Survival of children following Nissen fundoplication

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Abbreviations: GORD: gastro-oesophageal reflux disease

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AUTHOR CONTRIBUTIONS

Rebecca Wockenforth extracted and entered data. Colin Gillespie performed the statistical analysis and wrote the parts of the manuscript describing this analysis. Bruce Jaffray performed the surgery, entered data, and wrote the remaining parts of the manuscript. All have read and approved the manuscript.

ABSTRACT

Background: Analyses of survival after fundoplication in childhood are often restricted to 30 day mortality, or to the neurologically impaired. The objective of this study is to report actuarial survival and variables associated with mortality for all children undergoing fundoplication.

Methods: Prospective observational study of fundoplication surgery by one surgeon. The endpoint was survival. Using a Cox proportional hazards model, gastrostomy, neurological status, tracheostomy, congenital cardiac disease, syndromic status, presence of congenital anomaly, other chronic disease, weight z-score at time of surgery, need for revisional fundoplication, use of laparoscopic surgery, gastric drainage procedures, age and sex were assessed for their influence on survival.

Results: Two-hundred and thirty children underwent 256 fundoplications at median age 3.6 years. Forty-six children died during follow up (median 2.8 years, range 0.5-11.2 years). Statistical modelling showed gastrostomy (relative risk of death 11, $p = 0.0001$), cerebral palsy (relative risk 6.6, $p = 0.02$), and female sex (relative risk 2.1, $p = 0.015$) were associated with reduced survival. Revisional fundoplication was associated with improved survival (relative risk 0.3, $p = 0.03$). Survivors had significantly higher weight z-scores (-0.6 vs. -2.0 $p<0.0001$). Five year survival after fundoplication for children with cerebral palsy and gastrostomy is 33%.

Conclusions: Survival of children following fundoplication is principally related to the presence of gastrostomy and neurological status. Estimates of children's life expectancy should take account of the poorer survival of neurologically impaired children who undergo fundoplication, presumably due to the related co-morbidites which lead to a gastrostomy.

INTRODUCTION

In children, common complications of gastro-oesophageal reflux disease (GORD) include oesophagitis, vomiting with failure to thrive and aspiration. Children with these complications frequently undergo fundoplication[1], most often with the Nissen technique[2]. The efficacy of this procedure is usually measured by indices of reflux control[3,4]. There are few analyses of survival, with reports either restricted to deaths within one month of surgery[2], or failing to provide actuarial analysis of survival[5,6]. One recent study restricted to children with neurological impairment has suggested approximately 90% are alive five years after fundoplication[7].

Many children undergoing fundoplication suffer from cerebral palsy, where life expectancy is reduced. While some authors relate the short life of these children to the severity of the neuro-disability[8,9], others have suggested that functional abilities such as feeding are more important[10]. The degree to which life expectancy is reduced is controversial[11], but the use of a surgical intervention such as fundoplication as a predictive variable in assessing life expectancy among such children, has not previously been described.

This study presents an actuarial analysis of survival of children following fundoplication. The aim of the study is to identify variables independently associated with mortality.

PATIENTS AND METHODS

All children undergoing fundoplication by a single surgeon between January 1998 and December 2009 were prospectively recorded in a customised database at the time of their operation. Details recorded included indications for surgery, age at first surgery, whether the child had a gastrostomy, or a tracheostomy, whether a pyloroplasty was performed, whether the child subsequently underwent a revisional fundoplication and whether the procedure was performed using laparoscopic or conventional surgery.

Case note review allowed identification of the further following variables: weight at time of surgery, neurological impairment, congenital cardiac disease and any surgery performed to correct this, syndromic status, congenital anomalies, and co-existing chronic disease. The variables were examined for influence on survival.

The diagnosis of cerebral palsy was confirmed by cross referencing the database with the records of the North of England Collaborative Cerebral Palsy Study. Data were also cross referenced with the Northern Congenital Anomaly Survey and with the regional cardiac surgery database.

Gastro-oesophageal reflux disease was usually diagnosed with endoscopy and oesophageal biopsy, but occasionally with contrast swallow or 24 hour pH monitoring.

Details of surgery

In all cases a short floppy Nissen fundoplication was performed, with division of all short gastric vessels. The hiatus was tightened with non-absorbable sutures and a 360° wrap constructed by suturing the fundus of the stomach both to the hiatus and the oesophagus. An intra-oesophageal sizing bougie was not used.

