

Laparoscopy in Children: Physiology and Outcome

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I, Maurizio Pacilli, confirm that the work presented in this thesis is my own.
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Abstract

Background

Laparoscopy in adult started in the early 1980s, but it did not transfer into widespread application in the paediatric population for a number of reasons. Among these were the facts that paediatric surgeons did not have a commonly performed procedure, such as cholecystectomy, in which to refine their skills. In addition, the large instruments available initially and the small intra-abdominal working space in infants and young children could make the laparoscopic approach more difficult and time consuming. Moreover, as a general statement, children seem to recover more rapidly than adults and therefore it was unclear whether there would be further benefits to an already faster healing process and recovery time. Nowadays, in paediatric surgery, intra-abdominal procedures such as fundoplication, splenectomy, appendicectomy, and cholecystectomy are being commonly performed with a laparoscopic approach. Nevertheless, the effects and advantages of laparoscopic surgery in children have not been extensively investigated.

Aims

1. To quantify the absorption of carbon dioxide (CO₂) during laparoscopy;
2. To investigate if laparoscopic surgery provides benefits compared to open surgery in the management of common surgical conditions in children.

Methods

The thesis includes two parts: the first part focuses on the absorption of CO₂ during the pneumoperitoneum. The second part focuses on the outcome of laparoscopic surgery compared to open surgery in children. Data have been obtained by investigating two of the most common laparoscopic surgical procedures performed in children: the Nissen fundoplication for treatment of gastro-oesophageal reflux (GOR) and the Ramstedt pyloromyotomy for pyloric stenosis. For the laparoscopic Nissen fundoplication, a follow-up study on a randomised controlled trial including 38 children has been performed. In addition, a large review on patients who underwent a second operation (redo-Nissen fundoplication) for recurrent GOR has also been performed. For the laparoscopic pyloromyotomy, a double blind, multicentre, international, randomised controlled study has been performed enrolling 180 children.

Results

Regarding the absorption of CO₂ during laparoscopy, using a mass spectrometric technique, the work in this thesis demonstrates that 10-20% of CO₂ eliminated during laparoscopy in children is derived from the absorption through the peritoneum. The results of the randomised controlled trial comparing open and laparoscopic Nissen fundoplication showed that this antireflux procedure improves the quality of life and controls GOR independently of the technique used (open or laparoscopic). The laparoscopic technique seems to be associated with an improvement of gastric emptying in the immediate post-operative period

and lower incidence of retching at 4-year follow-up. In children requiring redo-Nissen fundoplication for recurrent GOR, there is a high failure rate and redo-fundoplication after primary laparoscopic Nissen has lower risk of failure. The multicentre prospective randomised controlled trial comparing open with laparoscopic pyloromyotomy revealed that both procedures are successful approaches with high levels of parental satisfaction. The laparoscopic pyloromyotomy has a number of advantages over the open technique in that post-operative recovery is shorter, post-operative analgesia requirement is lower and parental satisfaction is higher.

Conclusions

This thesis demonstrates that, regardless of the surgical procedure, a significant amount of CO₂ is absorbed during laparoscopy. In healthy children the resulting increase in end-tidal CO₂ is easily compensated by adjusting the minute ventilation.

The results of the Nissen fundoplication studies showed that the laparoscopic technique seems to be associated with an improvement of gastric emptying in the immediate post-operative period, lower incidence of retching at 4-year follow-up and better control of GOR in children requiring redo-Nissen fundoplication. The multicentre prospective randomised controlled trial on Ramstedt pyloromyotomy revealed that the laparoscopic technique has a number of advantages over the open technique in that post-operative recovery is shorter, post-operative analgesia requirement is lower and parental satisfaction is higher.

Acknowledgments

I dedicate this thesis to my parents, Concetta and Giulio who inspired and supported me in all that I endeavour. Thanks for their unconditional love.

I also dedicate this thesis to all the children and families that participated in the research.

Thanks to my brother Quirino and his lovely family; Laura, Benedetta and Giulio Jr. for always being there for me. Special thanks to Joanne Hook for her unconditional love and support during the writing of this thesis.

Thanks to my supervisors Prof. Agostino Pierro and Dr. Simon Eaton without whose help and guidance this work would not have been possible.

Also thanks to Prof. Lewis Spitz, Mr. David Drake, Mr. Edward Kiely, and Mr. Joe Curry for allowing me to approach their patients for the studies. Mr. Merrill McHoney for providing the data from his randomized controlled trial on Nissen fundoplication. Miss Vida Milovanovic for performing the pH studies on the children of the follow-up. Dr. Keith Lindley and all the team of the Gastroenterology Unit at Great Ormond Street Hospital for allowing me to use their rooms and instruments. Also thanks to Charlotte Kingsley for helping in recruiting patients and with sample collection for the CO₂ study. Mr. Nigel Hall that, together with Prof. Agostino Pierro and Dr. Simon Eaton, conceived and designed the Pyloromyotomy Trial. Mr. Nick Alexander and Mr. Ori Ron for assistance in randomising patients for the Pyloromyotomy Trial. Mr. Imran

Mushtaq, Dr. Mark Peters, and Miss Clare Rees for forming the data monitoring and ethics committee for the Pyloromyotomy Trial. All the collaborators for the Pyloromyotomy Trial: Prof. H. Ford, Children's Hospital Los Angeles, CA, USA; Dr. K. Reblock and Dr. B. Gaines, Children's Hospital, Pittsburgh, PA, USA; Prof. J. Langer, Ms. A. Pastor, Hospital for Sick Children, Toronto, ON, Canada; Prof. R. Rintala, Dr. A. Koivusalo, Dr. M. Pakarinen, University Hospital, Helsinki, Finland; Prof. M. Höllwarth, Dr. S. Beyerlein, Dr. L. Stroedter, University of Graz, Austria; Mr. M. Haddad, Mr. S. Clarke, Chelsea and Westminster Hospital, London, UK.

Thanks to all the research fellows, (Ori, Giorgio, Nick, Nigel, Emma, Katie, Yukiko, Francesco, Peng) who worked alongside me and made the years of research a very pleasant experience.

Thanks to God without who none of this would have been possible.

Funding

My work was funded by charitable grants from the **Fondazione Eugenio Litta**, Geneva, Switzerland and by a grant from **SPort Aiding medical Research for Kids** (SPARKS). Also, **Child Health Research Appeal Trust** (CHRAT) are thanked for a summer studentship to Charlotte Kingsley, and the **Philip Ullman Trust** are thanked for the isotope-ratio mass spectrometer. **Sir Arthur Halley Stewart Trust** are thanked for supporting the Pyloromyotomy Trial.

Declaration

The work presented in this thesis I performed in the Departments of Paediatric Surgery of the institute of Child Health. Patients were recruited and studied in the Surgery Unit and Gastroenterology Unit of Great Ormond Street Hospital. Patients enrolled in the Pyloromyotomy Trial were recruited from Great Ormond Street Hospital, London, UK; Children's Hospital, Pittsburgh, PA, USA; Hospital for Sick Children, Toronto, ON, Canada; University Hospital, Helsinki, Finland; Medical University of Graz, Austria; Chelsea and Westminster Hospital, London, UK.

Chapters 3 and 4: The data presented in these chapters are from a follow-up study of a cohort of patients originally recruited to a randomised controlled trial comparing open versus laparoscopic Nissen fundoplication. This trial was co-ordinated by Merrill McHoney, and short-term outcome data from this trial appear

in his PhD thesis. I designed and performed the follow-up study described in chapters 3 and 4 myself, and writing these chapters is entirely my own work.

Chapter 7: The pyloromyotomy trial was designed by Mr. Nigel Hall, Prof. Agostino Pierro, and Dr. Simon Eaton. I was responsible for enrolment of patients, data collection and follow-up, data entry and analysis. NH and SE were responsible for the final statistical analysis. I contributed to writing the published paper, and have rewritten the chapter appearing in this thesis from this paper with approval from NH, AP and SE. The pyloromyotomy trial is not being presented as part of any other thesis.

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Abbreviations

Ad lib	Ad libitum
BMI	Body Mass Index
^{13}C -OBT	^{13}C -Octanoic Acid Breath Test
CO_2	Carbon Dioxide
DMEC	Data Monitoring and Ethics Committee
ETCO_2	End-tidal CO_2
FEV1	Forced Expiratory Volume in one second
FLACC	Face, Legs, Activity, Crying, Consolability
FVC	Forced Vital Capacity
GE	Gastric Emptying
$\text{GEt}_{1/2}$	Gastric Emptying time
GOR	Gastro-Oesophageal Reflux
GOSH	Great Ormond Street Hospital
LNF	Laparoscopic Nissen Fundoplication
LP	Laparoscopic Pyloromyotomy
LOS	Lower Oesophageal Sphincter
NF	Nissen Fundoplication
NI	Neurologically Impaired
NN	Neurologically Normal
NPO	Nil Per Os
ONF	Open Nissen Fundoplication
OP	Open Pyloromyotomy

PaCO ₂	Arterial CO ₂ Pressure
PDB	Pee Dee Belemnite
PEEP	Positive End-Expiratory Pressure
PS	Pyloric Stenosis
RCT/RCTs	Randomised Controlled Trial/s
REE	Resting Energy Expenditure
RNF	Redo-Nissen Fundoplication
TKVO	To Keep Vein Open
$\dot{V}CO_2$	CO ₂ production

Chapter 1

Introduction

1.1 General Introduction

Laparoscopic surgery, also called minimally invasive surgery or keyhole surgery involves insertion of a telescope into the abdominal cavity for visualisation, and additional ports for therapeutic instrumentation under general anaesthesia. Initially, adequate illumination and clear images were obtainable only with relatively large telescopes, but in the past few years good quality telescopes as small as 2 mm in diameter have become available. The telescope is usually inserted through the umbilicus, resulting in an almost invisible scar. The image is transmitted to one or more television monitors. The number of instrumentation ports needed is related to the complexity of the therapeutic procedure. There are a number of advantages that have been reported over the last 20 years in the adult population including reduced pain due to smaller incisions and possibly shorter recovery time. The abdomen is usually insufflated, with carbon dioxide (CO₂). This elevates the abdominal wall above the internal organs like a dome to create a working and viewing space. CO₂ is used because it is common to the human body and can be absorbed by tissue and removed by the respiratory system. It is also non-flammable, which is important because electrosurgical devices are commonly used in laparoscopic procedures.

1.2 History of Laparoscopy

It is difficult to credit one individual with the pioneering of the laparoscopic approach. Georg Kelling (Figure 1.1), in 1901 performed laparoscopy on the abdomen of a dog using a Nitze-cystoscope, Kelling created a pneumoperitoneum by insufflating the abdomen with filtered air via a port (Kelling G, 1901).

Figure 1.1 – Georg Kelling (1866 – 1945).



In 1910 Hans Christian Jacobaeus (Figure 1.2) reported the first laparoscopic operation in humans and is credited with performing the first thoracoscopic diagnosis with a cystoscope. This technique was used in the treatment of a patient with tubercular intra-thoracic adhesions. In 1911 he published an article titled *"The Possibilities for Performing Cystoscopy in Examinations of Serous Cavities"* in the journal *Münchener Medizinischen Wochenschrift* (Jacobaeus HC, 1910). In the following several decades, numerous individuals refined and popularized the approach further for laparoscopy.

Figure 1.2 – Hans Christian Jacobaeus (1879 – 1937).



The introduction of computer chip television camera was a decisive event in the field of laparoscopy. This innovation in technology provided the means to project a magnified view of the operative field onto a monitor, and at the same time freed both the operating surgeon's hands, thereby facilitating performance of complex laparoscopic procedures.

Prior to its conception, laparoscopy was used mainly for purposes of diagnosis and performance of simple procedures in gynaecologic applications.

The first publication on diagnostic laparoscopy by Raoul Palmer, appeared in the early 1950s (Palmer et al., 1950). In 1972, Clarke invented, published, patented, presented and recorded on film laparoscopic surgery (Clarke, 1972) and in 1975, Tarasconi started his experience with organ resection by laparoscopy (salpingectomy) (Tarasconi, 1981). This laparoscopic surgical procedure was the first laparoscopic organ resection reported in the Medical Literature. In 1981, Semm performed the first laparoscopic appendicectomy (Semm, 1983).

1.3 Laparoscopy in Children

Paediatric surgeons were among the pioneers of laparoscopic surgery in the early 1970s (Gans et al., 1971) but for over two decades, paediatric laparoscopy was restricted mainly to diagnostic use. In the early 1990s, an explosive expansion of laparoscopic surgery occurred in adults as a result of the success of laparoscopic cholecystectomy. Nevertheless, interest in laparoscopic surgery in children remained confined to a few enthusiasts initially (Miller, 1992; Najmaldin, 1995; Sackier, 1991; Tan, 1994). More

recently however, with increasing experience in paediatric laparoscopic procedures (Chung et al., 1998; Lobe, 1998; Rothenberg et al., 1998), and advances in miniaturised instrumentation, laparoscopy's place in the modern paediatric surgical armamentarium has finally become accepted. These days, most paediatric laparoscopic instruments measure 2 – 5 mm in diameter. A 10 – 12 mm port is only needed for complex items such as stapling devices. Technological innovations such as ultrasonically activated (harmonic) scalpel and laser have greatly facilitated laparoscopic dissection and haemostasis. A pneumoperitoneum is usually obtained with insufflation of carbon dioxide to a pressure of 8 – 10 mmHg in children.

1.4 Advantages of Laparoscopy

Potential benefits of laparoscopic surgery have been mainly reported in adults and include less postoperative pain, reduced wound complications, minimal scarring, a shorter hospital stay, and an earlier return to normal activities including feeding, bowel movements and work (Leape et al., 1980; Rogers et al., 1992). From the socioeconomic point of view, although children's early return to normal activity after laparoscopic surgery does not add productivity directly, their parents' early resumption of work does. Hospital charges can also be lower for laparoscopic surgery as a result of reduced hospital stay and pain medications, but these may be offset by increased operating time and expensive consumables. More importantly, a

lower hospital charge for laparoscopic surgery is dependent on a low complication rate, which might be achieved only in experienced centres.

Laparoscopy can be particularly advantageous for operations in deep cavities of small children by offering good illumination and magnification. However, some of these advantages have not been clearly demonstrated in children.

1.5 Disadvantages and Complications of Laparoscopy

Technical limitations of laparoscopic surgery include a two dimensional visual image, a reduction of tactile feedback, difficulty in controlling bleeding (limited suction, no manual pressure), limitation in the number and directions of instruments, difficulty in suturing.

There is a learning curve and laparoscopic skills have to be maintained and improved (Dagash et al., 2003). This presents a bigger challenge to paediatric surgeons than to adult surgeons, who have a regular procedure such as laparoscopic cholecystectomy to refine their laparoscopic skills. For laparoscopic cholecystectomy, the learning curve ranges from 10 to 75 procedures (Firilas et al., 1998). For laparoscopic fundoplication in children, proficiency could be achieved after 25 procedures (Meehan et al., 1997). In a series of laparoscopic pyloromyotomies, good results were achieved after 23 procedures, but these were associated with seven complications (30%), six of which required reoperation (Ford et al., 1997).

Most complications of paediatric laparoscopic surgery are technique related.

The most significant risks are from trocar injuries to either blood vessels or small

or large bowel especially in patients with low body mass index (BMI) (Mirhashemi et al., 1998) or have a history of prior abdominal surgery. Haemorrhage is more difficult to control laparoscopically and children respond poorly to haemodynamic disturbances. Diathermy injury can lead to intestinal perforation (Voyles et al., 1992) and electrical burns can happen with the use of electrodes that leak current into surrounding tissue resulting in perforated organs and peritonitis. Inadvertent visceral injury during trocar insertion is another feared complication. The use of an open technique for the insertion of the first port and placement of subsequent ports under direct vision minimises unintentional major vessel and visceral injuries. New designs of trocars with safety mechanisms further reduce such risks.

Complications related to port sites include postoperative herniation of intra-abdominal contents, which can occur even through small port sites. Rarely, complications arise from CO₂ insufflation for pneumoperitoneum during laparoscopy. These include gas embolism, cardiovascular compromise, and hypercapnia. The risks are minimised by the use of low pressure CO₂ insufflation in children. Slight increases in end-tidal CO₂ (ETCO₂) and peak airway pressures might be detectable intraoperatively. This can usually be compensated for by slight hyperventilation. Children who have an unstable haemodynamic status are not suitable for laparoscopic procedures which involve prolonged operating times and laparoscopy should be avoided in patients with severe cardiac diseases and pulmonary insufficiency. Laparoscopy is more hazardous in patients with abdominal scars and adhesions resulting from repeated

abdominal procedures, and in patients with ileus, intestinal obstruction, and pregnancy. In the past an increased risk of hypothermia was described due to the use of cold gases during insufflation. The use of room temperature and humidified CO₂ reduces this risk (Peng et al., 2009). The elevation of the diaphragm can also exert pressure on the phrenic nerve leading to a sensation of pain that may extend to the patient's shoulders. In all cases, however, the pain is transient, as the body tissues will absorb the CO₂ and eliminate it through respiration (Alexander et al., 1987).

Overall, in large centres, a low complication rate (1 – 2%) of laparoscopic surgery in children can be achieved (Chung et al., 1998; Lobe, 1998; Rothenberg et al., 1998). Laparoscopic surgery has been carried out successfully in neonates as small as 1.3 kg body weight with no added complications (Rothenberg et al., 1998).

1.6 Indications for Laparoscopy in Children

Laparoscopy has found a wide range of applications in paediatric surgery; it is continuously evolving in its indications and it is gradually replacing most open procedures. Laparoscopic cholecystectomy is the method of choice for treating gallstones in adults and, although gallstones are rarer in children the superiority of laparoscopic cholecystectomy over open cholecystectomy in children has similarly been confirmed (Holcomb, III et al., 1999). Laparoscopic pull-through for Hirschsprung's disease has also been reported with reduced postoperative hospital stay (Jona et al., 1998). Laparoscopic

nephrectomy for non-functioning kidneys and duplex system, and partial nephrectomy can be effectively undertaken (Holbrook et al., 2011). Laparoscopic repair of inguinal hernia is also commonly performed but the results of this approach have not been extensively investigated (Zitsman, 2006). Common indications also include the diagnosis and management of impalpable testes (Baillie et al., 1998), and the evaluation of ovarian pathology.

Experience in laparoscopic appendicectomy and splenectomy has also been accumulated in children (Rescorla et al., 2008; Sauerland et al., 2010). Finally, laparoscopy has widely been accepted as the procedure of choice for surgical management of gastro-oesophageal reflux (GOR) and pyloric stenosis (PS). This thesis focuses on laparoscopic Nissen fundoplication and laparoscopic Ramstedt pyloromyotomy that are currently the most common laparoscopic procedures performed in children. These two techniques, together with a brief description of GOR and PS, are discussed below.

1.7 Gastro-Oesophageal Reflux and Nissen Fundoplication

1.7.1 Introduction

GOR is a physiological process characterized by the involuntary passage of gastric contents into the lower oesophagus not induced by noxious stimuli. The phenomenon is only considered as *GOR disease* when it causes the patient to be symptomatic or results in pathological complications. GOR represents a common condition in preterm infants and may occur in healthy neonates. In the former, the incidence of GOR can be as high as 85% (Newell et al., 1989) with male to female preponderance of 1:6 (El Mouzan et al., 2001). In the majority of cases GOR resolves spontaneously, with its prevalence decreasing to 18% in childhood (Bagucka et al., 1999). The incidence of GOR is highest in neurologically impaired children (70%), who comprise 44 to 67% of children undergoing antireflux surgery (Fonkalsrud et al., 1998; Inge et al., 1998; Rice et al., 1991).

1.7.2 Pathophysiology

A number of physiological and anatomical factors normally contribute to prevent chronic reflux of gastric contents into the lower oesophagus. The combination of oesophageal motility and gravity facilitates clearance of refluxed material as well as of saliva, which is rich in bicarbonate that coats the oesophagus. These oesophageal clearance mechanisms are usually developed by 31 weeks gestation (Omari et al., 1998). Other physiological barriers to GOR include antral contractions, facilitating gastric emptying,

and the production of mucus, prostaglandin and epithelial growth factors, which help to prevent damage to the oesophageal mucosa.

Anatomically, the length of the intra-abdominal oesophagus, the phreno-oesophageal ligaments, the gastric mucosal “rosette,” and the oesophageal hiatus (a sling formed by the right crus of the diaphragm causing a pinchcock effect) all contribute to a higher-pressure zone in the lower oesophagus. This high-pressure zone forms the lower oesophageal sphincter (LOS), a physiological rather than a true anatomical sphincter. Pressures at the gastro-oesophageal junction (10 – 30 mmHg) are greater than gastric luminal pressure (5 mmHg), thereby preventing retrograde passage of gastric contents. In addition, the acute angle of His (made by the oesophagus and the axis of the stomach) and the above physiological factors cumulatively contribute to limit the volume and frequency of gastric contents refluxing into the lower oesophagus. Much of these anatomical features however are poorly developed in the first weeks of an infant’s life, predisposing it to the higher risk of GOR within this period. For instance the angle of His is obtuse in newborns and only decreases as the infant grows while the length of intra-abdominal oesophagus is shorter, only 1 cm at birth, compared with 3 cm by 3 months of age. Other abnormalities that predispose to GOR include disruption of the gastro-oesophageal junction (with resulting hiatus hernia), weakness or incompetence of the LOS, and poor clearance of acid from the oesophagus (Cadiot et al., 1997). A mean intra-abdominal pressure of less than 10 mmHg is necessary for the LOS to remain competent thus, GOR is

made more likely in groups with raised intra-abdominal pressure, e.g., following repair of exomphalos (Koivusalo et al., 1999), congenital diaphragmatic hernia and chronic respiratory infections (Rasheed et al., 1992).

