Prophylactic effect of H2 blocker for anastomotic stricture after esophageal atresia repair

Anastomotic stricture is the main complication after esophageal atresia (EA) repair. In this study, we assessed the efficacy of long-term prophylactic H2 blocker in preventing stricture.

Methods: Twenty-seven patients who had undergone primary repair for EA (Gross type C) were reviewed retrospectively. The patients were analyzed in two groups: the H2 blocker group (n = 14), in which the patients were treated with prophylactic H2 blocker; and the control group (n = 13), in which they were not. To assess anastomotic stricture, contrast esophagography was performed and the number of patients who required balloon dilatation was recorded.

Results: Five patients (18.5%) required postoperative balloon dilatation within 1 year of primary repair. There was no difference in dilatation rate between the two groups. In the H2 blocker group, however, anastomotic stricture improved significantly in the late postoperative period relative to that in the early postoperative period. In contrast, in the control group, anastomotic stricture did not improve after a long postoperative period. The incidence of gastroesophageal reflux was 55.6%. Postoperative gastroesophageal reflux was a predisposing factor for balloon dilatation in the control group, but not in the H2 blocker group.

Conclusions: Long-term treatment with prophylactic H2 blocker may prevent anastomotic stricture caused by gastroesophageal reflux in the late postoperative period after EA repair.

Key words: anastomotic stricture, balloon dilatation, esophageal atresia, gastroesophageal reflux, prophylactic H2 blocker.
dilatation was recorded. In this study, 18 patients (nine in the H2 blocker group and nine in the control group) underwent routine contrast esophagography twice a year after the primary repair. The first round of contrast esophagography, in the early postoperative period, was performed between days 7 and 13 (median, day 7). The second round, in the late postoperative period, was performed between 3 and 10 months after repair (median, 6 months) and when anastomotic stricture was suspected. We used the anastomotic stricture index (SI) to quantify the severity of the stricture. SI is defined as: \( ((D–d)/D) \times 100 \), where D is the most dilated diameter of the esophagus below the stricture and d is the diameter of the stricture.\(^7\) We performed balloon dilatation to treat anastomotic stricture when a patient presented with severe symptoms of narrowing, such as dysphagia, regurgitation, or oxygen desaturation during feeding.

Esophageal pH was monitored for 24 h to evaluate GER before 1 year of age. The results were considered pathological if the percentage of time at pH <4 exceeded 4% of the total measured time. H2 blocker treatment was stopped temporarily 4 days before the pH examination.

### Statistical analysis

Data were collected from the institutional database and reviewed retrospectively. The study ended 1 year after the primary repair in each patient. The data for the H2 blocker group (birthweight, prevalence of cardiac anomalies, operation time, length of gap between upper and lower esophagus, frequency of GER, SI, and the number of patients who required balloon dilatation) were compared with those of the control group.

Statistical analysis was performed using the chi-squared test for categorical variables and the Mann–Whitney U-test for continuous variables. \( P < 0.05 \) was considered statistically significant. This retrospective survey was approved by the Ethics Committee of NUH.

### Results

Thirty-five patients underwent radical surgery for EA from 2004 to 2013. Data on their sex, birthweight, Gross classification, associated malformations, and survival are listed in Table 1. Eight patients were excluded from the study: three patients were not Gross type C and five patients were observed for <1 year (died or were lost to follow up). There were three deaths, with an overall mortality rate of 8.6%. One patient died of severe congenital heart disease and two patients died from associated trisomy 18. Twenty-seven patients who received primary repair for EA (Gross type C) were included in this study. Five (18.5%) of these 27 patients required postoperative balloon dilatation within 1 year of the primary repair. The incidence of GER was 55.6% \((n = 15)\). Anastomotic leakage occurred in 7.4% \((n = 2)\) of the patients.

The H2 blocker group \((n = 13)\) and the control group \((n = 14)\) were similar with regard to birthweight, prevalence of cardiac anomalies, operation time, the length of gap between upper and lower esophagus, and incidence of anastomotic leakage and GER. The number of patients who required balloon dilatation did not differ significantly between the H2 blocker group (7.7%) and the control group (28.6%; Table 2).

