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Prolonged use of proton pump inhibitors as stricture prophylaxis in infants with reconstructed esophageal atresia

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ABSTRACT

Introduction: Proton pump inhibitors (PPIs) are used as prophylaxis, guarding against anastomotic stricture (AS) in the aftermath of reconstructed esophageal atresia (EA). The incidence of stricture formation was studied in this setting, comparing outcomes of 3- and 12-month PPI prophylactic regimens.

Patients and methods: Patient characteristics (gestational age, birth weight, prevalence of chromosomal aberrations, and other malformations), as well as rates of survival, AS formation, and required balloon dilatation, were recorded in the following therapeutic subsets: 1) all infants undergoing primary surgical anastomosis for EA in years 2010-2014 and given postoperative PPI prophylaxis for 12 months and 2) all infants similarly treated for EA in years 2001-2009 but given postoperative PPI prophylaxis for 3 months only. Duration of follow-up was 1 year in each group.

Results: Patient characteristics and survival rates in 12-month (n=34) and in 3-month (n=32) treatment groups did not differ significantly. The prevalence of AS was 42% vs 43% in each group (12-month, 14/33; 3-month, 13/30; $p=1$). Median number of dilatations required was 3 (range, 1-9) per patient in each group ($p=0.69$). Median age at initial dilatation was 163 days and 63 days in 12- and 3-month groups, respectively ($p=0.04$).

Conclusion: Development of AS in the first year after reconstruction of EA was not reduced by prolonged PPI prophylaxis (12 vs 3 months), but initial balloon dilatation procedures were performed later in infants who were treated longer.

Keywords: esophageal atresia (EA); anastomotic stricture (AS); prophylactic proton pump inhibitor (PPI) treatment; balloon dilatation.

INTRODUCTION

Anastomotic strictures (AS) that require dilatation are in a review publication reported to develop in 9-79% of infants after surgical intervention for esophageal atresia (EA) ¹. A correlation between esophageal stricture in EA and gastroesophageal reflux (GER) has been reported ^{2,3}, and GER is further linked with a higher risk of esophageal ulcers and distal esophageal strictures or even mucosal metaplasia ⁴. Proton pump inhibitors (PPIs) are administered on a routine basis postoperatively to prevent negative effects of GER, such as AS. In a previous publication, researchers found no difference in development of AS with or without 3 months of PPI prophylaxis ⁵. The question then remains whether a longer duration of PPI use after surgical correction of EA might impact the frequency of AS.

This study was conducted to assess the effects of prolonged PPI treatment after reconstruction of EA in terms of AS occurrence and required dilatations in the first postoperative year, comparing infants treated with PPIs for either 12- or 3-month periods.

PATIENTS AND METHODS

All infants subjected to primary anastomosis for EA type C i.e. distal tracheoesophageal fistula, in years 2010-2014 were given 12-month regimens of postoperative PPI prophylaxis, serving as the study group. All infants similarly treated for the same types of EA in years 2001-2009, but given postoperative PPIs for 3 months only, served as controls. In the study group, data was collected prospectively, whereas the control group was assessed through retrospective review of hospital records. Excluded from the analysis were those who had emigrated, were lost to follow-up, patients who died within the first year because of associated malformations and those who did not have PPI as a regular treatment.

In all patients, intravenous or oral PPI (once daily omeprazole/esomeprazole, 1-2 mg/kg body weight) was initiated within the first 24 hours the first post-operative day and continued for 12 (study group) or 3 (control group) months postoperatively. All patients were analyzed in terms of mortality, presence of chromosomal aberrations and multiple malformations (i.e. VACTERL status). The type of reconstructive surgery and postoperative episodes of anastomotic leakages were registered. Then, AS, need for balloon dilatation, age at first time for balloon dilatation and the number of repetitive dilatations required for stricture resolution within the first postoperative year were registered. Primary outcome measures were onset and frequency of AS in postoperative year 1.

AS was defined as a narrowing of the esophagus at the site of the anastomosis, identifiable on X-ray through use of contrast and verified by esophagoscopy. Postoperative contrast esophagograms were performed routinely at Months 3, 6-8, and 12 in all patients or following clinical suspicion of emergent AS.