Previous studies indicated that GOR is a temporary condition and that symptoms resolve spontaneously without medical intervention (Boyle, 1989; Carre, 1959; Tolia et al., 2003). Indeed, physiological antireflux mechanisms, such as increasing length of the intra-abdominal oesophagus and maturation of the LOS, occur in the first few months after birth (Boix-Ochoa et al., 1976). However, some children develop serious symptoms related to GOR. These symptoms are more frequent in patients with neurological disorders (Spitz et al., 1985; Spitz et al., 1993; Turnage et al., 1989; Vane et al., 1985), and following repair of oesophageal atresia and/or tracheo-oesophageal fistula (Fonkalsrud et al., 1996; Jolley et al., 1980; Kimber et al., 1998; Parker et al., 1979; Snyder et al., 1997; Wheatley et al., 1993). Neurologically impaired patients have the highest incidence of GOR (65-70%) (St Cyr et al., 1986). This is due to a combination of poor oesophageal and gastric motility (due to vagal nerve dysfunction), chronic supine positioning, abdominal spasticity, diaphragmatic flaccidity, scoliosis, retching and increased use of gastrostomy for feeding. GOR occurs in 30 to 80% of children treated for oesophageal atresia, the incidence being related to the length of the atresia gap. The GOR is attributed partly to poor oesophageal motility in these patients and partly to a shortened oesophagus.

The shortened oesophagus, from the original anomaly and compounded by the surgical repair, results in upward displacement of the gastro-oesophageal junction.

Insertion of gastrostomy tubes has been reported to be associated with the development of or worsening of pre-existing GOR; the gastrostomy, which fixes the stomach to the anterior abdominal wall, potentially opens the angle of His (Papaila et al., 1987) and lowers the LOS pressure (Jolley et al., 1986) thereby predisposing to GOR.

1.7.3 Diagnosis

Investigations used for diagnosis of GOR include 24-hour pH monitoring (and more recently impedance study), upper gastro-intestinal contrast studies and oesophagoscopy. Gastric isotope scintiscan and oesophageal manometry are rarely used in children. The 24-hour pH monitoring is performed for 24 continuous hours, during which time the patient feeds normally. Impedance study is preferable as the alkaline content of the stomach after a feed may neutralize the gastric acid reflux and thereby potentially produce a false negative result. Acid reflux is defined by $\text{pH} < 4.0$ in the lower oesophagus. Oesophageal exposure to gastric acid is assessed in terms of the cumulative time during which the oesophageal pH is below 4.0, expressed as the percentage of the total 24 hours. A positive test for GOR is indicated by a pH below 4.0 for more than 5% of the duration of the study. Upper gastro-intestinal contrast studies may diagnose active episodes of GOR. However,

they are more useful for detecting anatomical abnormalities, e.g., hiatus hernia, stricture, oesophageal dysmotility, and might rule out the presence of malrotation of the bowel or gastric outlet obstruction as a cause of vomiting. Oesophagoscopy allows visualization of the gastro-oesophageal mucosa. However, only 40% of GOR will demonstrate unequivocal oesophagitis. Endoscopy is therefore a poor tool for diagnosis of GOR, and is more useful in the assessment of complications of reflux (e.g., oesophagitis, stricture) and in obtaining biopsies (e.g., *Helicobacter pylori* infections, development of Barrett's oesophagus). The presence of lipid laden alveolar macrophages in tracheal aspirates/broncho-alveolar lavage may indicate aspiration secondary to GOR. However, its sensitivity and specificity for detecting GOR is as low as 38% and 59%, respectively (Krishnan et al., 2002), and elevated levels of lipid laden macrophages are found in a number of pulmonary disease without any evidence of aspiration (Knauer-Fischer et al., 1999).

1.7.4 Medical Treatment

Main aims of treatment are to prevent the respiratory complications of GOR and improve the nutritional status of the child from resumption of normal feeding.

Conservative measures for GOR in children frequently advocated include the avoidance of medications that reduce LOS tone (caffeine, theophylline, anticholinergics), dietary modifications (changing the feed pattern with use of frequent, small volume feeds) and positioning manoeuvres. However,

many of these have no proven efficacy. Thickening of formula feeds in infants (e.g., with carob bean gum, rice flour or Gaviscon®) may reduce frank emesis but does not reduce GOR measurably compared with placebos (Bailey et al., 1987; Khoshoo et al., 1993; Orenstein et al., 1987; Vandennplas et al., 1994). Furthermore, there is no quality data to support that more frequent but smaller volume feeding reduce GOR (Carroll et al., 2002). With respect to positioning manoeuvres, positioning at a 60° head elevation increases GOR compared with the prone position (Orenstein et al., 1983). However, the association of the prone position with Sudden Infant Death Syndrome has brought controversy with this manoeuvre. No significant difference has been found between the flat and head-elevation prone positions (Orenstein et al., 1983). Pharmacotherapy forms the main first-line treatment modality of GOR. A wide spectrum of agents is now available, aimed at decreasing acid secretion (H₂-blocking agents or proton pump inhibitors) and to increase gastric emptying.

1.7.5 Surgical Management

The indications for antireflux surgery vary largely in reported series but for symptomatic children with GOR that does not respond to medical treatment, surgery is recommended to prevent further morbidity. The Nissen fundoplication (NF) is a 360° fundoplication and it is the most common surgical procedure performed in children to treat GOR when medical therapy has failed. The technique was initially described by Dr. Rudolph Nissen in

1955 (Figure 1.3) and published in 1956 (Nissen, 1956). In 1961 he published a more detailed overview of the procedure (Nissen, 1961).

Figure 1.3 – Rudolph Nissen (1896-1981).



Nissen originally called the surgery "gastroplication". The classic, "open" approach to the NF has been with a xipho-umbilical incision. The procedure aims to establish a high-pressure zone in the distal oesophagus. The hiatus is repaired by approximating the two limbs of the right crus of the diaphragm, the angle of His is accentuated, and a flutter valve is created at the oesophago-gastric junction. Adequate mobilization of the fundus and the great curvature of the stomach then allows division of the short gastric

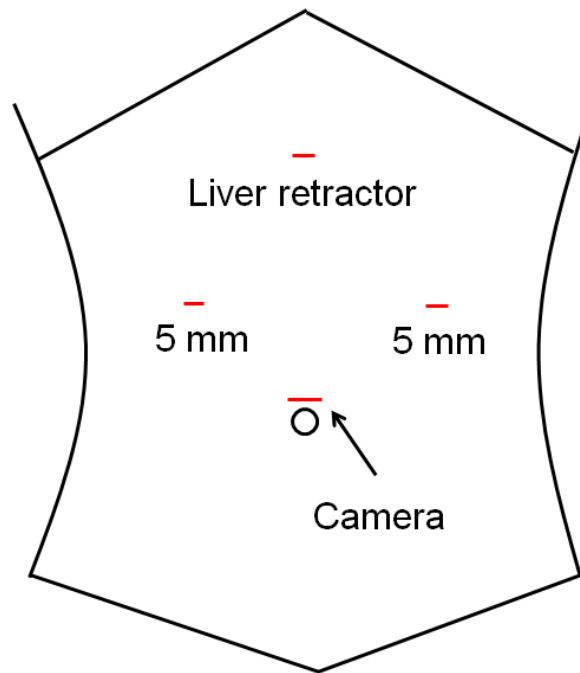
vessels. A point of the gastric fundus is passed posteriorly to the oesophagus and a 360° floppy wrap is performed with non-absorbable sutures. Alternatively, the short gastric vessels may not be divided (modified Rossetti technique). A potential advantage of the laparoscopic Nissen fundoplication (LNF) is reduction of the surgical trauma and has become the procedure of choice in many major centres. This technique is briefly described below.

1.7.6 Laparoscopic Nissen Fundoplication

Following general endo-tracheal anaesthesia, the patient is placed in the supine position with the legs at the end of the operating table (Lloyd-Davies with table head-up). The surgeon stands between the patients' legs. A 5 mm umbilical port for the camera (30° or 45° lens) is inserted under direct vision and pneumoperitoneum of 8 – 10 mmHg is created.

Ports of 3 – 5 mm diameter are inserted in the right flank and left flank for the operating instruments. A Nathanson liver retractor is inserted at the epigastrium and liver is retracted superiorly (Figure 1.4).

Figure 1.4 – Port-placement during laparoscopic Nissen fundoplication.



The first step of the procedure is to divide the gastro-hepatic omentum along the upper lesser curve of the stomach. Then, the stomach is retracted to the left to expose the right crus of the diaphragm. The anterior edge of the right crus is identified by incising the overlying peritoneum and is peeled gently off the oesophagus, allowing access to the mediastinum around the oesophagus. The stomach is retracted to the right hand side, and the left edge of the right crus is identified similarly and dissected and freed from the oesophagus. The oesophagus is elevated, and the posterior vagus nerve is identified. This is dissected gently and a window is created. The left and right limbs of the right crus are closed behind the oesophagus by one to three non-absorbable sutures. The upper 2 – 3 cm of the greater curvature of the stomach are mobilized by clipping and dividing the short gastric vessels and

peritoneal attachments to the spleen and diaphragm. A Babcock grasper is passed from the right sub-costal port behind the oesophagus to grasp the mobilized fundus which is then pulled through the window behind the oesophagus. The wrap is fixed around the oesophagus using 3 non-absorbable sutures, one of which is also anchored to the oesophagus. The contiguous part of the fundus of the stomach is used for the fundoplication to create a floppy wrap.

1.8 Pyloric Stenosis and Pyloromyotomy

1.8.1 Introduction

Infantile hypertrophic pyloric stenosis (PS) is a common condition of newborn infants with an incidence of approximately 1 – 3 per 1000 live births (Grant et al., 1984). The condition is more common in boys with a male:female ratio of 4:1. The precise aetiology remains unclear although it is likely to be multifactorial including a genetic component. Since the early 20th century the definitive treatment of choice for PS has been the pyloromyotomy, standardised by Ramstedt (Figure 1.5) in 1912 (Ramstedt, 1912).

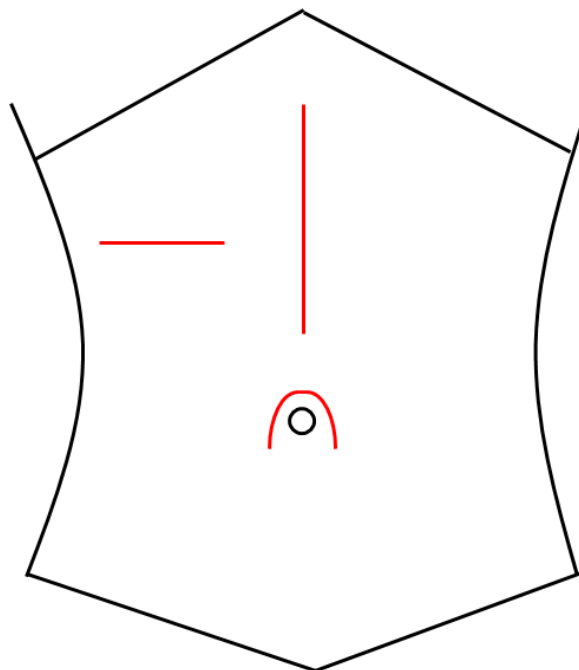
Figure 1.5 – Conrad Ramstedt (1867 – 1963).



In the era before it was recognised that this condition required surgical correction, death was common and PS was encountered at post-mortem examination. Indeed, the first report of PS from 1717 includes clinical and post-mortem findings (Blair, 1717). Survival rates now approach 100% and the Ramstedt pyloromyotomy has been successfully employed internationally for a number of decades.

The operation has a high success rate, a low incidence of complications and can be performed in a short length of time ensuring minimal anaesthetic time in a young infant. These factors have no doubt contributed to its popularity and success over the years. Different open surgical approaches have been used (Figure 1.6).

Figure 1.6 – Open approaches to pyloromyotomy: right upper quadrant; midline; periumbilical.



In the early 20th century an approach to the gastric pylorus via an incision in the right upper quadrant was described and used for many years. However, this incision often leaves a clearly visible and sometimes unsightly scar. Also a midline incision was initially used. More recently, a peri-umbilical incision (either in the upper or lower fold) has been described by a number of authors (Tan et al., 1986; Teehan et al., 1993). The cosmetic result following this appears more favourable with minimal if any scarring being present (Shankar et al., 2001). Many surgeons have adopted this approach into routine practice and this is now the most commonly practised technique in many hospitals.

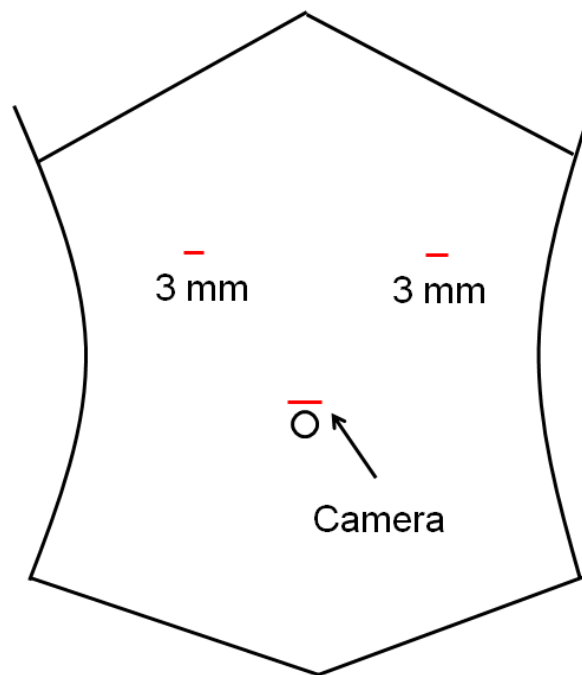
Increasingly, paediatric surgeons have taken to performing laparoscopic Ramstedt pyloromyotomy. Alain first described his experience with this approach to pyloromyotomy for PS in 1991 (Alain et al., 1991) and since then a number of other institutions have reported their experience (Bufo et al., 1998; Campbell et al., 2002; Downey, Jr., 1998; Ford et al., 1997; Fujimoto et al., 1999; Greason et al., 1995; Scorpio et al., 1995). The technique is briefly described below.

1.8.2 Laparoscopic Pyloromyotomy

Following general endotracheal anaesthesia, the patient is placed in the supine frog-leg position at the end of the operating table. The surgeon stands at the end of the table below the legs with the assistant to the patient's right. The monitor is placed at the head of the table. A 3 mm or 5 mm umbilical port for the camera (30° or 45° lens) is inserted under direct vision, either in the upper or lower fold of the umbilicus; the incision in the upper fold offers the advantage that can be

easily converted for an open procedure if requested, but the insertion of the camera in the lower fold offers generally a better view. Pneumoperitoneum of 8 mmHg is created. Two 3 mm instruments are inserted into the peritoneum via 2 'stab' incisions (Figure 1.7).

Figure 1.7 – Port-placement during laparoscopic pyloromyotomy.



An intestinal grasper is inserted through the right upper quadrant (RUQ). A laparoscopic knife is inserted in the left upper quadrant (LUQ) incision. Only 3 mm of the tip of the knife should be exposed (alternatively a diathermy hook can be used). The pylorus is gently stabilized with the grasper at the duodenopyloric junction just distal to the hypertrophic muscle. The incision is started from a point just proximal to the duodenopyloric junction continuing across the serosa of the

hypertrophic pylorus towards and onto the antrum. After the incision is made, a pyloric spreader is introduced through the LUQ incision.

Starting at the centre of the incision, the muscle is spread perpendicularly. Once the initial spread reaches the mucosa, spreading is continued proximally and distally for the length of the incision. The spreading is stopped 2 to 3 mm from the duodenopyloric junction.

Satisfactory pyloromyotomy is confirmed by the presence of two independently moving pyloric edges and mucosal integrity confirmed by insufflation of air into the stomach. The umbilical fascia is approximated with a 3/0 absorbable suture. The fascia at the stab sites is not sutured, and the skin at each site is approximated with Steristrips® or glue only.

Chapter 2

Absorption of Carbon Dioxide During Laparoscopy

2.1 Introduction

2.1.1 General Introduction

Carbon dioxide (CO₂) is commonly used for insufflating the abdomen to create the pneumoperitoneum in adults and children since it is non-combustible, inexpensive and least likely to cause embolism. CO₂ is the main by-product of cellular metabolism; it can be naturally eliminated by the human body. A small portion of CO₂ is dissolved in blood and is delivered directly to the lungs. The majority of CO₂ combines with water in red blood cells to form carbonic acid, which then dissociates into hydrogen and bicarbonate according to this equation:



The produced hydrogen ions complex with haemoglobin and the bicarbonate diffuses into the plasma. CO₂ absorbed through the peritoneum is handled in the same manner and, ultimately, is eliminated by respiratory exchange in the lungs.

2.1.2 Effects of Pneumoperitoneum

Insufflation increases the delivery of CO₂ to the lungs by as much as 50%, which necessitates a compensatory increase in minute ventilation to maintain eucapnia. While under general anaesthesia, minute ventilation volumes must be increased by up to 16% to maintain normocarbida (Zacks et al., 2002). Even if the increase in PaCO₂ is not fully compensated by hyperventilation, most healthy patients can adapt to the transient increase in end-tidal CO₂ (ETCO₂) and slight decrease in pH by maximizing the use of their intracellular and plasma buffering systems and increasing the rate of CO₂ transport. Some patients (i.e. those with decreased

pulmonary function), however, are unable to tolerate the increased CO₂ load during insufflation (Brown et al., 1976). Diaphragmatic movements are decreased resulting in decreased functional residual capacity and increase in alveolar dead space. Also, there is a rise in peak airway pressures, with a concomitant decrease in pulmonary compliance (Brown et al., 1976; Johannsen et al., 1989; Puri et al., 1992; Safran et al., 1994; Smith et al., 1971). In patients allowed to breathe spontaneously during laparoscopy, these factors can lead to hypoxemia (Baratz et al., 1969). Controlled ventilation, especially with large tidal volumes, however, decreases the risk of hypoxemia by minimizing alveolar atelectasis and the resultant ventilation/perfusion mismatch (Gutt et al., 2004). The recruitment of alveoli at the lung bases can be further enhanced with the addition of positive end-expiratory pressure (PEEP), though PEEP must be added with caution because of its cardiovascular effects.

Although there are seemingly deleterious effects of laparoscopy to intraoperative pulmonary mechanics, these do not appear to be clinically relevant in most healthy patients (Hardacre et al., 2000).

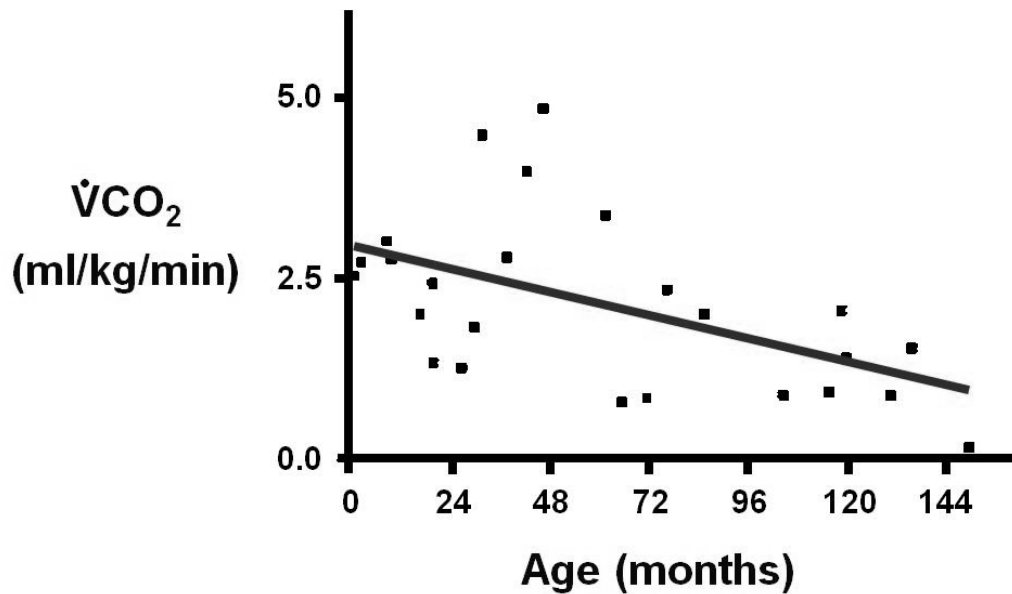
Schwenk et al (Schwenk et al., 1999), evaluated pulmonary function tests, including the forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and oxygen saturation of patients before and after open or laparoscopic procedures. Despite the fact that all patients demonstrated depressed pulmonary mechanics postoperatively, those who had an open operation had significantly more impairment than patients in the laparoscopic group, even in light of a shorter operative time for the open operations. These changes in pulmonary function tests

lead to worse outcomes. Similar results were obtained by Hasukic et al. (Hasukic et al., 2002) in patients undergoing either laparoscopic or open cholecystectomy. Insufflation alters cardiovascular performance because of both the effects of hypercarbia as well as the change in intra-abdominal pressure. Mild hypercarbia (PaCO₂ of 45 – 50 mmHg) has little effect on haemodynamics, whereas moderate to severe hypercarbia has both direct and indirect effects on cardiac function (Rasmussen et al., 1978). At a PaCO₂ of 55 – 70 mmHg, hypercarbia and acidosis cause significant hemodynamic changes. In addition, elevated CO₂ directly causes myocardial depression and vasodilation. These effects are counteracted by a centrally mediated sympathetic stimulation that causes tachycardia and systemic vasoconstriction with increase in heart rate, mean arterial pressure, central venous pressure, pulmonary artery pressure, cardiac output, and stroke volume.