Stricture index improved in 12 patients (66.7%) in both groups at the second round of esophagography (in the late postoperative period) compared with that in the early postoperative period. In the H2 blocker group \((n = 9)\), SI was 41.7–71.2% (median, 63.8%) and 30.7–70.9% (median, 40.5%) in the early and late postoperative periods, respectively. This improvement in the H2 blocker group was statistically significant \((P = 0.038)\). In the control group \((n = 9)\), SI was 40.5–70.6% (median, 51.8%) and 40.3–81.3% (median, 60.4%) in the early and late postoperative periods, respectively. Therefore, in the control group, SI did not improve significantly in the late postoperative period compared with that in the early postoperative period \((P = 0.17)\). SI in the late postoperative period was significantly better in the H2 blocker group than in the control group \((P = 0.031; Fig. 1)\).

Table 3 lists the predisposing factors for balloon dilatation. Postoperative GER and anastomotic leakage was significantly associated with subsequent balloon dilatation in all patients.

| Table 1 Subject characteristics (2004–2013) |
|--------------------------------------------|
| \( n = 35 \)                             |
| **Sex (male)**                            |
| 17 (48.6)                                 |
| **Birthweight**                           |
| <1500 g                                  |
| 2 (5.7)                                   |
| 1500–2500 g                              |
| 18 (51.4)                                 |
| >2500 g                                  |
| 15 (42.9)                                 |
| **Gross classification**                  |
| Type A                                   |
| 2 (5.7)                                   |
| Type C                                   |
| 32 (91.4)                                 |
| Type D                                   |
| 1 (2.9)                                   |
| **Associated malformations**              |
| Chromosomal                              |
| 2 (5.7)                                   |
| Vertebral                                |
| 5 (14.3)                                  |
| Anorectal                                |
| 8 (22.9)                                  |
| Cardiac                                  |
| 8 (22.9)                                  |
| Congenital esophageal stenosis            |
| 3 (8.6)                                   |
| **Survival**                              |
| 32/35 (91.4)                              |

| Table 2 Subject characteristics vs presence of H2 blocker |
|----------------------------------------------------------|
| **H2 blocker**   | **Control** |
| **2010–2013**    | **2004–2009** |
| \( n = 13 \) | \( n = 14 \) |
| \( n (\%) \) or median (range) | \( n (\%) \) or median (range) |
| **Birthweight** |
| <1500 g       | 2 (15.4) | 0 (0) |
| 1500–2500 g   | 6 (46.2) | 8 (57.1) |
| >2500 g       | 5 (38.5) | 6 (42.9) |
| **Cardiac anomalies** |
| 3 (23.1)       |
| 3 (21.4)       |
| **Operative time (min)** |
| 89 (80–121)    | 124 (34–200) |
| **Length of gap (vertebral bodies)** |
| 1 (0.5–2)       |
| 1 (0–2)       |
| **Anastomotic leakage** |
| 1 (7.7) | 1 (7.1) |
| **Gastroesophageal reflux** |
| 7 (53.4) | 8 (57.1) |
| **Balloon dilatation** |
| 1 (7.7) | 4 (28.6) |
Postoperative GER was a predisposing factor for balloon dilatation in the control group, but not in the H2 blocker group.

**Discussion**

Advances in neonatal intensive care, pediatric anesthesia, and surgical strategies have increased the survival rate after the repair of EA to as high as 91.5%. At NUH, all patients undergoing EA repair have survived, except those with severe cardiac anomalies or chromosomal abnormalities. Despite the improvement in survival rate, anastomotic stricture is reported to complicate the postoperative course of 40% of all patients with EA.

In the present study, only 18.5% of EA patients (Gross type C) required balloon dilatation within 1 year of the primary repair because balloon dilatation is performed to release only severe symptomatic stricture. Asymptomatic stricture on postoperative contrast esophagography is not deemed an indication for balloon dilatation of the stricture. In 66.7% of the present patients, anastomotic SI improved spontaneously after 6 months of age compared with that in the early postoperative period. It has been reported that an initial anastomotic stricture does not correlate with the later development of a symptomatic anastomotic stricture.