The procedure was identical when performed laparoscopically, using either 3mm or 5mm instrumentation according to the size of the child. Laparoscopic surgery was commenced in February 2004, from when all procedures were undertaken laparoscopically, including revisional surgery. Revisional fundoplication consisted of a complete dissection of the previous procedure and re-formation of the wrap. The indication for revisional fundoplication was always a recurrence of symptoms. Such recurrence signifies either wrap disruption or wrap migration or both, which were diagnosed by their endoscopic appearances.

Gastrostomies were formed using the Stamm technique, placing two purse-string sutures on the body of the stomach and using the outer suture to anchor the stomach to the abdominal wall. Laparoscopic gastrostomies used two full thickness sutures through the stomach wall passed through the abdominal wall and tied on the skin surface.

The gastric emptying procedure used was a pyloroplasty of the Heineke-Mikulicz configuration, incising the pylorus longitudinally and re-suturing transversely with absorbable sutures.

Post-operative assessment of reflux control was by endoscopy when there had been significant oesophagitis pre-operatively, or by symptom assessment when the indication for surgery was vomiting or aspiration.

Statistical analysis

Statistical analysis was performed using the program R with the survival package[12]. A full Cox-proportional hazards model was fitted to the data, and the residuals checked for deviations away from the model assumptions. The residuals indicated that there was strong evidence for non-proportional hazards for cerebral palsy. However, the inclusion of a gastrostomy/cerebral palsy interaction term corrected this problem. Interaction effects involving gender and age were also examined. Covariates were removed according to the Wald statistic. Model validity was checked by starting with an empty model and progressively adding significant terms. The final model contained five covariates including the non significant interaction term.

In a data set of this type, many variables are likely to be correlated. For example, patients with cerebral palsy were more likely to have had gastrostomies. Rather than modelling each covariate individually, which would suggest many spurious relationships, the risk factors were jointly modelled simultaneously, thereby significantly reducing the chance of type 1 errors.

Kaplan-Meier survival curves are presented with 95% confidence intervals. Five year survival rates and median survival were calculated from Kaplan-Meier analysis. Graphs were generated using the ggplot2 package[13].

Mortality rates were calculated for the following risk factors singly and in combination: cerebral palsy, gastrostomy, tracheostomy and congenital cardiac disease. A child was classed as normal by the absence of any of these variables or any syndrome or congenital anomaly.

Weights on the day of surgery were converted to z-scores using the data of the Child Growth Foundation for weight distribution among British children[14] and were

compared using Student's t-test. P values less than 0.05 were considered significant.

The regional ethics committee have confirmed that this study design does not require ethical committee approval.

RESULTS

Two-hundred and thirty children, of whom 105 were girls, underwent 256 fundoplication operations. Median age at first fundoplication was 3.6 years (range 0.1 to 18.9 years). Median follow up was 2.8 years (range 0.5 to 11.2 years). Forty-six children died during follow up. Indications for surgery are listed in table 1. The incidence of death according to the child's possession of risk factors is detailed in table 2.

Distribution of possible predictor variables.

Seventy-six children had cerebral palsy, 114 had a gastrostomy, 18 had a tracheostomy, 42 required at least one further fundoplication, and 145 underwent laparoscopic fundoplication. Two laparoscopic fundoplications were converted to open surgery; both were analysed as laparoscopic fundoplication.

Forty-one children were diagnosed with a named syndrome, 30 had other congenital anomalies and 22 had undergone surgery for congenital cardiac disease.

Pyloroplasty was performed on nine children early in our series and was abandoned after May 2002 because of the severity of dumping symptoms.

The mean weight z-score at the time of surgery was -1.8 (SD 2.2).

Survival analysis

Variables which significantly influenced survival were gastrostomy ($p<0.001$), cerebral palsy ($p=0.021$), gender ($p=0.015$), and need for revision surgery ($p=0.037$).

The strongest risk factor for death in this series was the presence of a gastrostomy. For children with a gastrostomy, the relative risk of death (to other children without a gastrostomy) was 11.0 (95% CI: 3.16, 38.63). When patients had both cerebral palsy and gastrostomy, there was a pronounced shortening in lifespan (Figure 1). The five year survival rate for a child with a gastrostomy following fundoplication is 60%, compared to 93% for children without a gastrostomy. For children with a gastrostomy and cerebral palsy, the five year survival rate is 33%.