Haemodynamic changes are also mediated by the absorption of the CO₂ through the peritoneal surface causing adverse effects on the cardiovascular system requiring increasing minute ventilation by 20% to 30% to prevent hypercarbia (Brown et al., 1976; Tan et al., 1992).

It has been demonstrated that compared to adults, small children eliminate relatively more CO₂ measured by indirect calorimetry during laparoscopy (McHoney et al., 2003) (Figure 2.1) and thus require scrupulous anaesthetic management, particularly in the presence of pre-existing pathological conditions (Bozkurt et al., 2002; Tobias et al., 1997).

Figure 2.1 – Elimination of CO₂ during laparoscopy at different ages.



(From McHoney et al. J. Pediatr. Surg. 2003, with permission)

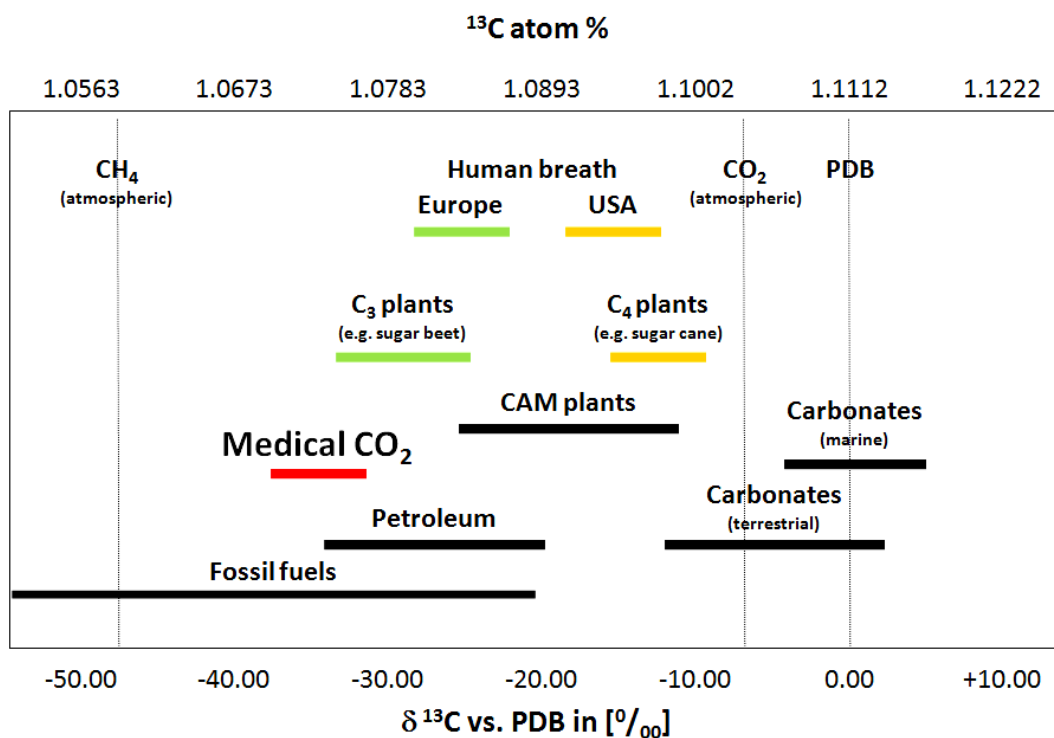
More recently, McHoney and colleagues (McHoney et al., 2008) reported that there is also a significant increase in ETCO₂ in children undergoing thoracoscopy, which is higher than during laparoscopy. The same authors documented that, similarly to what previously described for laparoscopy, changes in ETCO₂ are larger in smaller children. For these reasons, ETCO₂ is commonly monitored during minimally invasive surgery in children and minute ventilation is accordingly adjusted in order to avoid hypercapnia. However, some authors suggested that the ETCO₂ is not a reliable measure of arterial CO₂ pressure (Laffon et al., 1998; Wulkan et al., 2001). Furthermore, ETCO₂ measures total CO₂ elimination and does not allow quantification of the absorption of CO₂ from the peritoneum. Infants and children undergoing laparoscopy are hypermetabolic

(McHoney et al., 2006) and the increased elimination of CO₂ during laparoscopy may be metabolic in origin and not arise from the absorption of CO₂ from the pneumoperitoneum; thus changes in CO₂ production ($\dot{V}\text{CO}_2$) measured by indirect calorimetry are not a reliable measure of absorbed CO₂. Development of a method to specifically measure the amount of CO₂ absorbed from the peritoneum during laparoscopy would allow correlation of post-operative pain with the amount of CO₂ absorbed from the peritoneum.

2.1.3 Carbon Stable Isotopes: $^{13}\text{C}/^{12}\text{C}$ Ratio

There are two naturally occurring stable, non-radioactive isotopes of carbon, ^{12}C and ^{13}C . Of these, ^{12}C makes up about 99% of atmospheric CO₂ and can be measured with mass spectrometry as described in the next paragraph. An ideal way to study CO₂ absorption from pneumoperitoneum would be to insufflate with $^{13}\text{CO}_2$ and measure appearance of $^{13}\text{CO}_2$ in breath, however this would be prohibitively expensive at the flow rates of 1 – 2 l/min during pneumoperitoneum. There are very small differences in $^{13}\text{C}/^{12}\text{C}$ ratio in different naturally occurring carbon sources (natural abundance), and this is reflected in a range of % ^{13}C from 1.0563 to 1.1222 (Figure 2.2).

Figure 2.2 – Natural abundance of ^{13}C .



These differences are usually represented as $\delta^{13}\text{C}$ relative to PDB (Pee Dee Belemnite), a Cretaceous marine fossil that is used as the international standard for $^{13}\text{C}/^{12}\text{C}$. Interestingly, exhaled breath has a rather different $^{13}\text{C}/^{12}\text{C}$ ratio from medical CO_2 , reflected by their different $\delta^{13}\text{C}$ values: breath has δ of between -11 and -24 compared to PDB, whereas medical CO_2 has a PDB value of -32 to -34. The absorbed, exhaled medical CO_2 causes the overall $^{13}\text{C}/^{12}\text{C}$ ratio in CO_2 breath to alter, enabling absorption of CO_2 to be measured using a mass spectrometric technique.

2.1.4 Use of Mass Spectrometry in Clinical Measurement of Respiratory Gases

The respiratory mass spectrometer was first developed in the 1950s, and in some ways was ideally suited to real-time analysis of multiple gases, as needed for O₂ and CO₂ monitoring of patients undergoing intensive care or surgery (Fowler et al., 1957; Miller et al., 1950a; Miller et al., 1950b). Later developments, such as methods to minimise interference from volatile anaesthetic gases (e.g. nitrous oxide, which has a molecular weight of 44), allowed more routine clinical application (Davis et al., 1979; Heneghan et al., 1981). Eventually, the expense of the equipment and the advent of alternative, more portable, devices able to measure single gases in real time with high accuracy led to their gradual demise in routine settings, although the respiratory mass spectrometer still finds application in some research settings, for example where it is necessary to measure multiple tracer gases simultaneously (Rosenthal et al., 1995). Although these respiratory mass spectrometers found use in the measurement of ¹³CO₂/¹²CO₂, the low resolution of the analysers has limited application to the detection of ¹³CO₂ from labelled tracers such as ¹³C-bicarbonate (Rocker et al., 2001) or glucose (Rocker et al., 1996). Nevertheless, the high temporal resolution enabled changes in ¹³CO₂/¹²CO₂ during a single breath to be measured (Rocker et al., 1996; Rocker et al., 2001).

2.2 Aim

Aim of this study was to measure the elimination of exogenous CO₂ during laparoscopy in children using a novel mass spectrometry technique.

2.3 Methods

Ten children undergoing laparoscopic surgery and 9 children undergoing open surgery were enrolled in this prospective non-randomised study. This was a pilot study designed to assess the use of a mass spectrometry technique to measure the absorption of CO₂ during pneumoperitoneum. No similar studies were previously conducted and no data were available from the literature to perform a power calculation to determine the sample size to find differences between the open and laparoscopic group. Instead, the sample size of 10 patients in each group was chosen based on the study feasibility.

We chose a variety of surgical procedures (Table 2.1) but we tried to minimise the differences between patients by using an identical anaesthesia protocol in all of them. Furthermore, in patients undergoing laparoscopy, we used the same intra-abdominal pressure and flow rate assuming that the absorption of CO₂ was not related to a specific surgical procedure but to the characteristics of the pneumoperitoneum.

Table 2.1 – Procedures performed in the open and laparoscopic group.

***Posterior Sagittal AnoRectoPlasty; †Percutaneous Endoscopic Gastrostomy.**

Open group (n=9)		Laparoscopic group (n=10)	
Nissen fundoplication	2	Nissen fundoplication	4
PSARP*	2	Pancreatic biopsy and PEG†	2
Bilateral orchidopexy	1	Right inguinal herniotomy	2
Partial splenectomy	1	Ladd's procedure	1
Right inguinal herniotomy	1	De-roofing of liver cyst	1
Closure of ileostomy	1		
Right hemicolectomy	1		

2.3.1 Anaesthesia

All patients were anaesthetised in a standard manner with either 8% sevoflurane in oxygen or 2 – 5 mg/kg propofol. After induction, atracurium (0.5 mg/kg) was administered and the trachea intubated with an oral endotracheal tube of age appropriate size with minimal leak present. ETCO₂ was measured on a continuous basis using a positive sampling system (Hewlett Packard®; Boeblingen, Germany). All patients were ventilated throughout the procedure with a mixture of air, oxygen and isoflurane to an ETCO₂ physiological level of between 4.5 – 6.0 kPa depending upon the pre-existing pulmonary function.

Paralysis was maintained with boluses of atracurium and intraoperative analgesia achieved with up to 5 g/kg fentanyl in increments plus 30 mg/kg paracetamol per rectum and 1 mg/kg diclofenac for those patients over 10 kg. At the end of surgery up to 2 mg/kg of bupivacaine were infiltrated at the ports' insertion sites

and the patients were extubated and breathing spontaneously before going to the recovery room.

2.3.2 Laparoscopic Technique

An Hasson cannula was inserted under direct vision just above the umbilicus and unheated (room temperature) CO₂ was used to establish a pneumoperitoneum with a pressure of 8 – 10 mmHg and a maximum flow rate of 2 L/min. Laparoscopic procedures were performed using standard techniques.

2.3.3 Sample Collection

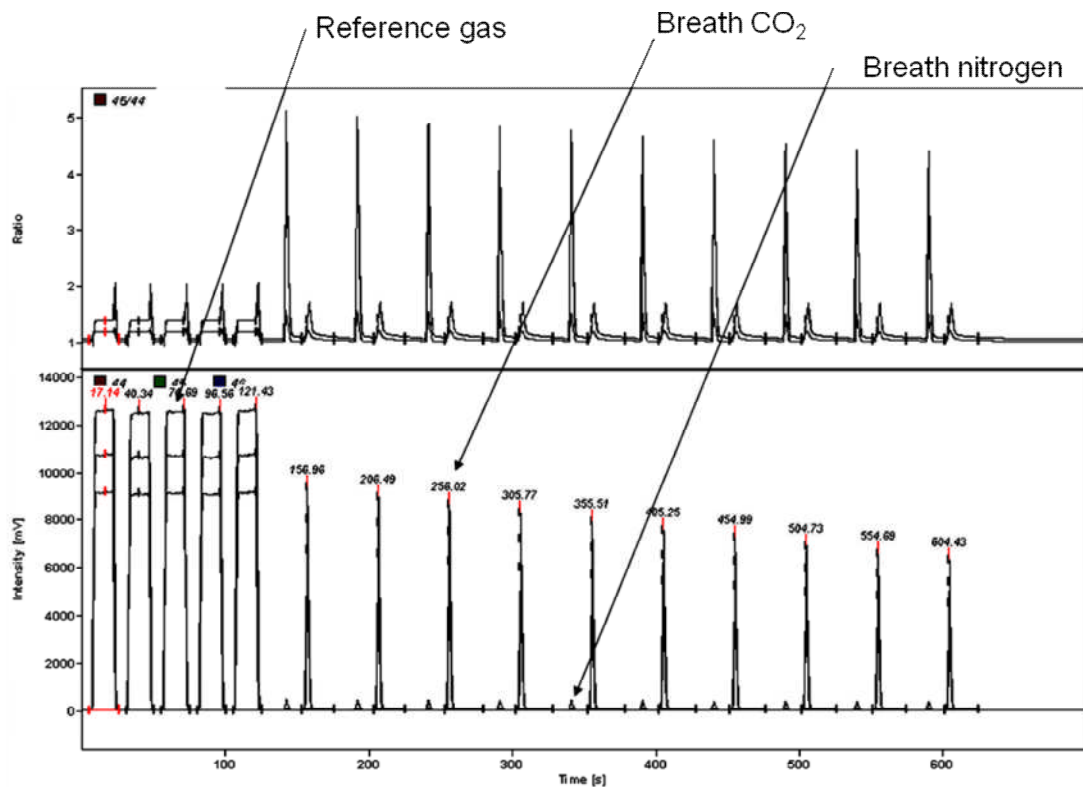
Breath samples were collected at 5-minute intervals using a 10 ml syringe connected to a 3-way valve at the sampling line for measurement of ETCO₂. The air was aspirated into a 10 ml syringe and transferred into 10 ml vacuum test tubes (Labco Limited®, High Wycombe, United Kingdom) for the analysis. Samples were collected before the start of the operation, during the operation, during pneumoperitoneum, and after the end of the operation. In addition, samples of air used for ventilation and of medical CO₂ used for the pneumoperitoneum were obtained for each operation. ETCO₂ and body core temperature were recorded at each sampling point.

2.3.4 Sample Analysis

Breath CO₂ was analyzed for ¹³CO₂/¹²CO₂ enrichment by gas chromatography on a CP-Poraplot-Q column (Varian Inc.®, Oxford, U.K.) followed by isotope ratio

mass spectrometry (Figure 2.3) on a Thermo Finnigan Delta-XP (Thermo Finnigan®, Bremen, Germany).

Figure 2.3 – Isotope ratio mass spectrometry trace from one patient at a specific time point.



Sample $^{13}\text{CO}_2/^{12}\text{CO}_2$ enrichment was standardised against a CO_2 cylinder (5.0 grade, BOC Special Gases®, Guildford, Surrey, UK), which had been calibrated against the international standard PDB (Iso-Analytical®, Sandbach, Cheshire UK). Samples at each time point were analyzed 10 times and the $^{13}\text{CO}_2/^{12}\text{CO}_2$ was calculated as mean from all results.

The percentage of exhaled CO₂ originating from the pneumoperitoneum at *time x* was calculated as:

$$100 \times \frac{[\text{breath } \delta^{13}\text{C at } \textit{time x}] - [\text{breath } \delta^{13}\text{C at } \textit{time zero}]}{[\delta^{13}\text{C of medical CO}_2] - [\text{breath } \delta^{13}\text{C at } \textit{time zero}]}$$

2.4 Data Analysis

Data are given as mean \pm SEM and were normally distributed. Data were compared by paired and unpaired t-tests, and by linear regression analysis, using Prism 4.03 software (GraphPad Software Inc.®, San Diego, USA). Results with a p value of <0.05 were considered significant, and results were corrected for multiple comparisons by Bonferroni's correction where appropriate.

2.5 Results

Mean age at operation was comparable between the two groups and was 27.6 ± 17.8 months for the laparoscopic group and 24.5 ± 5.7 months for the open group ($p = 0.7$). Weight at operation was 10.4 ± 2.6 kg and 11.8 ± 1.3 kg respectively ($p = 0.7$) (Table 2.2).

Table 2.2 – Patients’ demographic.

	Open surgery (n = 9)	Laparoscopy (n = 10)	p value
Age (Months)	24.5 ± 5.7	27.6 ± 17.8	n.s.
Weight (Kg)	11.8 ± 1.3	10.4 ± 2.6	n.s.

Core temperature did not show any significant variation remaining within normal range during the surgical procedure in all patients (Figure 2.4 and Figure 2.5).

Figure 2.4 – Variations of body temperature during open surgery (recorded in 8 patients).

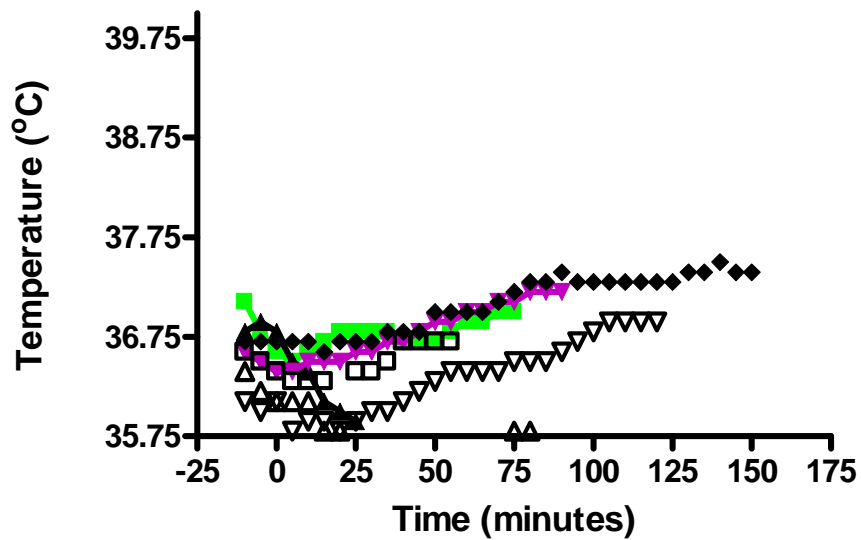
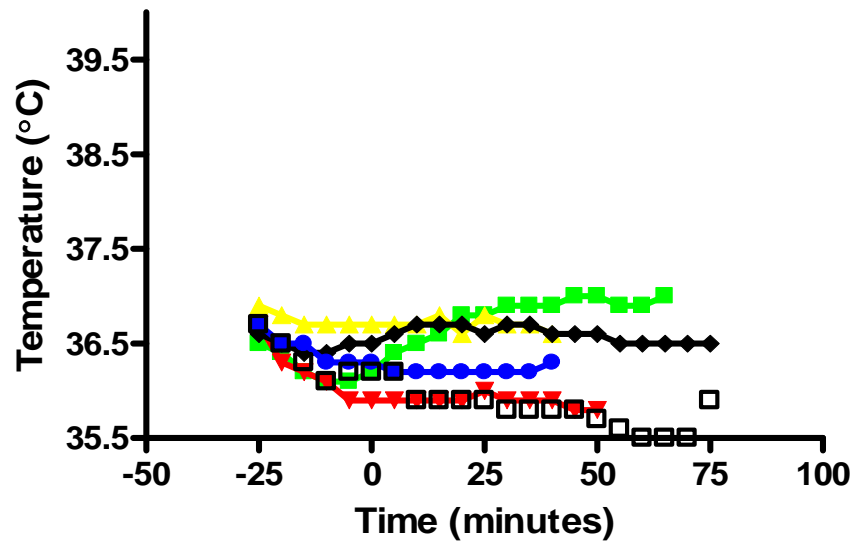


Figure 2.5 – Variations of body temperature during laparoscopic surgery (recorded in 6 patients).



Minute ventilation was adjusted by the anaesthetist and ETCO_2 was maintained between normal ranges in all children during surgery (Figure 2.6 and 2.7). One patient in the open group (Figure 2.6) that underwent inguinal herniotomy had a significant variation of the ETCO_2 that could not be explained. This patient was otherwise fit and well and recovered promptly from the anaesthesia.

Figure 2.6 – End-tidal CO₂ in patients undergoing open surgery (recorded in 8 patients).

