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Abstract

Introduction: Oesophageal stricture is a frequent complication following repair of oesophageal atresia. The aim of this study was to conduct a pre- and post-intervention study and analyse the incidence of stricture formation and need for balloon dilatation after introducing prophylactic proton pump inhibitor (PPI) treatment.

Children and design: All children operated for oesophageal atresia during 2001-2009 (n=39) were treated with prophylactic proton pump inhibitors (PPI group) for at least 3 months postoperatively. The frequency of stricture formation in the anastomosis and need for balloon dilatation was registered. A previously published group of children (n=63) operated for oesophageal atresia during 1983-1995 not treated with prophylactic PPI was used as control group. Duration of follow-up time in the PPI group was equal to the one in the control group, and set to one year after the last oesophageal dilatation procedure.

Results: The PPI and control group were comparable regarding patient characteristics, gestational age and birth weight, prevalence of chromosomal aberration and VACTERL malformations. Also survival rate and prevalence of surgery were similar in both groups. Mortality was mainly determined by associated malformations.
The dilatation frequency needed in each child did not differ between the two groups. The prevalence of stricture formation was 42% in the control group compared to 56% in the PPI group, p= 0.25. Number of dilatations needed varied between 1 and 21, with a median value of 3 and 4 respectively for the PPI and the control group. The children in the PPI group were significantly younger at the time of dilatation. This difference reflects a change in policy and increased experience.

Conclusion: The incidence of anastomotic stricture following repair for esophageal atresia remains high also after introduction of PPI. The results can not support that prophylactic treatment with PPI prevent anastomotic stricture formation.

Key words:

Oesophageal atresia, oesophageal stricture, prophylactic PPI treatment, balloon dilatation.

Introduction

Anastomotic strictures that require dilatation develop in 18-40% [1] of children operated for oesophageal atresia (EA) with or without trachea-oesophageal fistula (TEF). Predisposing factors are anastomotic tension, anastomotic leakage, and presence of gastro-oesophageal reflux (GER). Previous studies have shown a clear correlation between GER and oesophageal strictures secondary to EA/TEF, with an incidence as high as 60% [1]. These findings suggest the need for antireflux treatment in this patient category. Recent epidemiological data have indicated that treatment with PPI is effective in prevention of oesophageal peptic strictures in general when treated with PPI for a period of at least 3 months [2, 3]. In patients with peptic oesophageal strictures the healing of coexisting esophagitis is crucial and PPI treatment has been suggested to reduce dilatation frequency and to provide symptom relief [4].

It is reasonable to believe that PPI treatment in children at risk of developing strictures following corrective surgery for EA/TEF would have the same effect. We hypothesized that the introduction of postoperative proton pump inhibitor (PPI) treatment following corrective surgery of oesophageal atresia would have beneficial effects in preventing anastomotic stricture formation. The aim of this pre- and post-intervention study was to assess the potential of prophylactic PPI treatment in preventing stricture formation and reducing the number of dilatations needed.

Children and design

All newborn children operated on for oesophageal atresia with (type C) or without (type A) distal trachea-oesophageal fistula during 2001-2009, treated with prophylactic PPI (omeprazole/esomeprazole, 2 mg/kg body weight once a day) were included in the study (PPI) group. The first dose was given at the age of 3 days and then continued for at least three months and extended during the period of oesophageal dilatations. The endpoint of the study was one year after the last oesophageal dilatation of each patient. Data was collected retrospectively from hospital records.

During 2001 to 2009 42 patients were found through the diagnostic code (ICD-10) for EA/TEF. Ten of these patients were excluded from the study group. Two patients were lost to follow-up after emigration. Five children died due to associated anomalies; two already prior

to surgery and three postoperative. Three patients did not receive PPI treatment and were included in the control group (n=66).

All in all 32 patients were included in the PPI group. These patients were analysed for surgical procedure, anastomotic stricture formation, need for balloon dilatation, age at procedure, and numbers of dilatations required. Numbers of days on PPI were evaluated. Further, data was collected regarding presence of chromosomal aberrations and malformations associated with VACTERL. The PPI-group was compared to a control group of children operated on for oesophageal atresia at the same centre during 1983-1995 [5] and who did not receive prophylactic PPI.

Evaluation of stricture formation: In the case of suspect stricture formation a calibration was performed, but no earlier than 3 weeks after surgery. If a narrowing of the anastomosis was observed on x-ray during balloon inflation the procedure was defined a dilatation, otherwise the procedure was considered a calibration only.