Endoscopic dilatations were performed under general anesthesia, using CRE balloon dilators (Boston Scientific Corp, Watertown, MA, USA) and a GIFXP160 video endoscope (Olympus Corp, Tokyo, Japan). A dilatation procedure was regarded as reversal of constricted contours in a balloon filled with contrast during fluoroscopic imaging, thus equating dilatation with a widening of AS diameter. In the absence of balloon constriction, procedures were considered calibrations and were not included in reported data.

All children, in the study as well as in the control group, were operated on during the first 48 h after birth. According to the policy at our center dilatations started at the earliest 3 weeks after surgery and was repeated within 2 – 3 weeks or more if needed. The AS was dilated to

the same diameter as the child's thumb ⁶. With this follows an advancement of the dilatation diameter as the child grows older. Duration of follow-up was set at 1 year after reconstructive surgery for EA and was the same in each group. In the course of study, 24-hour pH measurements were not done routinely.

STATISTICAL CONSIDERATIONS

This analysis encompassed a case-controlled investigation of independent test subjects and controls in a 1:1 ratio. Prior data indicated a 0.4 probability of exposure among controls. Assuming 0.2 as the true probability of exposure among subjects, 32 study patients and 32 control patients were required to reject the null hypothesis (i.e., that exposure rates for study and control patients were equal) with a probability (power) of 0.8. Type I error probability in testing of this null hypothesis was 0.05. All analytics relied on standard software, specifically SPSS v22.0 (SPSS Inc, Chicago, IL, USA) or PASW Statistics 18 (freeware) for Windows. Between-group differences were analyzed using Fisher's exact test for dichotomous variables or Mann-Whitney U-test for continuous data, setting statistical significance at $p < 0.05$.

ETHICAL APPROVAL

The study was performed in accord with the Helsinki declaration and was approved by the Regional Ethical Review Board, Lund, Sweden (registration number 2010/49). Anonymity of data was maintained prior to calculations, and results are presented in such a way that it is impossible to identify any single patient.

RESULTS

In years 2010-2014, the study group was comprised of 34 infants, each of whom was treated by direct surgical anastomosis and given a 12-month postoperative PPI regimen as AS prophylaxis. In years 2001-2009, 32 infants were included in the control group, each given 3 months of PPI prophylaxis ⁵.

There were no differences between groups in terms of gender, gestational age, and birth weight or prevalence of chromosomal aberrations and VACTERL status. Episodes of anastomotic leakage did not differ between groups (Table 1). Mortality in patients with EA was determined solely by associated cardiac malformations and chromosomal aberrations.

In both groups, all AS were alleviated by dilatation only. No patients suffered from peptic strictures of distal esophagus during the 1-year follow-up period. The proportions of infants requiring dilatation did not differ between the groups (12-month: 15/34, 44%; 3-month: 14/32, 44%). Likewise, the number of repeated dilatations needed during the first postoperative year did not differ between the groups, with 8 or 9 done at maximum and a median of 3 per patient. Median age at first dilatation was lower in the 3-month (vs 12-month) PPI treatment group. Perforation of the esophagus occurred in one patient following dilatation. This infant was successfully managed through nasogastric tube feeding and 7 days of total parenteral nutrition (Table 2).

DISCUSSION

Outcomes of this study indicate that prolonging prophylactic PPI treatment for 12 months (vs a 3-month regimen) after surgical reconstruction of EA does not impact the development of AS or reduce the number of required postoperative dilatations.

The prevalence cited for AS after correction of EA varies considerably, ranging from 9-79% regardless of PPI treatment duration ¹. GER is linked with a higher risk of esophageal ulcers

and strictures in the distal esophagus. To prevent peptic esophageal strictures in circumstances other than EA, treatment with PPIs for a period of at least 3 months has been reported to be effective^{7,8}. Such data has thus prompted prophylactic PPI treatment of all infants with EA, although there is no proof of efficacy in this context. In conjunction with peptic strictures, the healing of underlying esophagitis is critical, reinforcing the view that PPI treatment may reduce repeated dilatations and provide symptomatic relief⁹. GER was not addressed in this study, but peptic strictures of the distal esophagus did not occur, which in hindsight may be attributable to PPI use. Anastomotic tension likewise was not regularly assessed or pursued but may influence the frequency of AS.

Ultimately, our PPI treatment groups (12-month vs 3-month) did not differ significantly in the frequency of AS after repair of EA. Hence, the PPI regimens used in this study cannot be advocated from a clinical perspective. However, this finding should not be interpreted as similarity of group outcomes (type 2 error).