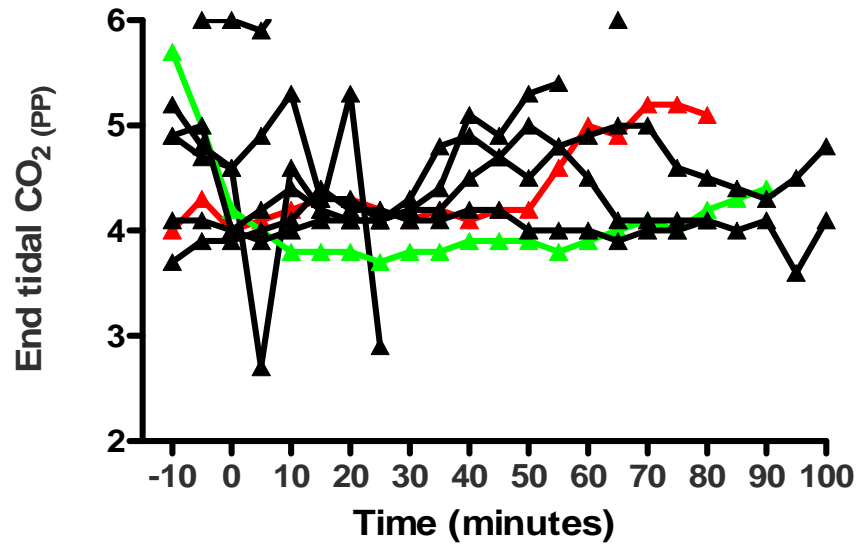
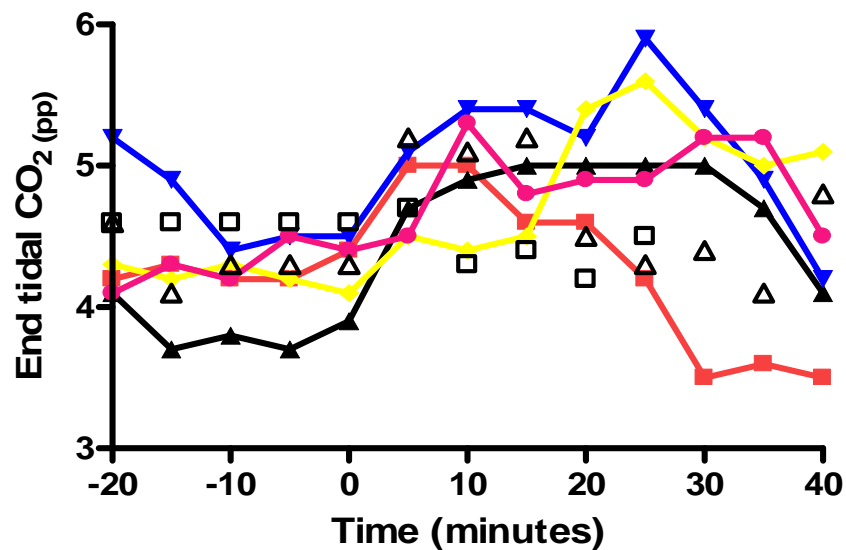
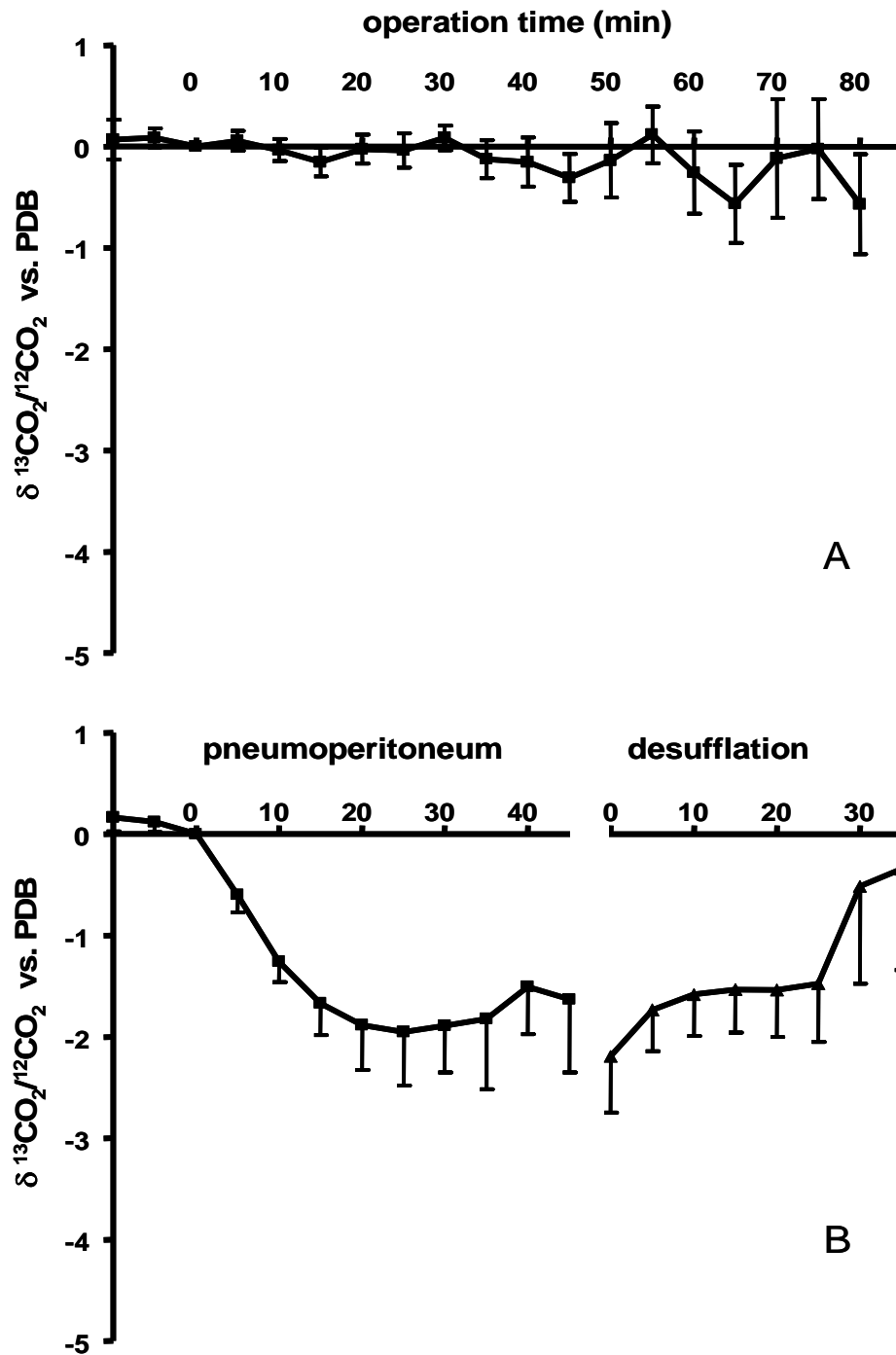


Figure 2.7 – End-tidal CO₂ in patients undergoing laparoscopic surgery (recorded in 7 patients).



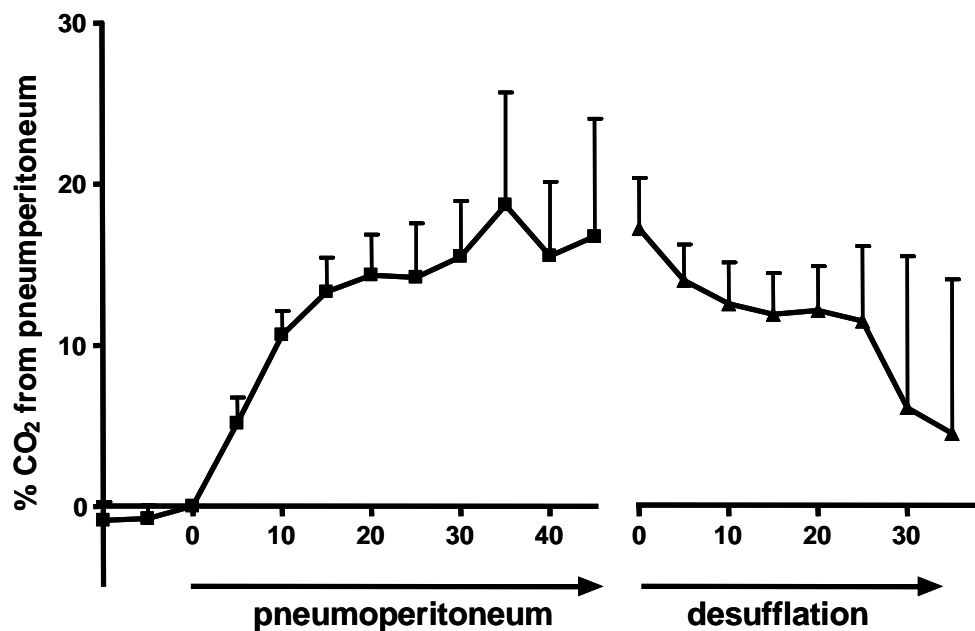
$^{13}\text{CO}_2/^{12}\text{CO}_2$ in medical CO_2 was -32.7 ± 0.9 δPDB . $^{13}\text{CO}_2/^{12}\text{CO}_2$ in exhaled breath of patients undergoing open procedures was -24.3 ± 0.8 δPDB at the start of operation and did not change significantly during the operation ($p > 0.2$) (Figure 2.8A). $^{13}\text{CO}_2/^{12}\text{CO}_2$ in exhaled breath of patients undergoing laparoscopy was -21.5 ± 1.7 δPDB at the start of insufflation, similar to baseline $^{13}\text{CO}_2/^{12}\text{CO}_2$ of patients undergoing open surgery ($p = \text{n.s.}$). $^{13}\text{CO}_2/^{12}\text{CO}_2$ progressively fell during pneumoperitoneum, falling by 2.5 ± 0.5 to -24.1 ± 1.3 ($p = 0.0015$ vs. baseline by paired t-test) at the end of pneumoperitoneum in each patient (35.0 ± 6.3 min), indicating absorption of exogenous CO_2 (Figure 2.8B). After the end of pneumoperitoneum, $^{13}\text{CO}_2/^{12}\text{CO}_2$ returned towards baseline, so that at the end of operation (51.5 ± 12.6 min after the end of pneumoperitoneum) $^{13}\text{CO}_2/^{12}\text{CO}_2$ was -22.4 ± 1.6 , which was -0.9 ± 0.4 different from baseline ($p = 0.12$ vs. baseline; Figure 2.8B).

Figure 2.8A and 2.8B – $\delta^{13}\text{CO}_2/^{12}\text{CO}_2$ versus PDB (Pee Dee Belemnite) in exhaled breath of patients undergoing open procedures (A) and in patients undergoing laparoscopic procedures (B).



Using the $^{13}\text{CO}_2/^{12}\text{CO}_2$ of the medical CO_2 used for insufflation to represent 100% of exhaled CO_2 originating from the pneumoperitoneum and baseline breath $^{13}\text{CO}_2/^{12}\text{CO}_2$ to represent 0%, we calculated the percentage of exhaled CO_2 originating from the peritoneum. The percentage of expired CO_2 absorbed rose to $16.0 \pm 7.0\%$ following 45 minutes of pneumoperitoneum, and then fell rapidly after discontinuing the CO_2 insufflation (desufflation) (Figure 2.9).

Figure 2.9 – Percentage of CO_2 originating from the pneumoperitoneum.



ETCO_2 showed no correlation with the percentage of CO_2 absorbed ($r^2 = 0.08$) in the laparoscopic group and did not change significantly in the open group during the operation. No patients in either group experienced cardiovascular or respiratory compromise during or after surgery and all had an uncomplicated postoperative recovery.

2.6 Discussion

Experimental models have documented that CO₂ excretion increases significantly during pneumoperitoneum causing acidaemia, hypercarbia and depressed haemodynamic function (Ho et al., 1992; Leighton et al., 1992; McDermott et al., 1995). Absorption of CO₂ through the peritoneal surface is also well documented in children and its physiological effects are of concern to the anaesthetists. CO₂ absorption may cause haemodynamic changes, leading to adverse effects on the cardiovascular system, cerebral oxygenation and cerebral blood volume (De Waal et al., 2002). This does not appear to be a problem in patients with normal cardiovascular function (Hsing et al., 1995; Kenefick et al., 1987; McMahon et al., 1993), and healthy children undergoing short procedures with insufflating pressures limited to 10 mmHg have minimal adverse effects (Tobias et al., 1997). However, an increase in minute ventilation is usually required to prevent hypercarbia (Brown et al., 1976; Tan et al., 1992) and CO₂ pneumoperitoneum is not recommended in high-risk patients. Small children eliminate relatively more CO₂ compared to older children and adults (McHoney et al., 2003) and may be at higher risk of cardiovascular adverse effects. Hence, measurement of arterial CO₂ and pH could be advisable during laparoscopy, particularly in small children. However, arterial gas blood analysis is not routinely performed because of its invasiveness. For this reason ETCO₂ is monitored and seems to have a good correlation with the arterial CO₂. Nevertheless, some authors suggest that ETCO₂ is not a reliable monitor of the arterial CO₂ during anaesthesia (Wahba et al., 1996) and during laparoscopy in children for specific pathological conditions

(Laffon et al., 1998; Wulkan et al., 2001). Furthermore, ETCO₂ accounts for the total CO₂ elimination and does not allow discriminating the absorption of CO₂ from the peritoneum. CO₂ elimination during laparoscopy can also be quantified by indirect calorimetry (McHoney et al., 2006; Streich et al., 2003; Sumpf et al., 2000). This technique allows measuring the total CO₂ eliminated which includes the metabolic produced and the CO₂ absorbed from the peritoneum and at the present is not routinely used during laparoscopy and is primarily a research tool. If there are changes in resting metabolic rate, or in the balance of substrate oxidation leading to a change in CO₂ excretion, then changes in expired CO₂ could be difficult to interpret. At the moment, there are no simple and reliable methods to quantify the absorption of exogenous CO₂ used for pneumoperitoneum during laparoscopy.

The high precision of the isotope ratio mass spectrometry enable us to utilize the small differences in natural carbon abundance in different sources (i.e. CO₂ metabolically produced from the patient and CO₂ used for pneumoperitoneum). Using this technique we have documented that 10-20% of CO₂ eliminated during laparoscopy in children is derived from the absorption through the peritoneum. None of the patient in the laparoscopic group in our study required desufflation of the pneumoperitoneum and conversion to an open procedure since the adjustments on the minute ventilation made by the anaesthetist were adequate to prevent adverse haemodynamic effects. However, it would be advisable to have a simple method accessible in the operating room to quantify the absorption of CO₂ during pneumoperitoneum. This could eventually help deciding if there is the need for

reducing or temporarily discontinuing the pneumoperitoneum and even conversion to an open procedure if haemodynamic, oxygenation, or ventilation difficulties arise during the laparoscopy. A real time analyser (Oridion BreathID®) has been validated in adults for ^{13}C urea breath test for *Helicobacter pylori* infection (Shirin et al., 2001). This system offers several advantages over conventional mass spectrometry that we used in our study including an immediate test result and a sampling method that does not require active cooperation. The breath samples are continuously collected from the patient and, the device continuously measures $^{13}\text{CO}_2$ and $^{12}\text{CO}_2$ concentrations from the patient's breath and establishes the $^{13}\text{CO}_2/^{12}\text{CO}_2$ ratio, which is displayed onscreen. This system has only found application for the ^{13}C urea breath test for *Helicobacter pylori* infection but a similar device could allow quantifying the CO_2 absorption during laparoscopy in a real time mode.

2.7 Conclusions

In conclusion, this study clearly demonstrated that in children after 10 minutes of laparoscopy, 16% of expired CO_2 is derived from the absorption of exogenous CO_2 . Adjustments on the minute ventilation made by the anaesthetist are adequate to prevent adverse haemodynamic effects in children with normal cardiopulmonary function.

Chapter 3

Open Versus Laparoscopic Nissen

Fundoplication: 4 – Year Follow-Up of a

Randomised Controlled Trial

3.1 Introduction

Regurgitation of gastric contents above the lower oesophageal sphincter is a normal physiologic process in infants and children. It becomes pathological and is then termed gastro-oesophageal reflux (GOR) disease when it is symptomatic and associated with significant sequelae. The aims of treatment of GOR are to achieve relief of symptoms and prevent complications. For patients who fail to achieve control with medical therapy or are long-term dependent on anti-reflux medications a surgical anti-reflux procedure is required. The open Nissen fundoplication (ONF) has been the treatment of choice in our Institution until 2000, but it is an invasive surgical procedure associated with frequent postoperative complications (up to 26%) (Pearl et al., 1990) including dysphagia, gas bloating, retching, dumping syndrome and recurrence of reflux (up to 30%) particularly in neurologically impaired children (Smith et al., 1992). The ONF it is an invasive surgical procedure performed through a large laparotomic incision and the metabolic response to this operation is a considerable challenge to the patient's homeostasis and recovery. Surgical trauma significantly affects energy metabolism in adults (Cuthbertson, 1959) however we know very little about the response in children. There is a brief "ebb" period of depressed metabolic rate immediately after surgery which is followed by a "flow phase" characterised by an increase in resting energy expenditure (REE) which can last up to several days. The increase in REE has been attributed to increased energy requirements of injured tissue, heat losses from the wound and increased cycling of metabolic substrates (Wilmore, 1986), and is thought to be mediated by catecholamines,

glucagon, cortisol and cytokines which are released in response to stress (Fraysn et al., 1985). The REE increases immediately after the operation, returning to baseline within 24 hours (Jones et al., 1993). This transient hypermetabolism is associated with elevation of heart rate, body temperature, ventilatory rate and circulating cytokines (Jones et al., 1994). Importantly, the increase in REE is linearly correlated with the degree of tissue trauma (Jones et al., 1993). Laparoscopic surgery leads to the reduction of the surgical trauma and it has been documented that both interleukin-6 and C-reactive protein levels were lower in patients that underwent laparoscopic hysterectomy on the first ($p = 0.01$ and $p = 0.03$, respectively) and on the second postoperative day ($p = 0.02$ and $p < 0.001$, respectively) compared with patients undergoing open hysterectomy (Härkki-Sirén et al., 2000). Similarly, the laparoscopic Nissen fundoplication (LNF) in children may partly reduce the post-operative immune suppression leading the reduce incidence of complications (McHoney et al., 2005). However its efficacy and long-term results, particularly in neurologically impaired children, are still questionable (Kawahara et al., 2004). A meta-analysis of randomised controlled trials (RCTs) in adults was performed in our institution to determine whether ONF or LNF provides best clinical outcome (*Chowdhury M et al, unpublished data*). The authors reviewed 195 articles and identified 8 RCTs in adults. Four trials, which performed pH studies post-operatively, all found that the two approaches improved acid reflux equally: the mean reflux index (% time pH < 4.0) was 3.4% (CI 2.3 – 4.1) after open and 1.3% (CI 1.27 – 1.46) after laparoscopic fundoplication ($p = 0.5$). ONF was associated with shorter operative time

(estimate weighted mean difference, eWMD = 23.4 mins; $p = 0.005$) and 35.9% less dysphagia (relative risk, RR = 0.62 (CI 0.39 – 1.00; $p = 0.05$). However, relative to open surgery, LNF was associated with 88% fewer abdominal complications ($p < 0.00001$), 77% fewer systemic complication ($p = 0.001$), significantly shorter hospital stay (eWMD = 2.4 days, $p = 0.0005$) and shorter sick leave (eWMD 17.1 days; $p = 0.02$). This meta-analysis showed that ONF and LNF in adults are equally effective in alleviating GOR. However laparoscopy was associated with significantly less morbidity.

In children, there are no similar studies and the results of LNF have been derived from retrospective or prospective non-randomised controlled studies. Following ONF failure rate can be high and re-operation is common, especially in neurologically impaired children (Kawahara et al., 2004; Kimber et al., 1998). Paediatric surgeons who perform the Nissen fundoplication laparoscopically believe that minimally invasive surgery is associated with more rapid postoperative recovery and early discharge from hospital. A study (Tovar et al., 1998) of 27 children who underwent LNF has shown that this technique is as effective as the ONF in reducing the GOR at short-term follow-up (19 months) and results of randomised controlled trials in the adult population show that the laparoscopic procedure is as effective as the open procedure in improving acid reflux at long-term follow-up (Salminen et al., 2007). Nevertheless, there are no studies in children that have objectively evaluated and compared the results after ONF and LNF at long-term follow-up. McHoney and colleagues previously performed a RCT on children assigned to receive ONF or LNF between 2001 and

2004 to evaluate the immediate postoperative metabolic response to surgery (McHoney et al., 2006). The RCT involved 38 children comparing ONF (n = 19) and LNF (n = 19). The aim of this trial was to compare the metabolic, endocrine and inflammatory response to surgery. Children were randomised to either laparotomy or laparoscopy by minimisation (Wade et al., 2006). The results showed that children undergoing LNF have less derangement of total energy metabolism, whole body protein turnover, immunological and inflammatory profile when compared to children undergoing ONF. Postoperative pain, morphine requirement, endocrine response, time to full enteral feeding and duration of hospital stay were similar between the two groups, suggesting that children undergoing LNF recover as quickly from operation as children undergoing ONF. Interestingly, however, the trial found that postoperative retching was significantly less frequent after laparoscopy (11%) compared to open surgery (44%); $p = 0.005$. Retching following fundoplication in children is associated with disturbed gastric electrical control activity resulting in gastric dysrhythmia (Richards et al., 1998), alterations in gastric emptying (Jolley et al., 1987b), and may be related to vagal nerve dysfunction (Lindeboom et al., 2004). Theoretically, the laparoscopic technique could reduce the incidence of vagal nerve dysfunction, and thus retching, by preserving the gastric physiology since during the procedure the dissection and manipulation of oesophagus and stomach are less traumatic compared to the open procedure. Retching is also present in a high percentage (50%) of patients requiring a second fundoplication for recurrent GOR (Kimber et al., 1998). Recurrent GOR is also a significant problem

following Nissen fundoplication. If left untreated, recurrent GOR may cause complications including failure to thrive, aspiration pneumonia, oesophageal stricture and anaemia and may lead to changes in the normal oesophageal mucosa leading to Barrett's oesophagus, which represents a risk factor for development of oesophageal adenocarcinoma (Hassall et al., 1993; Hoeffel, 1997). This may be extremely relevant in children which have a long life expectancy, and may be curable if diagnosed early. Evidence from the literature suggests that the median time from initial fundoplication to the recurrence of GOR in children is 1.5 years (Kimber et al., 1998). Since children randomised in the previous trial were operated at least 36 months prior starting this follow-up study, we were in a position to perform a long-term follow-up to establish which group had the best long-term outcome.