A well established risk factor for death is cerebral palsy. Relative risk of death compared to children without cerebral palsy was 6.6 when a child had cerebral palsy (95% CI: 1.32, 32.78) (Figure 1). The five year survival rate for a child with cerebral palsy after fundoplication is 53%, compared to 88% for children without cerebral palsy.

Revision of the fundoplication was associated with reduced mortality. Relative risk of death for children who did not undergo revision was 2.73 (95% CI: 1.06, 7.04).

Survival analysis also identified gender as a significant risk factor. Relative risk of death for female children compared to males is 2.12 (95% CI: 1.16, 3.89) (Figure 2).

None of the other possible explanatory variables, including congenital cardiac disease, tracheostomy, weight z-scores and syndromic status had a significant effect.

Effect of weight z-scores

Children with a gastrostomy were significantly lighter than children who did not receive a gastrostomy (mean z score among children without gastrostomy -0.6 (SD 1.7), mean z-score among children with gastrostomy -2.9 (SD 2), p <0.001, 95% CI of difference 1.6, 2.8).

Children with cerebral palsy were significantly lighter than children without cerebral palsy at the time of their fundoplication (mean z-score among children with cerebral palsy -2.8 (SD 2.2), mean z-score among children without cerebral palsy -1.1(SD 2), p <0.001, 95% CI of difference 0.9, 2.3).

Children who died were also significantly lighter than survivors at the time of their fundoplication (mean z-score among survivors -1.4 (SD 2.1), mean z-score among non-survivors -2.9 (SD 2.3), p=0.001, 95% CI of difference 0.6, 2.4).

DISCUSSION

The two principal findings are the association between gastrostomy and death, independent of the neurological status, and the extremely poor survival of neurologically impaired children, which is significantly worse than previous estimates.

Other variables affecting survival were gender and revisional fundoplication. Male sex appears to be protective. Other studies have suggested no effect of sex on survival among children with neuro-disability[10] and we cannot explain this observation. A gender effect on survival has, however, been reported for other chronic diseases[15].

Revisional fundoplication improved survival. The likely explanation is this group must survive long enough for their fundoplication to fail and are therefore selected for survival at least until their second operation. Alternatively restoration of protection from reflux by the revisional procedure may improve survival.

This is a single surgeon series, which removes the systemic error in multi surgeon or multi institutional series. The only changes in practice were the adoption of laparoscopic surgery and the abandoning of gastric drainage procedures, which had no effect on survival The integrity of the data was ensured by being prospectively recorded by the surgeon at the time of surgery..

Among limitations of the present study is the chance that patients were in some way a selected group with more severe disabilities. Referrals for fundoplication were taken from across the North of England, with no attempt to select or screen children. It is possible that this cohort had poorer survival by chance. There has been no evidence of increasing severity of neuro-disability from UK or European registries[16]

and studies of life expectancy among children with cerebral palsy suggest that survival is improving[17].

Another limitation is that the cause of death could not be ascertain. Many children did not receive a post-mortem examination. Although aspiration pneumonia could be suspected as the commonest cause of death, there is no proof for this.

A systematic review of gastrostomy feeding amongst neurologically impaired children suggested increased mortality, but there was heterogeneous use of anti-reflux procedures[18]. The current study supports the excess mortality associated with gastrostomy placement. The five year survival of 33% for children with cerebral palsy and gastrostomy undergoing fundoplication in the present series contrasts with the 61% reported by an Australian study, with heterogeneous use of an anti-reflux procedure[19]. Indirect support for the contention that gastrostomy is associated with poorer survival is the 21% mortality of neurologically impaired children treated with a gastro-jejunal tube, compared to 12% mortality among children treated with fundoplication[7].

The reasons why gastrostomy has such effects on survival may be questioned when a tracheostomy, which intuitively would seem a more hazardous tube, confers no excess risk. It seems likely that the underlying disease process which necessitates gastrostomy leads to early death.