The finding that infants in the control group (3-month PPI regimen) were younger at the time of first dilatation, which nevertheless took place within the first 3 months of treatment, possibly reflects differences in PPI therapeutic compliance or bias regarding indications for dilatation which makes it impossible to draw a strong conclusion from this result. Compliance with PPI treatment was not controlled during either study period. Given that emphasis placed on the importance of treatment may have increased over time or that the importance of daily PPI intake was underscored by virtue of its lengthy duration, better compliance would not be unusual in the 12-month treatment group.

To a large extent, the same surgeons were involved in both study periods with the exception of two colleagues retiring during the first period. However, two consultants were trained during the same period (2001-2009) to perform the surgery required. This might be a confounder to the results. The protocols and indications for dilatation procedures in patients with EA were unchanged at our department during the study intervals. However, a more liberal attitude towards dilatations or the definition of dilatation (vs calibration) among controls is feasible, owing to discrepancy in time frame. Furthermore, we cannot exclude that still longer periods of PPI treatment (e.g. up to 5 years) may help prevent AS occurrence long-term or that higher doses of PPIs may enhance their efficacy.

Limitations of this study are the low numbers of study subjects. There is a bias in the prospective collection of data in the study group versus the retrospective collection in the control group, and the fact that two different time periods were analyzed. Another limitation is that compliance with therapeutic regimens was not controlled in either group. Furthermore, as there was one patient with gastrostomy in the study group but not the control group, this may have influenced the results since placement of a gastrostomy might lead to worsening of reflux.

In the literature, there is no evidence supporting PPI treatment at all in infants with EA. Therefore, a prospective and perhaps multicenter trial (to assess more patients), would make sense. A randomized longitudinal study, including an untreated control population and possibly treatment periods >12 months, may more decisively reveal any benefits of PPI prophylaxis in children born with EA.

CONCLUSION

12 months PPI treatment following surgical reconstruction of EA did not influence the occurrence of AS in the first postoperative year, as compared to 3 months PPI treatment. The role of PPI after reconstruction of EA remains uncertain but may be clarified by a randomized study that incorporates an untreated reference group.

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Legends for the tables**Table 1**

Patient characteristics, stratified by proton pump inhibitor (PPI) therapeutic subset (study group, 12 months; control group, 3 months)

Table 2

Periodic balloon dilatations for anastomotic stricture and ages at onset, stratified by therapeutic subset

Table 1

Patient characteristics, stratified by proton pump inhibitor (PPI) therapeutic subset (study group, 12 months; control group, 3 months)

Type of atresia: Type C	Study group 2010-2014 N=33	Control group 2001-2009 N=30
Gender: Male/female	22/11 (67%/33%)	19/11 (63%/37%)
Gestational age - Full term (weeks ≥ 37) - Premature (weeks < 37)	18 (55%) 15 (45%)	18 (60%) 12 (40%)
Birth weight: - <1500 g - 1500-2500 g - >2500 g	2 (6%) 5 (15%) 26 (79%)	1 (3%) 8 (27%) 21 (70%)
Associated malformations	N=76	N=78
- Chromosomal	2 (6%)	1 (3%)
- Vertebral	3 (9%)	4 (13%)
- Anorectal	2 (6%)	1 (3%)
- Cardiac	5 (15%)	6 (20%)
- Tracheal	27 (82%)	28 (93%)
- Esophageal	33 (100%)	30 (100%)
- Renal	3 (9%)	4 (13%)
- Limb	1 (3%)	4 (13%)
Anastomotic leakage	3 (8%)	3 (10%)
Gastrostomy	1	0
Antireflux surgery	0	0

Table 2

Periodic balloon dilatations for anastomotic stricture and ages at onset, stratified by therapeutic subset

Treated with PPI and monitored	Study group PPI 12 months 2010-2014	Control group PPI 3 months 2001-2009	<i>P</i> value
Patient totals	33	30	1*
Female/male, n	9/24	8/22	
Patients in need of dilatation	14 (42%)	13 (43%)	1*
Female/male, n	3/11	4/9	1*
Dilatations required/patient			
Median, n (range)	3 (1-8)	3 (1-9)	0.69**
Age at first dilatation			
Median, days (range)	163 (36-334)	63 (28-346)	0.04**
Perforation during dilatation, n	1 (3%)	0%	1*

**Fisher's exact test, two-tailed.*

** *Mann-Whitney U test.*