3.2 Aim

Aim of this study was to evaluate the long-term results after ONF and LNF in children. I tested the hypothesis that LNF is associated with a better long-term outcome compared to the ONF.

3.3 Methods

This is a long-term follow study of a previous RCT conducted between 2001 and 2004 on children requiring Nissen fundoplication for GOR (McHoney et al, 2005). Patients were randomized to ONF or LNF using the computer program Minim® (Department of Clinical Epidemiology, London Hospital Medical

School). The minimization criteria used were patient age, neurologic status, and operating surgeon. The aim of the original study was to determine the metabolic response to open and laparoscopic surgery; the power calculation was performed assuming that REE would peak at a higher level in the open group and detection of a difference of 1 SD in the peak REE level between groups, using a significance level of 5%, would have required 16 and 21 per group for 80 and 90% power respectively. All operations were performed by or supervised by 4 consultant surgeons. The surgical techniques of ONF and LNF were standardized, as were the techniques of general anaesthesia and postoperative management and the LNF was performed as described in Chapter 1. The primary outcome of this trial was the immediate post-operative response to open and laparoscopic surgery. Patients in this cohort have been under regular post-operative follow-up and were invited to attend a special follow-up to determine the clinical outcome. The study was performed by myself and I was not involved in the clinical management of the children. Recurrence of GOR was investigated and failure was defined as the presence of recurrent GOR documented by 24-hour pH study ($\text{pH} < 4$ for more than 4% of the time) and/or upper gastro-intestinal contrast study. The 24-hour oesophageal pH monitoring represents the gold standard for quantifying the grade of GOR (Da Dalt et al., 1989) but was not performed in all patients; 11 patients that were asymptomatic at the time of follow-up refused to undergo a repeated pH study and were investigated only by upper gastro-intestinal contrast study. Nutritional status was evaluated for age and sex according to weight and height percentiles, body mass index (BMI) Z-score and weight Z-score were calculated.

Incidence of retching (unsuccessful effort to vomit), gas bloat syndrome (inability to belch and/or “degas” the stomach) and dumping syndrome (presence of flushing, sweating, dizziness, weakness, and vasomotor collapse after eating) was recorded for all patients. A quality of life questionnaire was also performed at the time of follow-up and results are described in detail in Chapter 4.

3.4 *Data Analysis*

Data are reported as median (range) and were compared by repeated measures ANOVA (Friedman test), Mann-Whitney U test, χ^2 test and Fisher's Exact Test using GraphPad Prism 4.03 (GraphPad Software, Inc.®).

3.5 *Results*

Thirty-eight children were randomized to ONF (n = 19) or LNF (n = 19). The groups are comparable with respect to age, weight, neurological status and surgeon performing the operation (Table 3.1).

Table 3.1 – Patients’ demographics from the Nissen fundoplication randomized controlled trial (ONF = open Nissen fundoplication; LNF = laparoscopic Nissen fundoplication).

	ONF	LNF	p value
Randomization	19	19	
Gender (M:F)	9:10	12:7	n.s.
Age at Nissen fundoplication (years)	4.4 (0.4-16.4)	5.5 (0.3-18.6)	n.s.
Weight at Nissen fundoplication (kg)	11.1 (4-37)	16.0 (4.7-43.4)	n.s.
Neurological impairment	15 (79%)	16 (84%)	n.s.
Gastrostomy insertion	8 (42%)	12 (63%)	n.s.
Age at follow-up (years)	8.6 (4.1-20.5)	11.3 (4.8-23.6)	n.s.
Length of follow-up (years)	4.1 (3.1-5.3)	4.1 (2.6-5.1)	ns
Alive at follow-up	16	15	n.s.

Median age at Nissen fundoplication was 4.4 years (0.4 – 16.4) for the open group and 5.5 years (0.3 – 18.6) for the laparoscopic group ($p = \text{n.s.}$).

There were 15 (79%) neurologically impaired children in the open group and 16 (84%) neurologically impaired children in the laparoscopic group ($p = \text{n.s.}$). Eight children (42%) in the open group and 12 (63%) in the laparoscopic group had insertion of gastrostomy at the time of Nissen fundoplication ($p = \text{n.s.}$).

Follow-up was 4.1 years (3.1 – 5.3) for ONF group and 4.1 years (2.6 – 5.1) for LNF group ($p = 0.9$). Sixteen ONF patients and 15 LNF patients were available at follow-up. Seven neurologically impaired children (3 ONF, 4 LNF) died at the

age of 3.6 years (0.6 – 10.1) within 10 months (1.0 – 29.0) after the Nissen fundoplication and the beginning of the study for causes reported in Table 3.2.

Table 3.2 – Characteristics of 7 neurologically impaired children that had died between surgery and the follow-up study (ONF = open Nissen fundoplication; LNF = laparoscopic Nissen fundoplication).

Patient	Nissen	Diagnosis	Gender	Age at Nissen (years)	Months from Nissen to death	Cause of death
1	ONF	Congenital myopathy	Male	0.5	2.9	Progressive respiratory failure
2	ONF	Cerebral palsy, microcephaly	Female	8.9	14.1	Varicella related pneumonia
3	ONF	Lesch-Nyhan syndrome	Male	8.0	23.1	Chronic renal failure
4	LNF	Cerebral palsy, tracheostomy	Male	3.5	1.0	Progressive respiratory failure
5	LNF	Cerebral palsy	Female	1.7	10.0	Progressive encephalitis
6	LNF	Sphingolipidosis	Male	3.5	29.0	Chronic renal failure
7	LNF	Congenital malformation of corpus callosum, epilepsy, tracheostomy	Female	0.3	4.2	Progressive respiratory failure

The failure rate of Nissen fundoplication, as defined in the methods, was similar for the two groups with 2 (12.5%) ONF patients and 3 (20%) LNF presenting with failure ($p = \text{n.s.}$). None of the others were receiving antireflux medications at the time of the follow-up. Four (80%) of the 5 patients with failure were neurologically impaired. One patient in each group required redo-Nissen fundoplication for recurrent GOR not responding to medical treatment. The remaining 3 patients (1 ONF and 2 LNF) with recurrent GOR were successfully managed with medical therapy. Nutritional status improved after surgery in both groups (excluding patients with failure) as indicated by a significant increase in weight Z-score ($p < 0.01$) (Figure 3.1) and BMI Z-score (Figure 3.2).

Figure 3.1 – Weight Z-score in the open and laparoscopic group before and after surgery (follow-up).

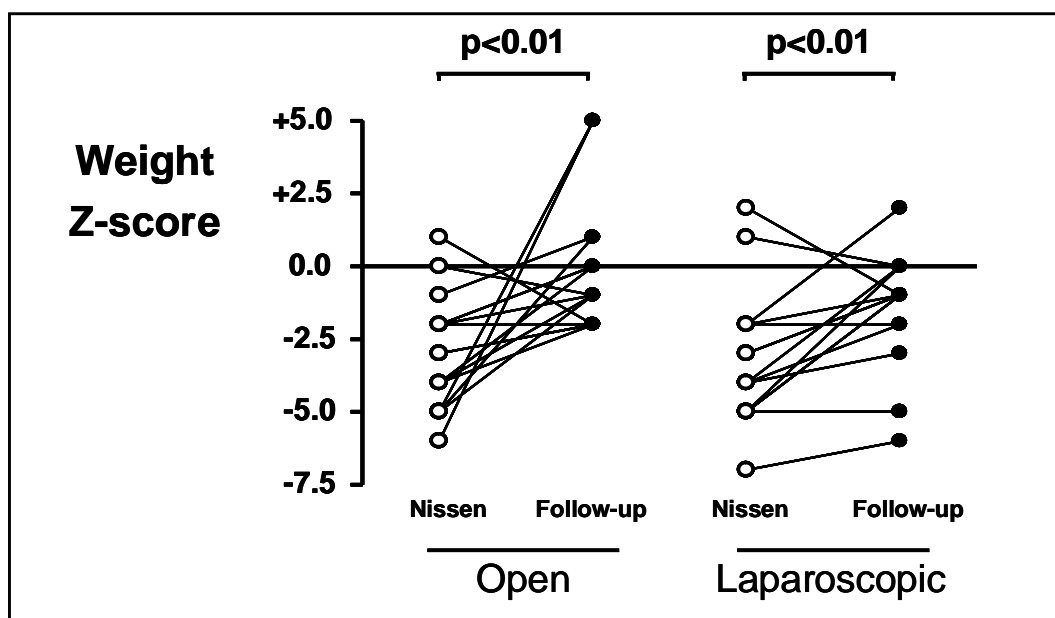
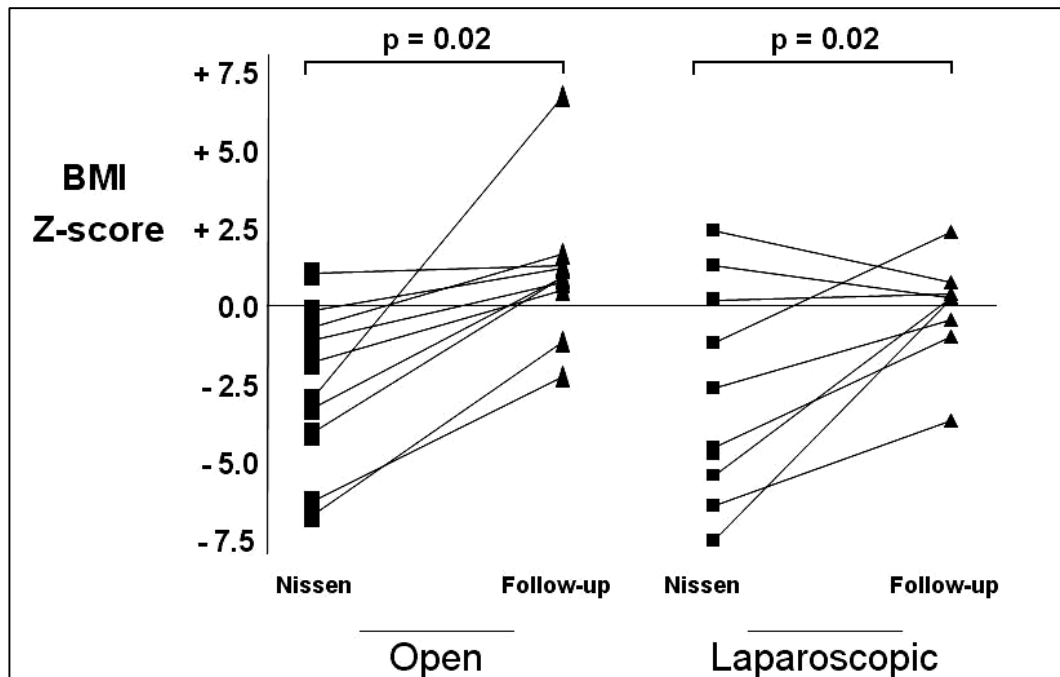


Figure 3.2 – Body mass index (BMI) Z-score in the open and laparoscopic group before and after surgery (follow-up).



Post-operative symptoms are reported in Table 3.3.

Table 3.3 – Post-operative findings at follow-up in 31 surviving patients (16 in open group and 15 in laparoscopic group).

	Open	Laparoscopic	p value
Retching	8 (50%)	1 (7%)	0.01
Gas bloat syndrome	5 (31%)	2 (13%)	n.s.
Dumping syndrome	1 (6%)	1 (6.5%)	n.s.
Any of the above	9 (56.2%)	4 (26.6%)	n.s.

Incidence of retching was significantly higher in the open group compared to the laparoscopic group (50% vs. 7%, $p = 0.01$). Six (66.6%) patients out of the 9 with post-operative retching were neurologically impaired (5 patients in the ONF group and the 1 patient in the LNF group). Nine (70%) patients out of the 13 with any symptoms were neurologically impaired (5 patients in the ONF group and 4 patients in the LNF group, $p = \text{n.s.}$).

3.6 Discussion

This is the first follow-up study of a RCT in children documenting that Nissen fundoplication controls GOR in the majority of children (84%) independently of the technique used (open or laparoscopic). However, LNF seems to be associated with a lower incidence of retching at 4-year follow-up. The ONF has been the treatment of choice in our Institution until 2000, but is an invasive surgical procedure associated with frequent postoperative complications (up to 20%) (Pearl et al., 1990) including gas bloating, retching, vomiting, dumping syndrome and recurrence of reflux (up to 30%) particularly in neurologically impaired children (Kimber et al., 1998; Spitz et al., 1993). The LNF offers the advantage of decreasing the surgical trauma and has become the procedure of choice in many major centres. However its efficacy, particularly in neurologically impaired children, is still questionable (Kawahara et al., 2004). Evidence from the literature suggests that the median time from initial fundoplication to the recurrence of GOR in children is 1.5 years (Kimber et al., 1998). Tovar and colleagues have shown that LNF is as effective as the ONF in reducing the GOR at short-term

follow-up (19 months) (Tovar et al., 1998). Other authors have also reported that laparoscopic fundoplication is a durable procedure in children with a failure rate of 2% at a median follow-up of 3 years (Bourne et al., 2003). The authors concluded that since the majority of wrap failures were reported to occur in the first 2 years postoperatively (Kimber et al., 1998) it could therefore be hoped that the results would remain good and that laparoscopic fundoplication in children was as durable as the open procedure. Furthermore long-term results of randomised controlled trials in the adult population show that the laparoscopic procedure is as effective as the open procedure in improving acid reflux (Salminen et al., 2007). Nonetheless, there are no studies that have objectively evaluated and compared the incidence of recurrent GOR in children after ONF or LNF at long term follow-up. In the current study we have investigated the results of the two techniques at a median follow-up of 4.1 years (at least 2.6 years from surgery). Importantly, the randomisation, which minimised for neurological status and age, at the start of the previous trial led to a similar distribution of neurologically impaired children in each arm of the trial, and similar age of children. We also tried to minimise the risk of bias associated with the researcher being part of the surgical team by having an independent surgeon performing the follow-up. We have a failure rate of 16% with similar results in the two groups and one patient in each group requiring redo-Nissen fundoplication. Nutritional status was similarly improved in both groups, as indicated by a significant increase in weight Z-score ($p < 0.01$) and BMI Z-score ($p = 0.02$ in ONF and $p = 0.02$ in LNF). Gas bloat and dumping syndrome were also similar in both groups

($p = \text{n.s.}$). Interestingly, we found that postoperative retching was significantly more frequent after ONF (50%) compared to LNF (7%), ($p = 0.01$). Similarly Bourne and colleagues reported a 13% incidence of retching following LNF (Bourne et al., 2003). The presence of retching after Nissen fundoplication might play a major role in wrap migration, wrap disruption and recurrence of GOR at long-term follow-up. RCT in adults comparing the ONF and LNF have shown higher incidence of dysphagia in laparoscopically operated patients. Bais and colleagues (Bais et al., 2000) reported a significantly higher incidence of dysphagia in the laparoscopic arm leading to early conclusion of the trial. However, in the recently published long-term follow-up study of this trial (Broeders et al., 2009), the authors found no differences in post-operative dysphagia between the two groups. Other RCT also reported similar postoperative dysphagia incidence in both groups (Ackroyd et al., 2004; Chrysos et al., 2002; Nilsson et al., 2004). It is possible that the mechanism leading to post-operative dysphagia in adults and retching in children (particularly in the neurologically impaired children) is different. Retching after antireflux surgery occurs in 20% to 40% of children, being more common in neurologically impaired children (Jolley et al., 1987c; Richards et al., 2001). In our series 66.6% of children with post-operative retching were neurologically impaired. Retching following fundoplication in children might be related to handling of the stomach that could impair autonomic pathways and it is associated with disturbed gastric electrical control activity resulting in gastric dysrhythmia, alterations in gastric emptying (Jolley et al., 1987c; Richards et al., 2001), and may be related to vagal nerve

dysfunction (Lindeboom et al., 2004). During the laparoscopic Nissen fundoplication the lower oesophagus is carefully exposed by sharp and blunt dissection around each side; the magnification provided by laparoscopy helps to clearly demonstrate the anterior and posterior vagal trunks coursing the oesophagus leading to reduction in the incidence of vagal nerve dysfunction and to preservation of the normal gastric motility.

3.7 Conclusions

This is the first follow-up study of a RCT in children requiring Nissen fundoplication. Open and laparoscopic operations provide similar control of the GOR after 4.1 year of follow-up. The study clearly demonstrated that LNF is associated with reduced incidence of retching, a finding not previously reported in children. The reduced incidence of retching with the laparoscopic technique might positively affect the failure rate at long-term follow-up.

Chapter 4

Quality of Life Following Open and Laparoscopic Nissen Fundoplication

4.1 Introduction

The quality of life in adults with gastro-oesophageal reflux disease (GOR) has been thoroughly investigated and it has been shown that GOR impose a significant burden on individuals in several studies that have used validated questionnaires (Dubois et al., 2007; Jones et al., 2007; Liker et al., 2005; Ronkainen et al., 2006; Wiklund et al., 2006). Indeed, even mild reflux symptoms have been shown to impair health-related quality-of-life (Wiklund et al., 2006). The burden associated with reflux symptoms involves impaired physical activity, psychosocial well-being and daily functioning, as well as reduced vitality and disturbed sleep. In adults this is particularly important since it can lead to reduced work productivity, which incurs substantial economic costs (Wahlqvist et al., 2006; Wahlqvist et al., 2008).

Recent studies (Borie et al., 2010) have investigated the long-term quality-of-life before and after laparoscopic Nissen fundoplication (LNF) in adults and documented that patients who undergo surgery after failure of medical treatment for GOR can expect an improved quality of life, although they may not be able to achieve normal levels. Other studies (Broeders et al., 2009) have confirmed that LNF is comparable to the open Nissen fundoplication (ONF) in terms of improvement of GOR symptoms and quality of life.

The prevalence of GOR is high in infancy (Campanozzi et al., 2009) and falls after 12 months of age (Hassall, 2005a). However, it continues to be a source of morbidity in children and adolescents, significantly affecting the quality of life of large number of families. Particularly, neurologically impaired children often are

totally dependent on caregivers for daily existence and caregiver satisfaction with the Nissen fundoplication should be taken into account in defining the quality of life following surgery. Bourne and colleagues (Bourne et al., 2003) followed up a cohort of children after LNF for a median of 3 years reporting that this technique is a durable procedure with a high degree of parental satisfaction. Nonetheless, there are no studies that have objectively compared the, parental or caregiver satisfaction following ONF and LNF in children.

4.2 Aim

Aim of the present study was to determine if Nissen fundoplication improves quality of life in children with GOR and to compare the results in children undergoing open or laparoscopic surgery.

4.3 Methods

The population of this study included 38 children that were part of the RCT comparing ONF and LNF for GOR as described in chapter 3 (see section 3.3 *Methods*). A standardized questionnaire (O'Neill et al., 1996) was used to assess the quality of life before surgery, six months after surgery and at follow-up. I performed this study and I was not involved in the clinical management of the children.

4.3.2 Quality of Life Questionnaire

The questionnaire was derived and adapted from a previously validated and published questionnaire (O'Neill et al., 1996). The questionnaire consisted of three different parts:

- The first part investigates the “Daily Care and the Overall Condition of The Child” and includes 8 different questions to assess the feeding, intestinal problems, presence of respiratory symptoms, comfort of the child and child developmental progress. The following questions were asked:

1. How easy is feeding your child?
2. Do you think your child is in pain while feeding?
3. How often your child does have a bowel movement?
4. Is your child often bloated?
5. How often your child has a chest infection?
6. Does your child look overall comfortable?
7. How would you rate your child’s ability to enjoy life?
8. How would you rate your child’s developmental progress?