Studies of survival following fundoplication are unsatisfactory either because of a lack of actuarial analysis, or a failure to assess the effects of other variables such as gastrostomy. Mortality rates seem unrealistic. This report's 20% mortality can be compared with the published range of 0%[20], 0.8%[2], 6.7%[6] or 9%[21]. One study describing poorer survival than the present cohort reported 51% mortality[5], but had a high rate of operative complications leading to death; nine of 35 (25%) children had

died within a month of surgery. The corresponding figure in the current study for death within 30 days of surgery among children with cerebral palsy is eight of 76 (10%).

The five year survival of children with cerebral palsy undergoing fundoplication in this study is 53%. This is notably worse than the approximately 90% survival recently reported from a multi-institutional American study utilising data from an administrative database[7], or the 83% survival reported from a Canadian study[22] possibly reflecting incomplete ascertainment of deaths.

Survival of children with cerebral palsy in this region has been described by Hutton et al[9]. The survival of such children undergoing fundoplication is much worse than their results for children with severe disability recorded on a whole population register of children with cerebral palsy. Whereas Hutton et al found that at least 74% of children with severe disability survived to age 20, in the current study less than 30% were alive by this time point. A study from Mersey region suggests that only 51% of children with severe disability are alive by age 20[8]; and although closer to the results of the present investigation , this still represents a major difference. This study most closely resembles the report of Strauss et al, who in 1998 noted the severe effects of feeding problems on survival of children with cerebral palsy in California[10]. Californian children with a gastrostomy had a median survival of only seven years, which is very similar to this report where the median life expectancy for a child with cerebral palsy undergoing fundoplication and receiving a gastrostomy was 4.9 years.

Mortality after this common operation is entirely related the presence of risk factors, principally gastrostomy and cerebral palsy; female sex is also influential. The 83

children who possessed no risk factors experienced zero mortality (table 2). Normal children do not die after fundoplication.

The short survival described may have implications for legal settlements based on the predicted life expectancy of neurologically impaired children.

The principal variables predicting early mortality are gastrostomy and cerebral palsy. Nutrition is clearly part of the problem. Children who died weighed significantly less than survivors, though both were below average. Whether more attention to nutritional issues in such children can alter survival should be the subject of research.

The common practice of gastrostomy insertion in neurologically impaired children who are failing to thrive seems to mark out the group with the poorest survival. Whether to insert a gastrostomy at the time of fundoplication in a neurologically impaired child may become a difficult decision. The present study does not address the alternative possibility of avoiding fundoplication by insertion of a gastro-jejunal tube[7], but it can be speculated that a gastro-jejunal tube will have the same effect on mortality as gastrostomy, in that it does not alter underlying disease processes.

This study shows that some children with cerebral palsy and profound feeding difficulties undergoing gastrostomy insertion and fundoplication have a severely limited life expectancy which may not be extended by anti-reflux surgery. Medical professionals and parents need to appreciate the severe consequences of the child's disabilities. Surgeons should be aware that some children may be close to their predicted time of death when approaching surgery, and are likely to die within 30 days of operative intervention.

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REFERENCES

1. Goldin AB, Garrison M, Christakis D. Variations Between Hospitals in Antireflux Procedures in Children. *Archives of Pediatrics & Adolescent Medicine.* 2009;**163**:658-663.

2. Fonkalsrud EW, Ashcraft KW, Coran AG, et al. Surgical treatment of gastroesophageal reflux in children: A combined hospital study of 7467 patients. *Pediatrics.* 1998;**101**:419-422.

3. Srivastava R, Berry JG, Hall M, et al. Reflux related hospital admissions after fundoplication in children with neurological impairment: retrospective cohort study. *Br. Med. J.* 2009;**339**:b4411.

4. Lee SL, Sydorak RM, Chiu VY, Hsu JW, Applebaum H, Haigh PI. Long-term antireflux medication use following pediatric Nissen fundoplication. *Arch. Surg.* 2008;**143**:873-876.

5. Smith CD, Othersen HB, Gogan NJ, et al. Nissen Fundoplication in Children with Profound Neurologic Disability - High Risks and Unmet Goals. *Ann. Surg.* 1991;**215**:654-659.

6. Tovar JA, Luis AL, Encinas JL, et al. Pediatric surgeons and gastroesophageal reflux. *J. Pediatr. Surg.* 2007;**42**:277-283.

