidity and mortality in newborns. Risk factors of mortality need to be identified to establish the best approach for treating this condition in order to decrease morbidity and mortality.

Objective To identify factors associated with mortality in newborns with oesophageal atresia.

Methods We reviewed all newborns with esophageal atresia using data from their medical records at Sardjito General Hospital from January 2007 to December 2012. Potential risk factors were analyzed using Chi-square test, with a level of significance of P<0.05.

Results Of 31 newborns that met our criteria, only 5 survived, and all 5 had one-stage surgery (primary anastomosis with fistula ligation). Thrombocytopenia and sepsis increased the risk of death with OR 10.857 (95%CI 1.029 to 114.578) and OR 13.333 (95% CI 1.242 to 143.151), respectively. However, anemia had a protective effect against mortality with OR 0.688 (95%CI 0.494 to 0.957).

Conclusion Thrombocytopenia and sepsis are the risk factors associated with mortality in newborns with esophageal atresia at our institution. Anemia has a protective effect against mortality.

Keywords: esophageal atresia, risk factor of mortality, thrombocytopenia, sepsis, anemia

This study was presented at The 4th Congress of the World Federation of Pediatric Surgery (WOFAPS), Berlin, Germany, October 13-16, 2013.

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to the EA mortality rate in developing countries, particularly at our institution. As such, we aimed to identify factors associated with mortality in newborns with esophageal atresia at our institution.

Methods

We performed a retrospective study using medical records at Dr. Sardjito Hospital. We included all neonates who were admitted to the neonatal intensive care unit of our institution for management of EA/TEF from January 2007 to December 2012. The surgical management consisted of either a one-stage operation (primary anastomosis with fistula ligation), a multi-stage operation (including gastrostomy or esophagostomy), or no operation at all. Neonates were diagnosed with EA/TEF based on the physician’s inability to pass an 8-French nasogastric tube into the stomach, with the tube coiling in the upper esophageal pouch on chest x-ray. Parents consented to telephone interviews regarding history of pregnancy, physical activity and education. We analyzed the data using logistic regression analysis with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) software version 15.0.

This study was approved by the Ethics Committee of Gadjah Mada University Medical School and Dr. Sardjito Hospital, Yogyakarta.

Results

The subjects’ characteristics are shown in Table 1. The most common type of EA/TEF was the C-type (esophageal atresia with distal tracheoesophageal fistula) in 27/31 neonates, followed by A-type (isolated esophageal atresia) in 4/31 neonates. None of the neonates who were admitted to our institution had the other types of EA/TEF. Primary anastomosis with fistula ligation was performed in 12/31 patients. Multi-stage surgical procedures (gastrostomy and esophagostomy) were performed in 11/31 patients. Based on prognostic factors, there were 8/31, 10/31, and 13/31 neonates with Waterston classifications A, B, and C, respectively. Therefore, the incidence of EA/TEF in low birth weight infants was high at our institution.

Table 2 shows the associated congenital malformations. Twenty-six out of 31 patients had no other congenital malformations, but the remaining 5/31 patients had one or more congenital malformations associated with EA/TEF. Anorectal malformations were seen in 3 patients; vertebral anomalies, anal atresia, cardiovascular, renal and limb anomalies (VACTERL) syndrome in 2 patients, while a cardiac anomaly (patent ductus arteriosus) was observed by echocardiography in 1 patient.

We analyzed the subjects’ perioperative hemoglobin levels, and found 16/31 neonates with low hemoglobin levels (<13 g/dL) and 15/31 neonates with normal hemoglobin levels (≥13 g/dL). We found that anemia had a protective effect on the mortality rate with OR 0.69 (95%CI 0.49 to 0.96; P=0.042) (Table 3).

### Table 1. Subjects’ characteristics

| Basic characteristics | Total N=31 |
|-----------------------|------------|
| Gender, n             | 19         |
| Male                  | 12         |
| Female                | 17         |
| Gestational age, n    |            |
| ≥ 37 weeks            | 23         |
| ≤36 weeks             | 8          |
| Birth weight, n       |            |
| ≥2,500 grams          | 14         |
| ≤2,499 grams          | 17         |
| Associated congenital anomalies, n | |
| Present               | 5          |
| Absent                | 26         |
| Type of esophageal atresia, n | |
| Type A                | 4          |
| Type B                | 0          |
| Type C                | 27         |
| Type D                | 0          |
| Type E                | 0          |
| Surgical management, n|            |
| One-stage operation   | 12         |
| Including gastrostomy and esophagostomy | 11 |
| No operation          | 8          |
| Hemoglobin level, n   |            |
| <13 g/dL              | 16         |
| ≥13 g/dL              | 15         |
| Platelet count, n     |            |
| <150x10^3/mm^3        | 20         |
| ≥150x10^3/mm^3        | 11         |
| Sepsis event, n       |            |
| Present               | 21         |
| Absent                | 10         |
| Waterston’s classification, n | |
| Waterston A           | 8          |
| Waterston B           | 10         |
| Waterston C           | 13         |
| Outcomes, n           |            |
| Died                  | 26         |
| Survived              | 5          |

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Table 2. Congenital malformations associated with EA

| Patient | Gender | Gestational age, weeks | Associated anomalies |
|---------|--------|------------------------|----------------------|
| A       | Male   | 38                     | VACTERL, anorectal malformation without fistula |
| B       | Female | 34                     | VACTERL, anorectal malformation with vestibular fistula |
| C       | Male   | 38                     | Anorectal malformation with midraphae fistula |
| D       | Male   | 38                     | CTEV, bilateral undescended testes, patent ductus arteriosus |
| E       | Male   | 33                     | Down syndrome, bilateral undescended testes, anorectal malformation with perineal fistula |