- The second part investigates the “Child’s and Parents’ Overall Quality of Life” and includes 6 questions to assess the ease of caring for the child, the enjoyment of the child and the overall quality of life. The following questions were asked:

1. How easy is caring for your child?
2. How much do you enjoy spending time with your child?

3. How would you rate the quality of time that you spend with your child?
 4. What is your level of frustration in taking care of your child?
 5. What is your level of concern in taking care of your child?
 6. How would you rate your overall quality of life?
- The third part investigates the “Child’s Special Medical Needs” and includes 2 questions to assess the time spent for special medical needs and number of visits to doctors or health care programs. These questions were asked:
 1. How much time do you spend caring for your child’s medical and physical needs?
 2. How many times have you visited your doctor or hospital in the last 3 months?

Each question scored from 1 (best) to 5 (worst). Parents were also asked to classify the results of surgery “better than expected”, “about as expected” and “worse than expected”.

4.4 Data Analysis

Data are reported as median (range) with interquartile range, mean \pm SD and were compared by repeated measures ANOVA (Friedman test), Mann-Whitney U test, χ^2 test and Fisher's Exact Test using GraphPad Prism 4.03 (GraphPad Software, Inc.®).

4.5 Results

At the time of follow-up there were 16 children alive in the open group and 15 in the laparoscopic group (Table 4.1). There were 15 (72%) neurologically impaired (NI) children in the open group and 16 (84%) in laparoscopic group ($p = \text{n.s.}$).

The questionnaire was completed in 13 (81%) of the families in the open group and 11 (73%) of the families in the laparoscopic group.

Table 4.1– Patients’ demographics from the Nissen randomised controlled trial (ONF = open Nissen fundoplication; LNF = laparoscopic Nissen fundoplication).

	ONF	LNF
Randomisation	19	19
Alive at follow-up	16	15
Completed questionnaire	13/16 (81%)	11/15 (73%)
Redo-Nissen fundoplication	1	1
Follow-up (years)	4.1 (3.1-5.3)	4.1 (2.6-5.1)

The outcome of surgery is reported in Table 4.2. The overall parents' satisfaction following surgery was significantly high: 62% in the ONF and 73% in the LNF groups described the operation as “better than expected” ($p = \text{n.s.}$), 38% and 27% respectively described the operation as “about as expected” ($p = \text{n.s.}$). None of the families described the operation as “worse than expected”.

Table 4.2 – Outcome of surgery in the open (ONF) and laparoscopic (LNF) Nissen fundoplication group.

	ONF	LNF	p value
Better than expected	62%	73%	n.s.
As expected	38%	27%	n.s.
Worse than expected	0%	0%	n.s.

The results of the quality of life questionnaire regarding the daily care and the overall condition of the child are summarized in Table 4.3 and Figure 4.1. Daily care and overall condition of the child improved significantly 6 months after surgery and at follow-up. Significant improvement was perceived in the ease of feeding and physical comfort during feeding. Parents felt that postprandial discomfort improved after the operation. The comfort of the child and the ability of the child to enjoy life also improved significantly after the surgery. There were no differences between the ONF and LNF group.

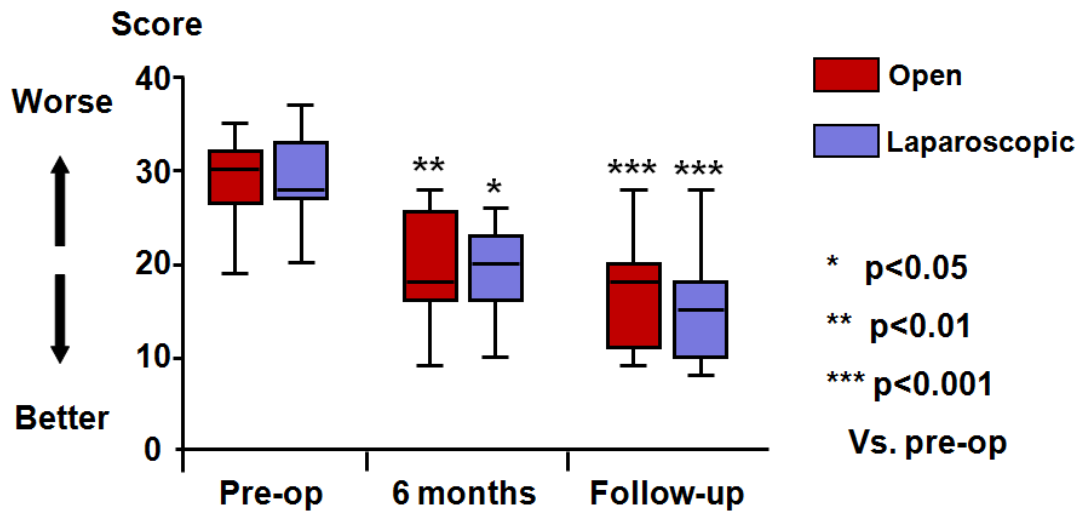
Table 4.3 – Daily care and the overall condition of the child (Mean \pm SD) in the open (ONF) and laparoscopic (LNF) Nissen fundoplication group.

Scale: 1, Excellent; 2, Good; 3, Average; 4, Poor; 5, Terrible.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs. 6 months before surgery

	ONF	LNF
Ease of feeding		
6 months before surgery	4.3 \pm 0.7	4.1 \pm 1.0
6 months immediately post-surgery	2.6 \pm 0.9***	2.5 \pm 1.2**
At follow-up	2.2 \pm 0.9***	1.5 \pm 0.8***
Physical comfort during feeding		
6 months before surgery	3.9 \pm 1.3	4.1 \pm 1.0
6 months immediately post-surgery	2.4 \pm 1.1*	2.8 \pm 1.2*
At follow-up	2.3 \pm 1.3*	1.7 \pm 1.1***
Constipation		
6 months before surgery	1.7 \pm 1.3	2.4 \pm 1.6
6 months immediately post-surgery	1.8 \pm 1.3	2.4 \pm 1.6
At follow-up	1.6 \pm 1.3	2.2 \pm 1.5
Gas-bloat		
6 months before surgery	2.4 \pm 1.1	1.6 \pm 1.5
6 months immediately post-surgery	2.4 \pm 1.0	2.5 \pm 1.6
At follow-up	2.6 \pm 1.0	2.2 \pm 1.1
Pneumonias		
6 months before surgery	4.3 \pm 0.6	3.5 \pm 1.2
6 months immediately post-surgery	2.6 \pm 1.3**	2.1 \pm 0.9**
At follow-up	2.3 \pm 1.4***	2.2 \pm 1.2**
Comfort of child		
6 months before surgery	4.1 \pm 1.1	4.4 \pm 0.5
6 months immediately post-surgery	2.1 \pm 1.2***	2.1 \pm 0.7***
At follow-up	1.7 \pm 0.9***	1.7 \pm 1.0***
Child's ability to enjoy life		
6 months before surgery	4.2 \pm 1.1	4.4 \pm 0.5
6 months immediately post-surgery	2.7 \pm 1.1**	2.1 \pm 0.8***
At follow-up	1.9 \pm 1.1***	1.7 \pm 0.9***
Child's developmental progress		
6 months before surgery	3.6 \pm 1.2	3.8 \pm 0.9
6 months immediately post-surgery	2.6 \pm 1.0**	2.6 \pm 0.9*
At follow-up	1.9 \pm 0.9***	2.0 \pm 0.9***

Figure 4.1 – Daily care and overall condition of the child in the open and laparoscopic Nissen fundoplication group (median, IQR, range).



The child's and parental overall quality of life also improved 6 months after surgery and at follow-up when compared to the 6 months prior to surgery (Table 4.4 and Figure 4.2). Particularly, parents reported that caring for the child was much easier and the quality of time spent with the child was much improved postoperatively. There was a significant improvement in the caregiver's level of frustration and concern with respect to caring for the child. There were no differences between the ONF and LNF group.

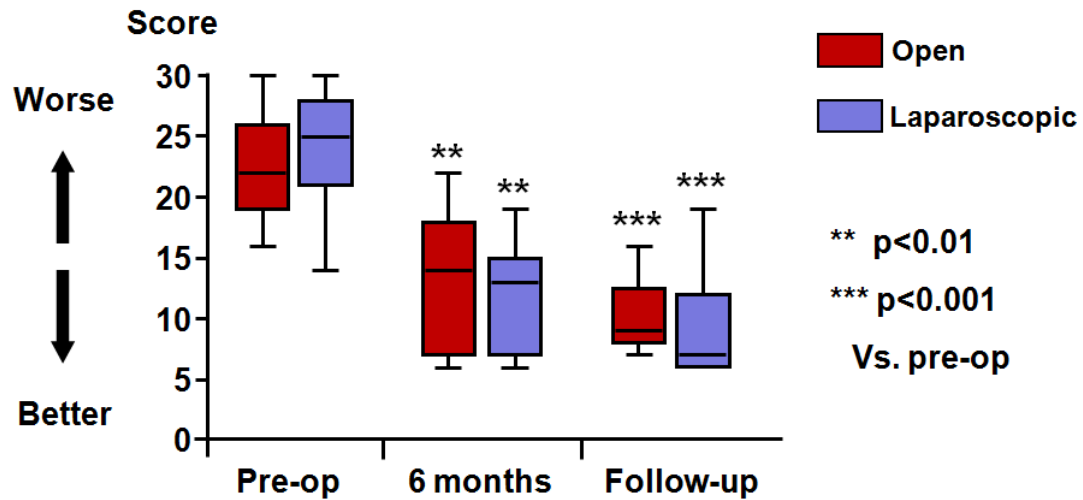
Table 4.4 – Child’s and parental overall quality of life (Mean \pm SD) in the open (ONF) and laparoscopic (LNF) Nissen fundoplication group.

Scale: 1, Excellent; 2, Good; 3, Average; 4, Poor; 5, Terrible.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs. 6 months before surgery

	ONF	LNF
Overall ease of caring for the child		
6 months before surgery	4.3 \pm 0.7	4.3 \pm 0.6
6 months immediately post-surgery	2.4 \pm 1.0***	2.0 \pm 0.8***
At follow-up	2.2 \pm 0.5***	1.9 \pm 1.2***
Overall enjoyment of the child		
6 months before surgery	3.9 \pm 0.9	4.0 \pm 1.1
6 months immediately post-surgery	2.1 \pm 1.1***	2.1 \pm 1.0***
At follow-up	1.6 \pm 0.7***	1.4 \pm 0.6***
Quality of time spent with the child		
6 months before surgery	4.1 \pm 1.1	4.1 \pm 0.7
6 months immediately post-surgery	1.2 \pm 1.3***	2.1 \pm 0.9***
At follow-up	1.5 \pm 0.7***	1.8 \pm 1.0***
Level of frustration		
6 months before surgery	3.6 \pm 1.1	3.9 \pm 1.2
6 months immediately post-surgery	2.4 \pm 1.1**	2.3 \pm 1.2**
At follow-up	1.7 \pm 0.7***	1.6 \pm 1.0***
Level of concern		
6 months before surgery	2.4 \pm 1.5	3.0 \pm 1.5
6 months immediately post-surgery	2.0 \pm 1.0	1.5 \pm 0.9**
At follow-up	1.1 \pm 0.3***	1.0 \pm 0.3***
Overall quality of life		
6 months before surgery	4.1 \pm 0.6	4.1 \pm 0.7
6 months immediately post-surgery	2.3 \pm 0.8***	1.9 \pm 1.0***
At follow-up	1.7 \pm 0.7***	1.5 \pm 0.6***

Figure 4.2 – Child’s and parental overall quality of life in the open and laparoscopic Nissen fundoplication group (median, IQR, range).



Finally, the child’s special medical needs also improved significantly at 6 months and at follow-up after surgery (Table 4.5 and Figure 4.3). With respect to their child's special medical needs, the amount of time spent caring for a child's needs was decreased significantly postoperatively with decreased physician/hospital visits. There were no differences between the ONF and LNF group.

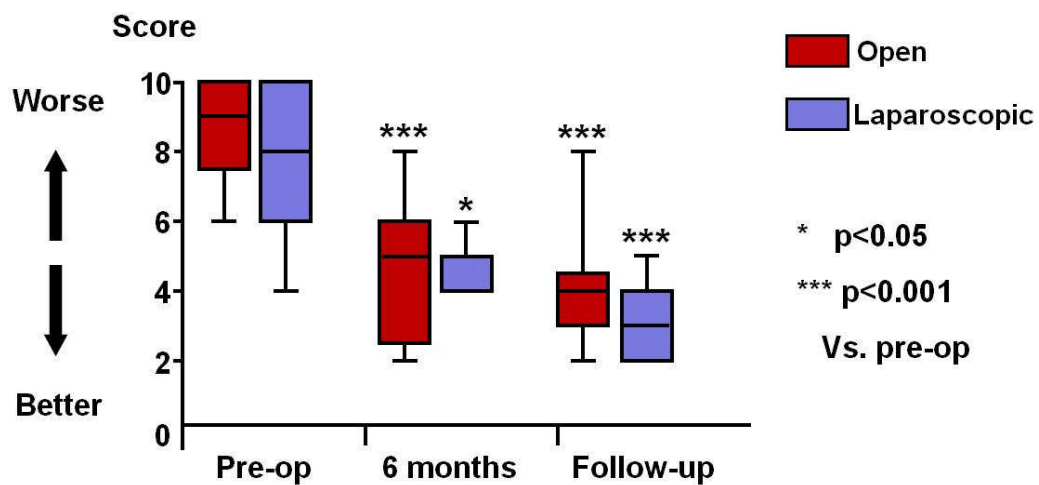
Table 4.5 – Child’s special medical needs (Mean \pm SD) in the open (ONF) and laparoscopic (LNF) Nissen fundoplication group.

Scale: 1, Excellent; 2, Good; 3, Average; 4, Poor; 5, Terrible.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs. 6 months before surgery

	ONF	LNF
Time for medical/physical needs		
6 months before surgery	4.2 ± 0.8	3.7 ± 1.1
6 months immediately post-surgery	$2.2 \pm 1.0^{***}$	$2.2 \pm 0.4^{***}$
At follow-up	$1.8 \pm 0.8^{***}$	$1.8 \pm 0.6^{***}$
Visits to doctors and hospital		
6 months before surgery	4.4 ± 0.7	3.9 ± 1.2
6 months immediately post-surgery	$2.3 \pm 1.0^{***}$	$2.1 \pm 0.4^{***}$
At follow-up	$2.1 \pm 0.8^{***}$	$1.4 \pm 0.5^{***}$

Figure 4.3 – Child’s special medical needs in the open and laparoscopic Nissen fundoplication group (median, IQR, range).



Overall, the care-givers felt that they were informed about the operation and about what to expect postoperatively; 12 families (92%) in the open group and 8 (72%) ($p = 0.3$) families in the laparoscopic group strongly agreed when asked if they were fully informed about what to expect as result of the surgery.

4.6 Discussion

GOR is a common condition in children and adolescents and recent surveys shows that up to 8.2% of children and adolescents aged 10 to 17 years reported experiencing heartburn, epigastric pain, and regurgitation significantly affecting their quality of life (Nelson et al., 2000). GOR is particularly common in neurologically impaired children that are often totally dependent on caregivers for daily existence and caregiver satisfaction with the Nissen fundoplication should be taken into account in defining the quality of life following surgery. There are no studies that have objectively assessed the, parental or caregiver satisfaction following ONF and LNF in children.

In adults, recent studies (Borie et al., 2010) have investigated the long-term quality-of-life before and after LNF and documented that patients who undergo surgery after failure of medical treatment for GOR can expect an improved quality of life, although they may not be able to achieve normal levels. Other studies (Broeders et al., 2009) have confirmed that LNF is comparable to ONF in terms of improvement of GOR symptoms and quality of life. The Nissen fundoplication has been an established

method for treating GOR in children with generally excellent results as documented in large series (Fonkalsrud et al., 1998). Many studies have documented that the Nissen fundoplication has a low rate of morbidity, mortality, and reoperation with good control of the GOR. Nonetheless, postoperative dysphagia, retching, dumping and gasbloat are acknowledged to be serious postoperative problems that can compromise the quality of life of the patients and families even in the absence of recurrent GOR particularly in neurologically impaired children. Thus, to be considered successful, surgery must improve quality of life for the child as well as the care-giver. Consequently, some centres treating neurologically impaired children perform less antireflux surgery or choose other less invasive procedures (Gilger et al., 2004; Hassall, 2005b; Orenstein et al., 2001) to reduce postoperative dysphagia, retching, dumping and gasbloat that have negative effects on the quality of life. Few studies have focused on parental satisfaction after antireflux surgery (O'Neill et al., 1996). We found that the majority of the parents were satisfied with the result after the Nissen fundoplication. Better quality of life based on care-givers evaluation was found both after ONF and after LNF after a median of 4.1 years. Improvement from severe vomiting is the most plausible explanation for the positive outcome of surgery. Nonetheless, the improved ease of feeding and physical comfort during feeding, together with an improved ability of the child to enjoy life might have certainly contributed to the better overall quality of life. In this respect, the gastrostomy was performed in more than 50% of children (Chapter 3, Table 3.1) and might have influenced the child's condition by improving the ease of feeding; prior to surgery

these children were mainly fed by naso-gastric tube that has numerous disadvantages including frequent dislodgment, nose bleeding and skin excoriation caused by repeated applications and removals of plasters. We also believe that the reduction of the amount of time spent caring for the child's needs and the decreased numbers of physician/hospital visits had a significant effect in the parents' satisfaction following surgery and this is particularly important since it can lead to improved work productivity and reduced economic costs for the family.

Finally, none of the parents of impaired children in our study said that the condition of the child got worse after the Nissen fundoplication although more than 30% of the family described the results of surgery “about as expected”.

4.6 Conclusions

In conclusion, the vast majority of parents and caregivers of children that undergo a Nissen fundoplication for GOR assess their child to have benefited from the surgery at long-term follow-up. Open and laparoscopic operations appear to provide similar quality of life at follow-up.

Chapter 5

Gastric Emptying Following Laparoscopic Nissen Fundoplication

5.1 Introduction

The relationship between gastro-oesophageal reflux (GOR) and gastric emptying (GE) in children remains controversial and the effects on gastric motility following Nissen fundoplication are poorly understood. Some authors (Jolley et al., 1987a; Rosen et al., 1984; Spiroglou et al., 2004) have found no correlation between GOR and GE although severe GOR has been reported associated with delayed GE by other authors (Argon et al., 2006; Aktas et al., 1999; Cucchiara et al., 1997; Estevao-Costa et al., 2001), particularly in neurological impaired children. Following Nissen fundoplication children may present symptoms related to an abnormal gastric motility (Jolley et al., 1987c; Samuk et al., 1996; Vu et al., 1999), and for this reason some paediatric surgeons advocate additional procedures at the same time of fundoplication, such as a pyloroplasty or pyloromyotomy, to enhance GE (Bustorff-Silva et al., 1999; Bustorff-Silva et al., 2000; Fonkalsrud et al., 1992; Fonkalsrud et al., 1995; Okuyama et al., 1997). Nevertheless, it has been documented that post-Nissen patients have a significantly reduced postprandial gastric relaxation and significantly accelerated GE (Vu et al., 1999) and indeed, some authors have reported that the addition of a draining procedure to the fundoplication provides no further benefit (Maxson et al., 1994; Mousa et al., 2006). The Nissen fundoplication is increasingly performed laparoscopically which may results in fewer disturbances to gastric motility possibly due to less trauma to the vagus nerves and stomach since it is easier to demonstrate the anterior and posterior vagal trunks during the laparoscopic

dissection but the effects on gastric motility of this technique have not been investigated.

5.2 Aim

Aim of this study was to determine whether laparoscopic Nissen fundoplication (LNF) without pyloroplasty affects GE.