7. Srivastava R, Downey EC, O'Gorman M, et al. Impact of Fundoplication Versus Gastrojejunal Feeding Tubes on Mortality and in Preventing Aspiration Pneumonia in Young Children With Neurologic Impairment Who Have Gastroesophageal Reflux Disease. *Pediatrics.* 2009;**123**:338-345.

8. Hutton JL, Pharoah POD. Effects of cognitive, motor, and sensory disabilities on survival in cerebral palsy. *Arch. Dis. Child.* 2002;**86**:84-89.

9. Hutton JL, Colver AF, Mackie PC. Effect of severity of disability on survival in north east England cerebral palsy cohort. *Arch. Dis. Child.* 2000;**83**:468-473.

10. Strauss DJ, Shavelle RM, Anderson TW. Life expectancy of children with cerebral palsy. *Pediatr. Neurol.* 1998;**18**:143-149.

11. Strauss D, Shavelle R. Life expectancy in cerebral palsy. *Arch. Dis. Child.* 2001;**85**:442-442.

12. R core development team. R: A language and environment for statistical computing. 2009; http://www.R-project.org.

13. Wickham H. *ggplot2: Elegant graphs for data analysis*. New York: Springer; 2009.

14. Child Growth Foundation UK. *The British 1990 growth reference. Revised September 1996*: Child Growth Foundation, 2 Mayfield Avenue, London W4 1PW; 1996.

15. Rosenfeld M, Davis R, FitzSimmons S, Pepe M, Ramsey B. Gender gap in cystic fibrosis mortality. *Am. J. Epidemiol.* 1997;**145**:794-803.

16. Colver AF. Personal communication2010.

17. Strauss D, Shavelle R, Reynolds R, Rosenbloom L, Day S. Survival in cerebral palsy in the last 20 years: signs of improvement? *Dev. Med. Child Neurol.* 2007;**49**:86-92.

18. Sleigh G, Brocklehurst P. Gastrostomy feeding in cerebral palsy: a systematic review. *Arch. Dis. Child.* 2004;**89**:534-U522.

19. Catto-Smith AG, Jimenez S. Morbidity and mortality after percutaneous endoscopic gastrostomy in children with neurological disability. *J. Gastroenterol. Hepatol.* 2006;**21**:734-738.

20. Albanese CT, Towbin RB, Ulman I, Lewis J, Smith SD. Percutaneous Gastrojejunostomy Versus Nissen Fundoplication for Enteral Feeding of the Neurologically Impaired Child with Gastroesophageal Reflux. *J. Ped.* 1993;**123**:371-375.

21. Pearl RH, Robie DK, Ein SH, et al. Complications of Gastroesophageal Antireflux Surgery in Neurologically Impaired Versus Neurologically Normal-Children. *J. Pediatr. Surg.* 1990;**25**:1169-1173.

22. Wales PW, Diamond IR, Dutta S, et al. Fundoplication and gastrostomy versus image-guided gastrojejunal tube for enteral feeding in neurologically impaired children with gastroesophageal reflux. *J. Pediatr. Surg.* 2002;**37**:407-411.

Table 1 Indications for performing fundoplication

Indication for surgery	Number
GORD	68
GORD & Vomiting	40
Vomiting	37
Acute Life Threatening Incident	30
Failure to thrive	22
Aspiration	19
Combination	9
Other	5

Table 2. Death rates according to child's risk factor status

Child status	N	Deaths	%
Normal (no risk factors)	83	0	0
Cerebral palsy only	15	2	13%
Cerebral palsy + Gastrostomy	47	17	36%
Cerebral palsy + Gastrostomy + Tracheostomy	5	2	40%
Cerebral palsy + Gastrostomy + Congenital cardiac	5	3	60%
Gastrostomy only	20	5	25%
Tracheostomy only	1	0	0%
Gastrostomy + Tracheostomy	3	1	30%
Congenital cardiac only	6	2	33%
Congenital cardiac + Gastrostomy	8	2	25%
All patients	230	46	20%

Note. Not all possible combinations of risk factors are presented, so the number of children will differ from the totals presented in the results section.

Legend for Figure 1

Effect of gastrostomy and cerebral palsy on survival. Numbers at risk are shown in grid. Dashed lines are 95% confidence intervals.

CP; cerebral palsy

Legend for Figure 2

Effect of gender and cerebral palsy on survival. Numbers at risk are shown in grid. Dashes lines are 95% confidence intervals.

CP; cerebral palsy