Endoscopic dilatation was performed in general anaesthesia using Balloon dilatators CRE® (Controlled Radial European Balloon Dilatators, provided by Boston Scientific, Watertown, Ma, USA) and the GIFXP160® video endoscope (provided by Olympus) was used for the dilatation. Duration of follow-up in the PPI group was equal to the follow-up time in the control group, and set to one year after the last oesophageal dilatation procedure, the endpoint of the study.

Statistical considerations

Analyses of data were performed using SPSS (statistical package for social sciences) PASW statistics 18 for Windows. Differences between groups were analysed by means of the Fisher's exact test or the Mann-Whitney U Test when appropriate. The level of significance was defined as $p < 0.05$.

By use of a two-sided test 85 patients are needed to be enrolled in the PPI group and the control group to have 80% power to detect a significant difference between groups with 50% lower frequency of strictures in the PPI group.

Ethical considerations

The regional research ethics committee approved the study (registration number 2010/49).

Results

40 children were operated for oesophageal atresia during the PPI study period (2001-2009), whereas 63 children were operated during 1983-1995 (period of the control group). The data on demographics, type of atresia, associated malformations, surgery and survivals in the study and control group, respectively, are presented in Table 1.

The study (PPI) and the control group were comparable regarding patient characteristics, gestational age and birth weight, prevalence of chromosomal aberration and VACTERL malformations. Also survival rate and prevalence of surgery were similar in both the groups. The mortality of oesophageal atresia was mainly determined by associated malformations.

Occurrence of anastomotic leakage and oesophageal perforation during dilatation within the respective groups is summarized in Table 2. Significant differences were found when comparing the two groups. Data on number of dilatations and age at the first and last dilatation in both the PPI and the control group are presented in Table 2. The dilatation frequency needed in each child did not differ significantly between the two groups.

Approx. 50% (42 respective 56%) of the children required postoperative balloon dilatations. Number of dilatations needed varied between 1 and 21, with a median value of 3 and 4 respectively for the PPI and control group.

The children in the PPI group were significantly younger at the time of dilatation. This difference reflects a change in policy and increased experience of the team of surgeons taking care of children with oesophageal atresia.

In the control group (n=66) 28 patients, 42%, underwent dilatation. Eighty-five patients are needed for 80% power, and 36 patients of these need to be dilated to achieve a prevalence of 42%. In the study group 32 patients were included of whom18 underwent a dilatation, prevalence = 56%. Eighty-five patients are needed in this group of whom 18 patients need to undergo a dilatation to achieve a 50% reduction of the prevalence to 21% and a significant difference between the groups. Thus, fifty-three more patients are needed of whom none patients being dilated, prevalence = 0%, Table 3. Such a low prevalence of dilatations does not exist in the literature. Thus, we concluded that continuing the study is not reasonable.

With these sample sizes our study offered sufficient power to significantly detect a difference in stricture formation of 55% and a stricture prevalence of 19%.

Discussion

The prevalence of stricture formation did not differ significantly between the control (42%) and PPI (56%) group, indicating that we can not support the hypothesis that PPI prevents anastomotic stricture formation.

Complications following dilatation occurred more frequently in the control group (1983-1995). Possible explanations for this might be the treatment with PPI, continuous technical advancement and improvement of surgical skills and intensive care being advantageous for the PPI group (2001-2009).

The majority of patients in the PPI group (81%) with confirmed anastomotic stricture formation presented with signs of oesophageal obstruction, as e.g. swallowing difficulties and vomiting. The remaining 19% were asymptomatic even though a stricture was present on control x-ray. In the group of patients with no verified stricture the prevalence of obstructive symptoms was 50%. The reason why these patients had clinical signs of oesophageal narrowing could be explained by the fact that patients with oesophageal atresia have a higher prevalence of oesophageal dysmotility, GER as well as tracheomalacia [6, 7, 8].

Medication with PPI (omeprazole/esomeprazole) was commenced at day three after birth in all patients and then continued for at least three months postoperatively and extended during the period of oesophageal dilatation. Anastomotic calibration was performed no earlier than three weeks postoperatively. There was no correlation between the duration of PPI treatment and the time of appearance of the oesophageal stricture. On the other hand, in the group of patients that did not develop strictures the mean time on PPI treatment was 43 days longer compared to the group of patients with strictures. This data could be indicating that three months of PPI treatment may be too short to prevent stricture formation. However, the difference is not statistically significant.