CTEV = congenital talipes equino varus

Table 3. Risk factors that affected mortality rate

| Risk factors | Dead | Survived | OR   | 95% CI | P value |
|--------------|------|----------|------|--------|---------|
| Hemoglobin   | <13 g/dL | 11       | 0.688| 0.49 to 0.96| 0.043 |
|              | ≥13 g/dL | 15       | 0    |        |         |
| Platelet count| <150x10^3/mm^3 | 19 | 10.857| 1.03 to 114.58| 0.042 |
|              | ≥150x10^3/mm^3 | 7        | 1    |        |         |
| Sepsis       | Present   | 20       | 13.333| 1.24 to 143.15| 0.027 |
|              | Absent    | 6        | 1.333| 1.035 to 1.717| 0.133 |
| Albumin level| ≤2.6 g/dL | 11       | 1.333| 1.035 to 1.717| 0.133 |
|              | >2.6 g/dL | 15       | 0    |        |         |

Neonates with low platelet counts (<150x10^3/mm^3) in our study showed a significantly higher mortality rate than those who had platelet counts ≥150x10^3/mm^3 (16/26 vs. 7/26, respectively; P=0.042) with OR 10.85 (95%CI 1.03 to 114.58) (Table 3). Perioperative hypoalbuminemia (<2.6 g/dL) was present in 11/31 neonates, whereas 20/31 neonates had normal albumin serum (≥2.6 g/dL). None of the neonates with hypoalbuminemia survived, whereas 5 neonates with normal albumin serum survived (0/26 vs. 5/26, respectively; P=0.133).

Sepsis was the most frequent perioperative complication and a significant risk factor for death. Table 3 shows that 21/31 neonates had sepsis. Only 1 neonate with sepsis and 4 neonates without sepsis survived (OR 13.3; 95%CI 1.24 to 143.15; P=0.027).

Discussion

Esophageal atresia (EA) and/or TEF are common congenital anomalies. Although the mortality rate of patients born with EA/TEF has decreased from 61% to 11% since 1947, and a study showed a significant decrease in mortality from 87.5% to 0%, over 42 years,12 we found the mortality rate to be high (26/31 in the last 6 years) at our institution. In recent years, 78% of mortality was reported to be caused by associated congenital anomalies in these EA/TEF patients, followed by sepsis (50%).13 Our findings were similar.

A significant contributor to mortality in our study was sepsis (20/26). Unfortunately, we could not determine whether this sepsis was isolated or a result of other complications, such as pneumonia or postsurgical infections. We analyzed hemoglobin level and platelet count as other risk factors. No other studies have reported associations of these variables with mortality in EA patients. However, we found that patients with low platelet counts had a significant higher mortality rate.

The function of red blood cells is to transport oxygen (O2) to tissues to meet metabolic demands. Hemoglobin is the most abundant protein in erythrocytes, facilitating oxygen delivery by reversibly binding O2 molecules. At birth, nearly 80% of circulating hemoglobin is fetal hemoglobin, and remains so until the age of 2 to 3 months when most hemoglobin constitutes the adult type. This fetal
hemoglobin has a P50 value 6 to 8 mmHg higher than that of the adult-type hemoglobin, and a high content of fetal hemoglobin is associated with higher oxygen affinity.\textsuperscript{12,14} We assumed that neonates with EA/TEF are in a condition of perioperative stress. The stress response is initiated and coordinated by several messengers, affects whole-body systems, and could be considered a form of 'controlled' injury that results in alterations in metabolic, inflammatory, endocrine, and immune responses. In this condition, oxygen consumption is elevated in affected neonates, but it cannot be fulfilled due to their anemic condition. As neonates with EA/TEF are in a condition of perioperative stress, some changes occur, such as elevated serum insulin, catabolic hormones (glucagon, cortisol, catecholamines), and specific cytokines known to interact with the inflammatory process. The prostaglandin family includes the leukotrienes and thromboxanes, all of which serve as mediators in such wide-ranging processes as vascular permeability, smooth muscle reactivity, and increased platelet aggregation. Such is a possible reason why low platelet count is one of the prognostic factors contributing to the mortality rate in our study. The platelet count is a measurement of the adequacy of platelet numbers to provide initial hemostasis. Thrombocytopenia (platelet count $< 150 \times 10^3/mm^3$) is one of the most common problems that occur in hospitalized patients, especially newborns. Some researchers noted that the risk of bleeding is inversely proportional to the platelet count. Therefore, platelet counts of less than $50 \times 10^3/mm^3$ are considered to be the cut-off criteria for prophylactic transfusions in any invasive procedures.\textsuperscript{15,16} At our institution, this platelet level cut-off is still debated between the pediatric surgeons and neonatologists.

At our institution, echocardiography was not routinely done to assess cardiac malformations in EA/TEF patients. This condition results in difficulty to assess associated cardiac anomalies for this case. Previous studies claimed that cardiac malformations occur in 13 to 49\% of EA/TEF incidences.\textsuperscript{7-10} Due to the aforementioned limitation, we could not make an assessment based on the Spitz classification for survival in esophageal atresia.\textsuperscript{10} These conditions present challenges to the pediatric cardiologists, pediatric surgeons, and neonatologists.

In conclusion, the largest contributor to mortality in this study is sepsis (64.5\%). The other risk factors for mortality in our EA/TEF patients are high hemoglobin levels and low platelet counts. Further studies with a larger sample size are needed to increase the precision of the results.

Conflict of interest

None declared.

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