We used SI, as proposed by Said et al., to assess anastomotic stricture and quantify the severity of the stricture. Said et al. defined SI >50% as anastomotic stricture. In the present study, the anastomotic SI of patients who underwent balloon dilatation was >65%. From this perspective, SI is a useful tool for the assessment of anastomotic stricture.

A strong relationship has been demonstrated between the acid reflux caused by GER and anastomotic stricture. To prevent the formation of anastomotic stricture, we introduced long-term prophylactic acid-suppression treatment. Two reports, however, showed that the acid-suppression treatment was not effective for anastomotic stricture. One report showed that treatment with a prophylactic proton pump inhibitor for 3 months did not prevent anastomotic stricture. Prophylactic treatment with a proton pump inhibitor for 3 months after EA repair might be too short to prevent anastomotic stricture, especially when it is associated with late-onset postoperative GER. The other report provided no detailed data on duration of prophylactic acid-suppression. We consider that long-term prophylactic acid-suppression treatment is crucial for preventing anastomotic stricture in the late postoperative period. In the present study, treatment with prophylactic H2 blocker was continued until pH monitoring confirmed the absence of GER. All patients with GER continued to be treated with the H2 blocker for >1 year after the primary repair, and patients without GER were treated with the H2 blocker for at

![Fig. 1](image-url) Changes in stricture index (SI) from the early to the late postoperative period in (a) the H2 blocker group and (b) the control group. ---, without balloon dilatation; - - -, with balloon dilatation. *P < 0.05. NS, not significant.

| Table 3 | Predisposing factors for balloon dilatation |
|---------|------------------------------------------|
|         | With dilatation, n (%) | P |
| Total (n = 27) | GER | Present n = 15 5/15 (33.3) | 0.027 |
|       | Absent n = 12 0 |  |  |
|         | Anastomotic leakage | Present n = 2 2/2 (100) | 0.002 |
|       | Absent n = 25 3/25 (12) |  |  |
| H2 blocker (n = 13) | GER | Present n = 7 1/7 (14.3) | 0.335 |
|       | Absent n = 6 0 |  |  |
| Control (n = 14) | GER | Present n = 8 4/8 (50) | 0.040 |
|       | Absent n = 6 0 |  |  |

GER, gastroesophageal reflux.
least 6 months after the primary repair. NUH has considerable clinical experience in H2 blocker treatment for neonates, therefore we preferred H2 blocker to proton pump inhibitor considering the safety of long-term use. In the present study, there were no patients for whom anti-reflux surgery was considered for apparent life-threatening events (ALTE), such as refractory pneumonia or obstructive apnea because of GER. In our opinion, once GER causes ALTE regardless of acid-reflux medication, anti-reflux surgery should be considered promptly.

The patients were analyzed in two groups: the H2 blocker group and the control group. It is a problem that the two groups were not selected from the patients in the same period, but we consider that the two groups were comparable because they did not differ in their birthweight, prevalence of cardiac anomalies, operation time, surgical methods, postoperative management except for prophylactic acid-suppression treatment, the length of gap between upper and lower esophagus, and incidence of anastomotic leakage and GER. The number of patients who required balloon dilatation did not differ significantly between the H2 blocker group (7.7%) and the control group (28.6%). The treatment of one patient in the H2 blocker group who required balloon dilation, however, was complicated by anastomotic leakage. Anastomotic stricture in the perioperative period can be caused by many factors. We showed that GER and anastomotic leakage were significantly associated with subsequent anastomotic stricture formation. The anastomotic stricture in one patient in the H2 blocker group may have resulted from complications due to anastomotic leakage and GER.

In the control group, postoperative GER was closely related to symptomatic anastomotic stricture. In the H2 blocker group, however, symptomatic stricture was not significantly associated with GER. This suggests that long-term H2 blocker medication after EA repair prevents the anastomotic stricture caused by acid reflux. A recent large study reported that prophylactic medication for GER is prescribed for only 51.6% of all patients undergoing EA repair.10 If all EA patients were medicated with acid-suppressive drugs, postoperative anastomotic stricture could occur less frequently.

We conclude that a long period of prophylactic H2 blocker treatment may prevent anastomotic stricture after EA repair.

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