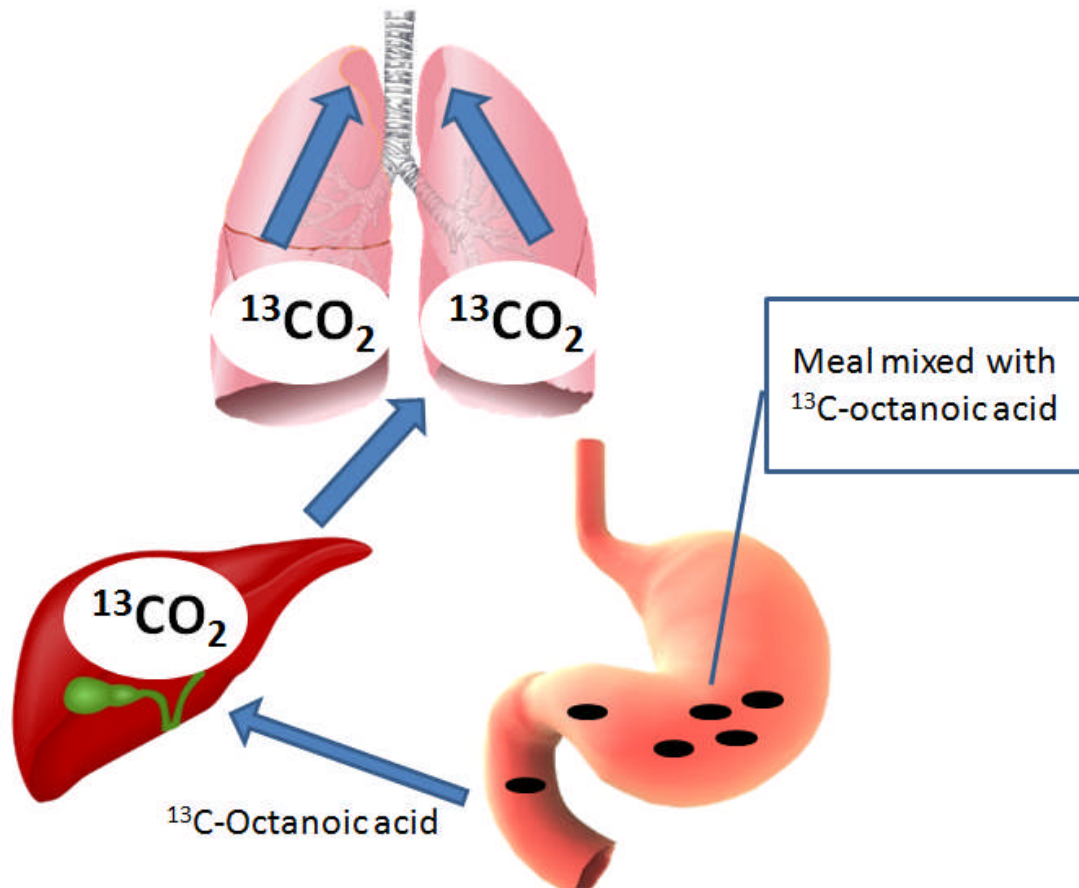
5.3 Methods

5.3.1 Measurement of Gastric Emptying Time

Gastric emptying time (GE_{t1/2}) was measured by the ¹³C-octanoic acid breath test (¹³C-OBT). This non-invasive test (Ghoos et al., 1993; Maes et al., 1994; Veereman-Wauters et al., 1996) has been used successfully to assess GE_{t1/2} in infants and children. The main advantage of breath test technology is represented by the lack of radiation burden. Moreover, breath tests are non invasive, non operator-dependent and can be performed several times in the same subject without biological hazard. The method relies on the rapid absorption (in the duodenum) and metabolism (to ¹³CO₂) of ¹³C-octanoic acid. The rationale of the ¹³C-OBT to measure GE is based on the retention of ¹³C-octanoic acid in the test meal during its passage through the gastric environment, followed by a rapid disintegration in the duodenum with

subsequent absorption of ^{13}C -octanoic acid and hepatic oxidation to $^{13}\text{CO}_2$ (Figure 5.1).

Figure 5.1 – ^{13}C -octanoic acid breath test.



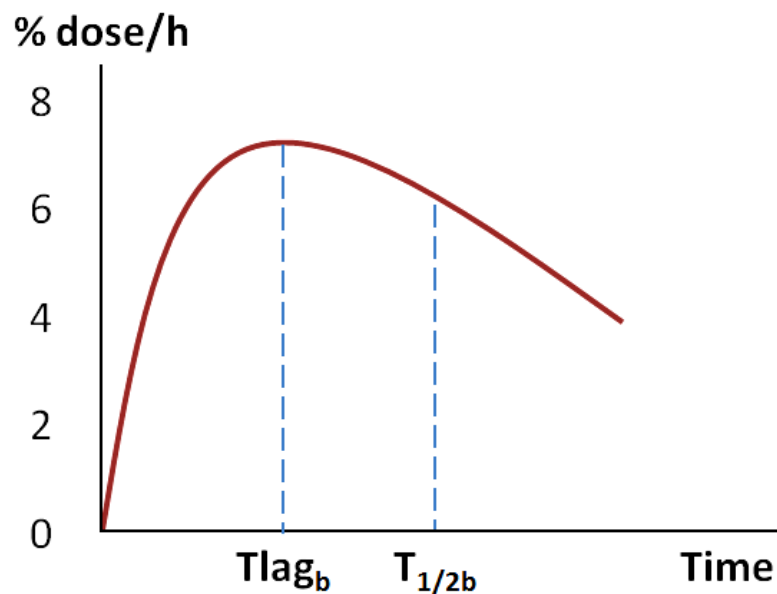
Once the meal reaches the duodenal lumen, ^{13}C -octanoic acid is rapidly absorbed through intestinal mucosa and oxidised to $^{13}\text{CO}_2$ in liver. The appearance of $^{13}\text{CO}_2$ in breath after oral administration of ^{13}C -octanoic depends mainly on the GE of the test meal into the duodenum (rate-limiting step). The other metabolic steps (absorption

and oxidation) do not influence the rate of breath $^{13}\text{CO}_2$ excretion as shown by studies (Ghoos et al., 1993) in which, after duodenal instillation of ^{13}C -octanoic acid, $^{13}\text{CO}_2$ appears in breath almost immediately with a very little inter-subject variability.

5.3.2 Mathematical Analysis of $^{13}\text{CO}_2$ Excretion Curves for Gastric Emptying

A percentage of dose/h curve after ingestion of a ^{13}C -octanoic acid labelled test meal is characterized by an ascending slope, a peak of excretion, and a descending exponential slope (Figure 5.2).

Figure 5.2 – $^{13}\text{CO}_2$ breath excretion curve (in % dose/h).



In the formula by Ghooos (Ghooos et al., 1993), the cumulative dose of $^{13}\text{CO}_2$ excreted as a function of time is given by:

$$z = m (1 - e^{-kt})^b$$

where z is the cumulative dose of $^{13}\text{CO}_2$ excreted in breath per hour; t is the time (in hours); m , k , and b are estimated regression constants, with m the total amount of $^{13}\text{CO}_2$ recovered when time is infinite. As the curve z (% cumulative dose curve) is obtained after integration of a curve z' (% dose/h curve), the curve z' can be expressed as:

$$z' = mkbe^{-kt}(1 - e^{-kt})^{b-1}$$

Non linear regression analysis is performed on the data of the curve z' to estimate m , k and b , using the least square method. This analysis can be easily performed by using the “Solver” procedure in Excel® (Microsoft). Two parameters can be derived from this formula:

$$t_{1/2\text{exc}} = (-1/k) \ln (1 - 2^{-1/b})$$

i.e. the area under the fitted curve until half of the dose of CO_2 is excreted of the cumulative $^{13}\text{CO}_2$ excretion when time is infinite, and

$$t_{\text{lagexc}} = (\ln \beta)/k$$

i.e. the time corresponding to the maximum of the curve z' .

5.3.3 Test Meal

The test was performed before and after the LNF in children after ingestion of a standardised volume for different age of milk or milk-shake mixed with 1 mg/ml of ^{13}C -octanoic acid up to a maximum of 150 mg.

The volume of milk was chosen according to the age of the child as follows:

- **Newborn (birth – 1 month):**

Weight: 2 – 6 kg	50 ml
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- **Infant (1 – 23 months):**

Weight: 6 – 10 kg	100 ml
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- **Preschool child (2 – 5 years):**

	150 ml
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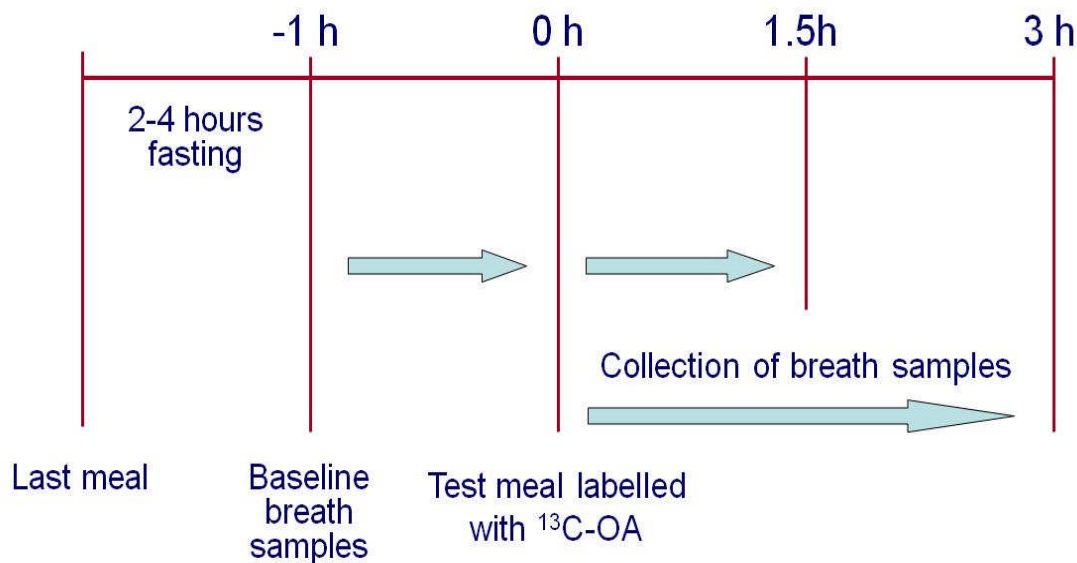
- **Child (6 – 12 years):**

	150 ml
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5.3.4 Samples Collection and Analysis

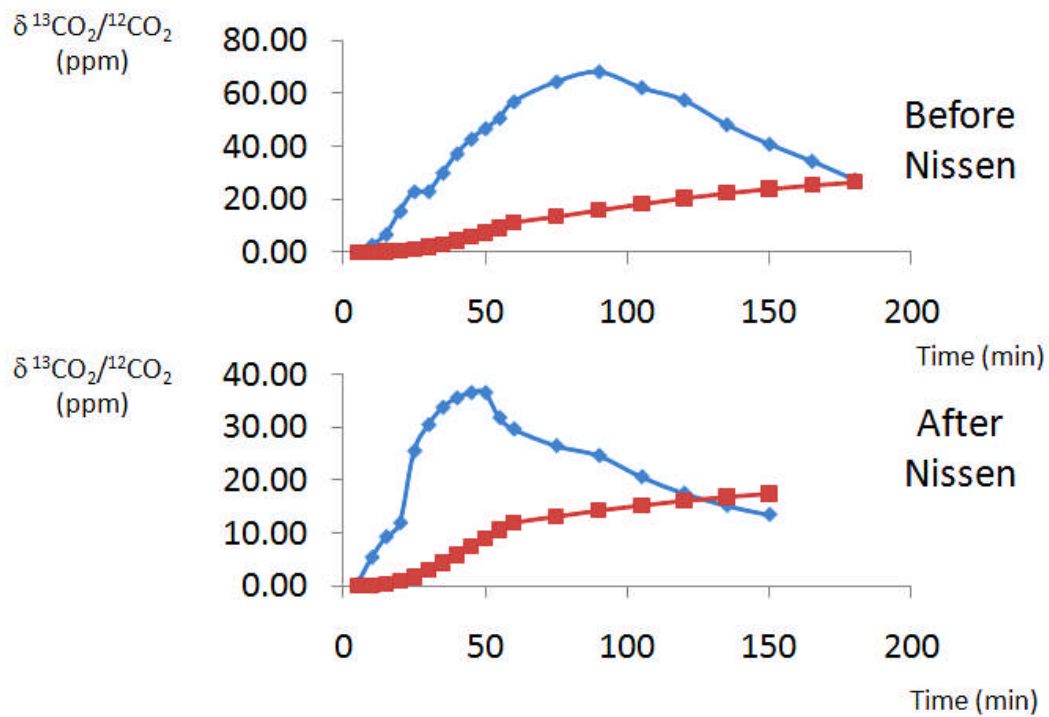
Breath samples were collected using a 10 ml syringe connected to a facial mask at baseline (2 – 4 hours after the last meal and 1 hour before the ingestion of ^{13}C -octanoic acid) and every 15 minutes up to 3 hours (Figure 5.3).

Figure 5.3 – Timeframe for sample collection.



The air was transferred into 10 ml vacuum test tubes (Labco Limited®, High Wycombe, United Kingdom) for the analysis. Breath CO_2 was analysed for $^{13}\text{CO}_2/^{12}\text{CO}_2$ enrichment by gas chromatography on a CP-Poraplot-Q column (Varian Inc.®, Oxford, U.K.) followed by isotope ratio mass spectrometry on a Thermo Finnigan Delta-XP (Thermo Finnigan®, Bremen, Germany) as described in Chapter 2. Sample $^{13}\text{CO}_2/^{12}\text{CO}_2$ enrichment was standardised against a CO_2 cylinder (5.0 grade, BOC Special Gases®, Guildford, Surrey, UK), which had been calibrated against the international standard PDB (Iso-Analytical®, Sandbach, Cheshire UK). $\text{GEt}_{1/2}$ was derived from the curve of $^{13}\text{CO}_2/^{12}\text{CO}_2$ ratio against time as reported by Maes et al (Maes et al., 1995) (Figure 5.4).

Figure 5.4 – $^{13}\text{CO}_2$ breath excretion in $\delta^{13}\text{CO}_2/^{12}\text{CO}_2$ part per million (ppm) in one patient (blue line) before and after the laparoscopic Nissen fundoplication. $\text{GET}_{1/2}$ was 80.05 minutes (delayed) pre-operatively and 48.16 minutes (normal) post-operatively. Red line: cumulative $^{13}\text{CO}_2$ recovery.



5.3.5 Laparoscopic Technique

The LNF was performed as described in Chapter 1. Briefly: a 5 mm Hasson cannula was inserted under direct vision just above the umbilicus and CO_2 pneumoperitoneum was established with a pressure of 10 – 15 mmHg and flow rate of 2 – 4 litres per minute. A 30° laparoscope was used for inspection of the intestine and intraperitoneal contents. Ports of 5 mm diameter were inserted in the right flank and left flank for the

operating instruments. A Nathanson liver retractor was inserted at the epigastrium to retract the liver superiorly. A 360° floppy Nissen fundoplication was performed following repair of the oesophageal hiatus with non-absorbable sutures.

5.3.5 Patients' selection

This was a pilot study designed to determine whether laparoscopic Nissen fundoplication (LNF) without pyloroplasty affects GE. No similar studies were previously conducted and no data were available from the literature to perform a power calculation to determine the sample size. Instead, the sample size of maximum 10 patients was chosen based on the study feasibility.

5.4 Data Analysis

Data are reported as median and range or mean \pm SD and were analysed by Mann-Whitney U Test using Prism 4.03 software (GraphPad Software Inc.®, San Diego, USA). Results with a $p < 0.05$ were considered significant.

5.5 Results

Eight consecutive children undergoing LNF for clinically significant GOR were enrolled in this prospective non-randomised study (Table 5.1).

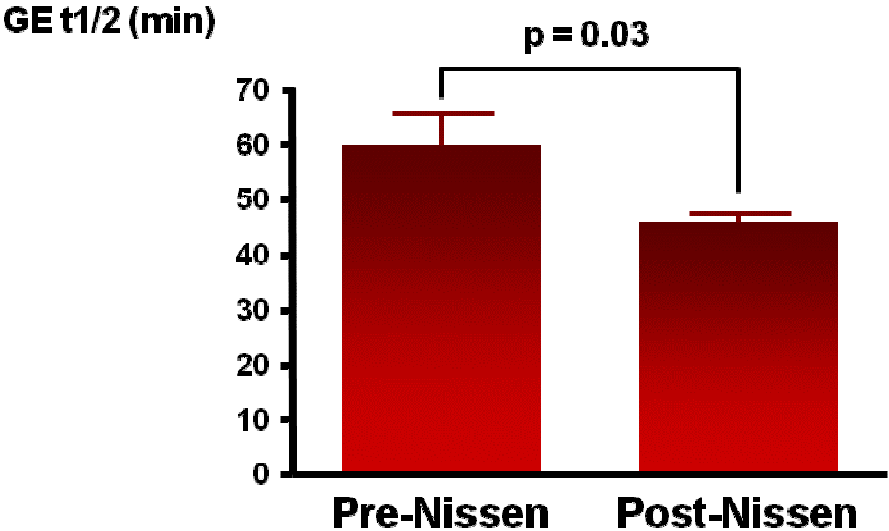
Table 5.1 – Patients demographics.

Male:Female	4:4
Age at surgery	3.3 ± 3.0 years
Median time to start feeding	28 hours (24-36)
Time to full feed	3 days (2-4)

LNF was successfully completed in all patients. None of the patients underwent GE procedures or insertion of gastrostomy tube prior or at the time of fundoplication. There was no macroscopically visible damage to the two branches of vagus nerve during the operation and no other intra-operative or post-operative complications.

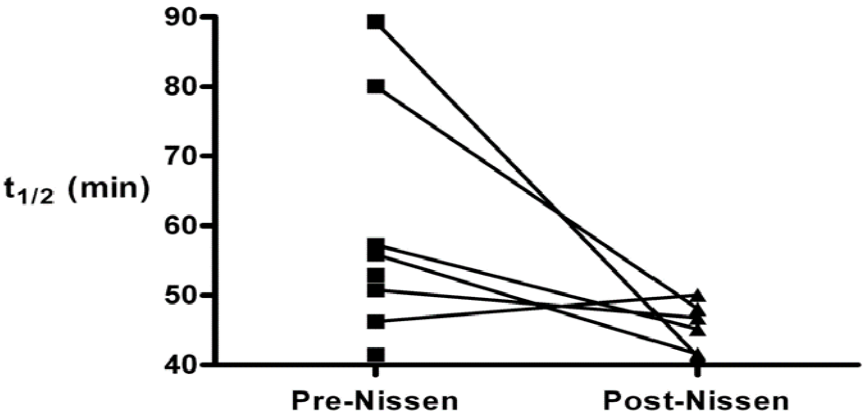
The median time to start enteral feeding was 28 hours (24 – 36) and the time to full feed was 3 days (2 – 4). Six children were available for the post-operative study. Mean $GEt_{1/2}$ was 59 ± 17 min prior to LNF and was 45 ± 4 min following surgery ($p = 0.03$) (Figure 5.5).

Figure 5.5 – Mean (SD) GE_{t1/2} before and after laparoscopic Nissen fundoplication.



GE was accelerated following the LNF in all except one patient (Figure 5.6).

Figure 5.6 – Gastric emptying $t_{1/2}$ (minutes) in each patient before and after laparoscopic Nissen fundoplication.



5.6 Discussion

The relationship between GOR and GE in children remains controversial and gastric motility following fundoplication is poorly understood. Some authors (Jolley et al., 1987a; Rosen et al., 1984; Spiroglou et al., 2004) have found no correlation between GOR and GE although severe GOR has been reported associated with delayed GE by other authors (Argon et al., 2006; Aktas et al., 1999; Cucchiara et al., 1997; Estevao-Costa et al., 2001), particularly in neurological impaired children. Surgery (with or without pyloroplasty) may unmask underlying gastric and small bowel dysmotility by delivering gastric contents more rapidly to the small bowel. Some paediatric surgeons (Bustorff-Silva et al., 1999; Bustorff-Silva et al., 2000; Fonkalsrud et al., 1992; Okuyama et al., 1997) advocate additional procedures at the same time of fundoplication, such as a pyloroplasty or pyloromyotomy, to enhance GE. The addition of these procedures lessens outflow resistance and thereby promotes GE. Nevertheless following Nissen fundoplication without GE procedures, children may present symptoms related to an abnormal gastric motility including dysphagia in 5%, gas bloat in 2% to 4%, and dumping syndrome in up to 30% (Jolley et al., 1987c; Lundell et al., 1994; Samuk et al., 1996; Vu et al., 1999). It has been documented that post-Nissen patients have a significantly reduced postprandial gastric relaxation and significantly accelerated GE (Vu et al., 1999). In addition, it has been suggested that pyloroplasty may cause excessive risk of postoperative dumping when combined with fundoplication (Pittschieler, 1991; van Kempen et al., 1992), and may be responsible

for the induction or increase of symptoms such as nausea, early satiety, and belching in those with normal gastric emptying before surgery. Indeed some authors (Jawaid et al., 2006; Maxson et al., 1994; Mousa et al., 2006) have reported that the addition of a draining procedure to the fundoplication provides no further benefits and it is associated with a significant increase in the rate of immediate postoperative complications and longer time to reach full feeding (Maxson et al., 1994). Maxson and Colleagues studied, 58 neurologically impaired children undergoing fundoplication grouped based on GE scan results and found no differences in postoperative feeding tolerance, postoperative complications, recurrent symptoms, readmissions, or reoperations between children with normal GE and children with delayed GE. Symptoms of accelerated or delayed GE after Nissen fundoplication occur in up to 30% of the patients and can be due to several factors including vagus nerve injury, alteration in gastric compliance, incomplete lower oesophageal relaxation, motor and sensory dysfunction of the stomach with alteration of the sensations of fullness or nausea etc. The effects of LNF have been poorly investigated but it may results in fewer disturbances to gastric motility due to less extensive tissue trauma on the vagus nerves and stomach as reported in adults (Lindeboom et al., 2004) but the effects on gastric motility of this technique have never been studied extensively in children. In our study we found that GE was accelerated in all except one patient and none of the patients experienced post-operative symptoms related to abnormal gastric motility. These findings could also explain the reduced incidence of post-operative retching found in the laparoscopic group as reported in Chapter 3.

5.7 Conclusions

The results presented in this chapter demonstrate that GE for liquids is accelerated following LNF in children. Procedures aimed to improve GE time such as pyloroplasty or pyloromyotomy might not be justified at the time of surgery. The improved gastric emptying following the LNF could explain the lower incidence of post-operative retching found in this group as reported in Chapter 3.