Number of dilatations needed was equivalent in the PPI and the control group. In the present study strictures were detected significantly earlier in children receiving prophylactic PPI and age at last dilatation was significantly lower in the PPI group, Table 2. This difference is in

line with proneness to earlier intervention along with continuous and extensive advancement of technical equipment, surgical skills and intensive care. As strictures were detected and treated earlier, and more serious obstructions were prevented, leading to shorter treatment periods, possibly unrelated to the PPI treatment. One limitation of this study is the fact that the control group was historical and there was no randomization.

Even though this study did not show a significant decrease in the frequency of strictures after oesophageal atresia repair in children treated with prophylactic PPI, it cannot be ruled out that PPI treatment is of value to these children. Children with oesophageal atresia have a higher prevalence of GER which may lead to mucosal damage of the lower oesophagus resulting in ulcerative esophagitis enhancing the risk of developing oesophageal ulcers and formation of lower oesophageal strictures or even metaplasia and thus PPI treatment may prove useful. We cannot exclude that longer periods of PPI treatment might help prevent stricture formation. However, the strictures treated in the study group all developed during a period of PPI treatment suggesting no effect of PPI on stricture development after surgery for oesophageal atresia in new-borns.

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Table 1

Patient characteristics documented in the study (PPI) group and the control group.

	Study group 2001-2009 N = 32	Control group 1983-1995 N = 66*
Gender: Male/female	66% / 34%	55% / 45%
Gestational age		
- Weeks $\geq$ 37	56%	52%
- Premature weeks < 37	44%	48%
Birth weight:		
- <1500g	1 (3%)	5 (8%)
- 1500-2500g	9 (28%)	26 (39%)
- - >2500g	22 (69%)	35 (53%)
Type of atresia; Type A/Type C	6%/94%	13%/72%
Associated malformations	N = 32	N= 63
- Chromosomal	3%	5%
- Vertebral	13%	3%
- Anorectal	3%	4%
- Cardiac	25%	14%
- Trachea	94%	71%
- Oesophageal	100%	100%
- Renal	9%	6%
- Limb	13%	3%
Anastomotic Leakage	13% (n=4)	15% (n=10)
Survival	88% (37/40)	87%

*63 from the control group and 3 children operated during the study period 2001-2009 who did not receive PPI.

Table 2

Numbers of dilatations performed in the PPI and control group, respectively. Minimum, maximum and mean ages at first and last dilatation in patients with stricture formation are presented in days. P<0.05 was considered statistically significant.

Treated with PPI:	Yes	No	Statistics p value
Number of children:	32	66	
Number who needed dilatation:	18 (56%)	28 (42%)	0,283*
Number of dilatations needed: - Median (range)	3 (1 – 21)	4 (1 – 20)	0,520
Age at first dilatation, - Days: Median (range)	63 (28 – 346)	210 (15 – 1159)	0,011
Age at last dilatation, - Days: Median (range)	138 (28 – 1959)	420 (61 – 1586)	0,005
Perforation during dilatation	0%	18%	0,017*

*Fisher's Exact Test.

Table 3

The statistical calculations used in the study. A power calculation is compared with the initial findings of the study. These suggest no significant, 50%, reduction of strictures when using PPI postoperatively after an oesophageal atresia operation in new-borns.

	PPI group	**Control group**	**P value**
Power calculation suggests: - A 50% reduction of strictures dilated. - Number of patients (dilated strictures)	85 (18 (21%))	85 (36 (42%))	$p<0.05$*
Findings in the study: - Number of patients (dilated strictures)	32 (18 (56%))	66 (28 (42%))	
Thus missing: - Number of patients (dilated strictures)	53 (0 (0%) **)	19 (8 (42%))	

*Fisher's Exact Test.

**That would be the lowest frequency of strictures ever reported.

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Competing interests:

When performing this work, there were no external influences or conflicts of interests.

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

All authors declare:

(1) No financial support for the submitted work from anyone other than their employer;

(2) No financial relationships with commercial entities that might have an interest in the submitted work;

(3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work;

(4) No non-financial interests that may be relevant to the submitted work.

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Contributors:

LH and EA formulated the study hypothesis. CM and KS collected data. CM and EA wrote the first draft of the manuscript. All the authors provided critical input at all stages and critically reviewed and contributed to the final draft.

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