Chapter 6

Results of Redo-Nissen fundoplication

6.1 Introduction

The recurrence of gastro-oesophageal reflux (GOR) following antireflux surgery represents a clinical problem and requires redo-surgery in the majority of cases. Few reports have evaluated the efficacy of redo-Nissen fundoplication (RNF) in children and the success rate in these series varies from 95 – 98% in neurologically normal (NN) children to 70 – 85% in neurologically impaired (NI) children (Dalla Vecchia et al., 1997; Kimber et al., 1998; Rothenberg, 2006).

Failure after a second antireflux operation requires a more critical assessment of the attendant morbidity before further surgical intervention is undertaken. In those patients who do not respond to a second Nissen fundoplication, alternative procedures should be considered including insertion of a gastro-jejunal feeding tube, jejunostomy or gastric dissociation with Roux-en-Y oesophago-jejunostomy (Dalla Vecchia et al., 1997; Morabito et al., 2006).

6.2 Aim

Aim of the present study was to appraise the results following repeated surgery for recurrent GOR on a large series of children in order to identify factors predicting failure of RNF.

6.3 Methods

A review of patients that underwent RNF for recurrent GOR between January 1994 and May 2005 at Great Ormond Street Hospital (GOSH) by 5 different paediatric surgeons was conducted. Patients' characteristics, incidence of symptoms, management and outcome were reviewed from inpatient and outpatient records. Recurrence of GOR and failure of intervention was defined by the presence of recurrent vomiting after surgery and confirmed by 24-hour pH study and/or by an upper gastro-intestinal contrast study.

6.4 Data Analysis

Data are reported as median (range), or as numbers of cases, and were compared by Fisher's exact test or Mann-Whitney U test where appropriate. Multiple logistic regression analysis (SPSS® v 13.0) was used to produce a model to identify factors predicting recurrent vomiting (failure) after RNF. The model was generated using the following factors: type of first fundoplication, neurological status, presence of gastrostomy, age-weight, length of follow-up, presence of associated anomalies and oesophageal atresia, retching (unsuccessful effort to vomit) and/or gas bloat (abnormal gaseous distension of the stomach) after the first fundoplication.

6.5 Results

During the study period 850 children underwent a Nissen fundoplication for GOR. Overall, 81 children (9%) underwent an open RNF for recurrent GOR (Table 6.1) at a median of 15.9 months (0.2-176) after the initial fundoplication. No patient underwent a laparoscopic RNF since the operating surgeons had no experience with this procedure prior to this study. In 29 (36%), the first Nissen fundoplication was laparoscopic.

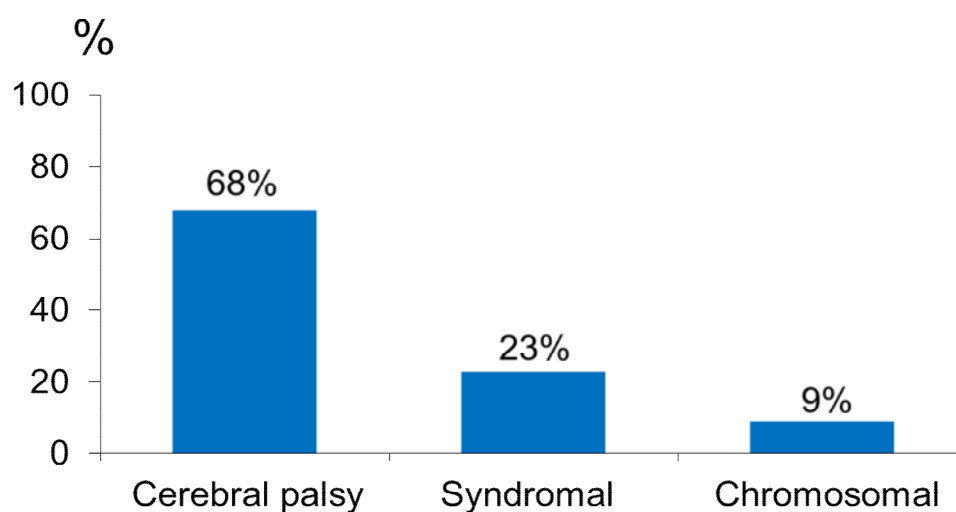
Table 6.1 – Failure rate after first Nissen fundoplication.

***p = n.s. versus open**

	Number of patients	Redo	%
Open Nissen	603	52	9
Laparoscopic Nissen	247	29*	12
Total	850	81	10

Among the 81 children that underwent RNF there were 31 neurologically normal (NN) children (15 males) and 50 neurologically impaired (NI) children (32 males). The majority of NI children had cerebral palsy (Figure 6.1).

Figure 6.1 – Type of neurological impairment.



The age at first fundoplication was 16 months (0.2 – 174) and weight was 8.4 kg (1.7 – 53.3). The age and weight at RNF were 40 months (3.4 – 193) and 12.8 kg (5.0 – 60.0) respectively (Table 6.2).

Table 6.2 – Patients demographics in children undergoing redo-Nissen fundoplication.

	Median (range)
Age at first Nissen fundoplication (months)	16 (0.2-174)
Age at redo-Nissen fundoplication (months)	40 (3.4-193)
Follow-up after redo (months)	22 (1.5-121)

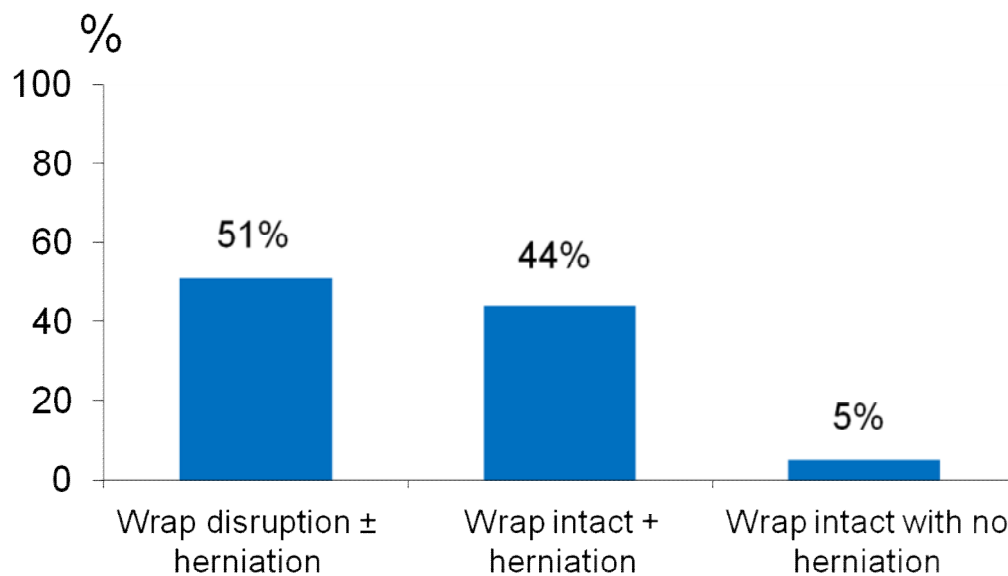
The time to redo-fundoplication was 17.7 months (1.1 – 176) for the NN children and 12.6 months (0.2 – 110) for the NI children and was not statistically different between the 2 groups ($p = 0.27$). Duration of follow-up after the RNF was 22 months (1.5 – 121).

Associated anomalies were present in 16 (52%) of the NN patients and in 27 (54%) of the NI patients. Oesophageal atresia and tracheo-oesophageal fistula accounted for 38% of the anomalies in the NN group.

The intra-operative findings at RNF were (Figure 6.4):

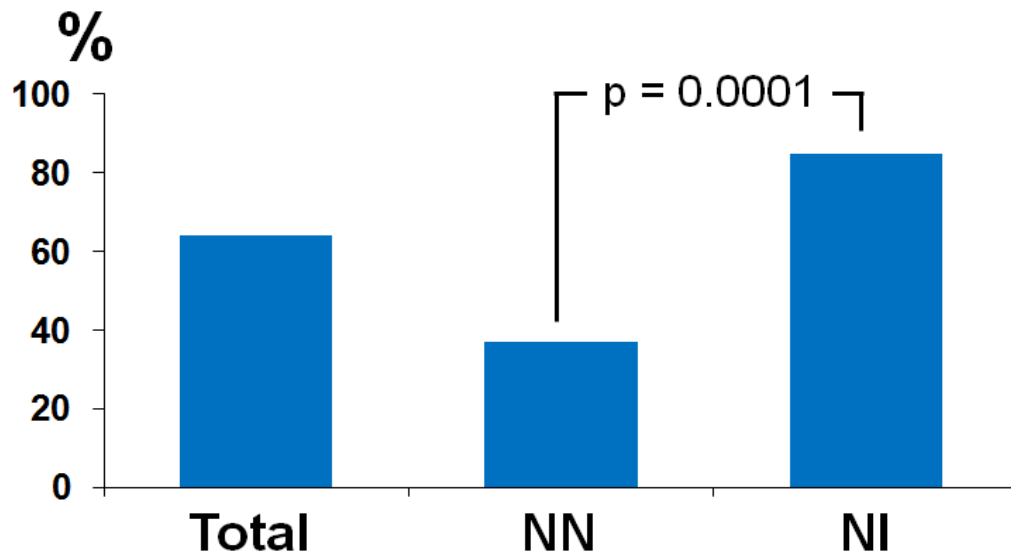
1. disruption \pm herniation of the wrap in 41 patients (51%);
2. intact wrap herniation in 36 patients (44%);
3. intact wrap in 4 patients (5%).

Figure 6.2 – Mechanism of failure after Nissen fundoplication.



A concomitant gastrostomy was inserted in 10 (32%) NN children and 39 (78%) NI children during the first fundoplication and in 13 (42%) NN children and 42 (84%) NI children at RNF (Figure 6.3).

Figure 6.3 – Gastrostomy at redo-Nissen fundoplication.

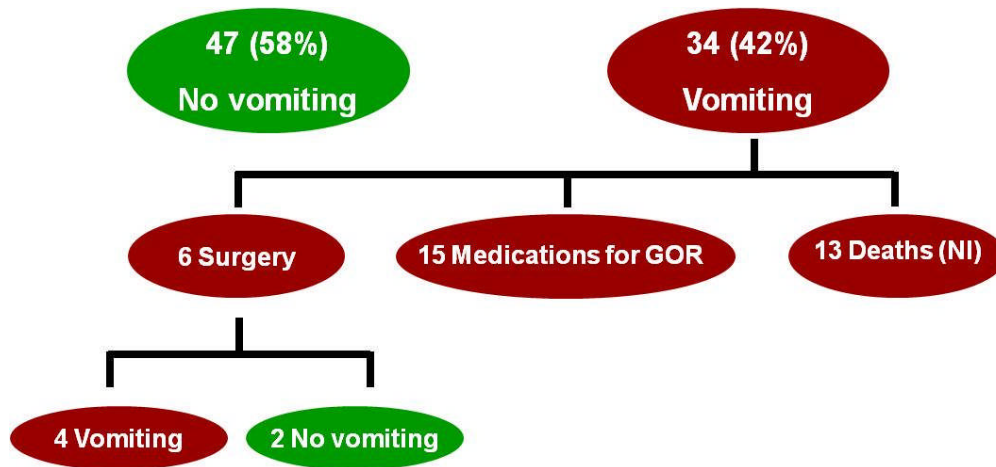


Intraoperative complications at RNF occurred in 1 NI child (left pneumothorax).

Postoperative complications, including chest infections, prolonged mechanical ventilation and bleeding from the gastrostomy site, occurred in 4 (13%) of NN children and 14 (28%) of NI children.

Overall 34 (42%) children (10 NN and 24 NI; $p = \text{n.s.}$), presented with recurrent vomiting following RNF (Figure 6.4).

Figure 6.4 – Results following redo-Nissen fundoplication.



Thirteen patients with recurrent GOR in the NI group died in other hospitals (6 of them were under medication for GOR). Fifteen patients (7 NN and 8 NI) were under medical treatment for GOR at the time of this follow-up study. Six patients (3 NN and 3 NI) underwent a third fundoplication that was unsuccessful in 4 (2 NN and 2 NI).

Retching, was present in 31 (38%) of children following the first fundoplication and in 39 (48%) children following RNF (Table 6.3).

Table 6.3 – Incidence of retching.

Retching	First Nissen fundoplication (81)		p
	Laparoscopic (29)	Open (52)	
After first fundoplication	7 (24%)	24 (46%)	0.05
After redo-fundoplication	17 (58%)	22 (42%)	0.17

Respiratory symptoms, including recurrent aspiration pneumonia, asthma and bronchopulmonary dysplasia were present in 43 (53%) after the first fundoplication and in 14 children (17%) following RNF ($p = 0.001$).

The multiple logistic regression model successfully predicted vomiting (failure) after RNF ($p = 0.009$), with a Nagelkerke pseudo- r^2 value (analogous to the r^2 value obtained for a linear regression) of 0.34. The results from the multiple logistic regression analysis are summarized in Table 6.4.

Table 6.4 – Results of the multiple logistic regression analysis.

Factors	Risk	p value
Open vs. Laparoscopic (first Nissen)	5.0	0.011
Neurological impairment vs. Neurological normal status	4.8	0.046
No gastrostomy vs. Gastrostomy	5.1	0.035
Younger-lighter vs. Older-heavier (redo Nissen)	1.005	0.028

Open surgery at first fundoplication ($p = 0.011$) and neurological impairment ($p = 0.046$) were both significant predictors of redo failure in the model, whereas presence of gastrostomy ($p = 0.035$) and older-heavier age-weight ($p = 0.028$) were associated with better results. Retching-gas bloat, associated anomalies and oesophageal atresia were not significant predictors of failure.

6.7 Discussion

This study demonstrates that RNF is associated with a high incidence of failure. Risk factors are open fundoplication at first operation and neurological impairment.

The overall failure rate for first Nissen fundoplication at GOSH is 9%. These data reflect the data in the literature on large series of patients (Fonkalsrud et al., 1998). Interestingly, the failure rate has remained unchanged in the last 10 years when

compared to a previous study conducted at GOSH including patients between 1980 and 1995 (Kimber et al., 1998).

As in previous reports (Dalla Vecchia et al., 1997; Graziano et al., 2003; Kimber et al., 1998), we found that the surgical failure is mainly related to the herniation and disruption of the wrap (51%).

The data in this thesis suggest that RNF is ineffective in controlling GOR in 42% of the children. Other authors (Dalla Vecchia et al., 1997; Siewert et al., 1989a; Siewert et al., 1989b) have reported a recurrence rate following redo-Nissen fundoplication of between 28% and 34%. Similarly to what we reported in the follow-up study (Chapter 3), we documented that following the first Nissen fundoplication, the incidence of retching was less in the group that had the procedure performed laparoscopically (24%) compared to the group that had the procedure performed with the open technique (49%) although this difference is not statistically significant ($p = 0.05$). A possible explanation could be that the incidence of retching was based on the data retrospectively collected from the medical notes. Following RNF we also documented an elevated incidence of retching (48%), but there was no difference between the groups ($p = 0.17$); this could be due to the fact that the redo-Nissen fundoplication was performed with the open technique in all children. Retching is a symptom of altered gastric motility and Lundell and colleagues (Lundell et al., 1996) reported that GOR is often associated with an altered motility of the whole intestine. Alexander and colleagues (Alexander et al., 1997) have documented that an altered gastric motility is frequently present in NI children with GOR. In particular, retching

is a common problem following Nissen fundoplication and it is been reported in a high percentage (50%) of children requiring redo-fundoplication for recurrent reflux. Persistent retching might itself lead to wrap disruption due to an increased pressure on the wrap. In this respect, the laparoscopic technique could be beneficial by causing less retching thus less risk of wrap disruption compared to the open technique. The recurrence rate following RNF in these series is higher for NI children (48%). Different studies have documented that the results of the first fundoplication are negatively influenced by the presence of neurological impairment and associated anomalies, both in children (Dalla Vecchia et al., 1997; Dedinsky et al., 1987; Kimber et al., 1998; Spitz et al., 1985; St Cyr et al., 1989; Turnage et al., 1989; Wheatley et al., 1993), and infants (Kubiak et al., 1999) and several authors (Caniano et al., 1990; Corbally et al., 1992; Curci et al., 1988; Kubiak et al., 1999; Lindahl et al., 1989; Snyder et al., 1997; Wheatley et al., 1993) have reported that the fundoplication is associated with a higher recurrence rate in patient with repaired oesophageal atresia (up to 24%). Associated anomalies were present in about 50% of the patients that required redo-fundoplication. In particular, oesophageal atresia was the most frequent associated anomaly in the NN children. The results of the multivariate analysis suggest that the presence of neurological impairment is also a risk factor for failure after redo-Nissen fundoplication; however, we found that the presence of associated anomalies is not a risk factor for failure after RNF.

The presence of gastrostomy seems to be associated with better results following RNF. Up to 50% of patients following antireflux surgery are incapable of belching

(Negre, 1983; Tew et al., 2000) and this could lead to increase of the intragastric pressure with consequent disruption of the wrap. In patients with gastrostomy the opening of the gastrostomy tube during feeding leads to a decompression of the stomach and thus less tension on the wrap. Finally, the multiple regression analysis showed that the results of RNF are better in older children with higher weight and this could be related to the physiological “maturation” of the gastro-oesophageal junction with ageing.

6.8 Conclusions

In conclusion, the data on a large series of patients that underwent RNF suggest that this procedure has a high failure rate since it is ineffective in controlling GOR in approximately 30% of the NN children and 50% of NI children. Risk factors are open fundoplication at first operation and neurological impairment. Redo-fundoplication after primary laparoscopic Nissen has lower risk of failure.

Chapter 7

Open versus Laparoscopic pyloromyotomy:

Results of a randomised controlled trial

7.1 Introduction

Laparoscopic pyloromyotomy (LP) is reported to carry a number of advantages over the open procedure including improved cosmesis, shorter post-operative recovery and shorter length of hospital stay (Bufo et al., 1998; Campbell et al., 2002; Downey, Jr., 1998; Ford et al., 1997; Fujimoto et al., 1999; Greason et al., 1995; Scorpio et al., 1995). This new approach however has a number of potential disadvantages owing to the fact that it is technically more demanding. Longer operation and anaesthetic time and a higher incidence of complications have all been reported (Ford et al., 1997; Fujimoto et al., 1999; Sitsen et al., 1998). There remain proponents and opponents to both techniques and overall it is difficult to draw any conclusion from the literature as to which approach is superior. Prior to the current study's inception, Hall and colleagues performed a systematic review and meta-analysis of the literature to 2004 (Hall et al., 2004b) which suggested that a shorter post-operative recovery could be achieved following laparoscopy but raised concerns of a higher complication rate. The meta-analysis was unable to conclude that one approach was superior to the other. This study concluded that the open pyloromyotomy (OP) was associated with fewer complications and higher efficacy but recovery time appeared significantly shorter following LP and that a prospective randomised controlled trial was warranted.

7.2 Aim

Aim of this study was to determine whether LP offers any clinical advantage over OP.

7.3 Methods

7.3.1 Trial Design

This study was carried out prospectively at 6 centres: Great Ormond Street Hospital, London, UK; Children's Hospital of Pittsburgh, PittsburghUSA; Hospital for Sick Children, Toronto, Canada; University Medical Centre, Graz, Austria; University Hospital of Helsinki, Helsinki, Finland; Chelsea & Westminster Hospital, London, UK. The trial was co-ordinated by the Institute of Child Health and Great Ormond Street Hospital for Children, London, UK.

Institutional ethical approval was obtained at all centres prior to recruitment and written informed consent was obtained from the infant's parents or legal guardian prior to enrolment in the study.

Recruitment began in June 2004 and ceased following an interim analysis of the existing data in May 2007 since a statistically significant difference in primary outcome measure between the two groups was found (see paragraph 7.6 Results). Infants were randomised to undergo either OP or LP and were managed post-operatively using a standard care pathway.

Standardised protocols for anaesthesia, postoperative analgesia, and postoperative feeding were used (see below). Infants with a diagnosis of PS were eligible for inclusion with the exception of those with co-morbid conditions which could have influenced the post-operative recovery, those requiring an additional procedure during the same operation and those who had undergone previous abdominal surgery were excluded.

Diagnosis was made on clinical evidence of a palpable pyloric ‘tumour’ and/or sonographic assessment, although it was not a requirement of this study that the diagnosis was confirmed sonographically.

7.3.2 Randomisation

Allocation to groups was weighted minimisation (Wade et al., 2006) at the time of enrolment into the study using the criteria in Table 7.1.

Table 7.1 – Minimisation Criteria.

Minimisation criteria	Definition
Centre	Treatment centre
Age	< or ≥ 28 days
Weight	< or ≥ 3.5 kg
Birth gestational age	< or ≥ 36 completed weeks
Feeding type	Breast or bottle
Pre-op duration of symptoms	< or ≥ 48 hours
Bicarbonate at presentation	< or ≥ 30 mmol/l

7.3.3 Sample Size Estimation

This trial aimed to detect differences between the primary outcome measures which were felt to be of clinical relevance. The sample sizes were therefore chosen to ensure that if the expected differences actually existed, they would have been detected.

All calculations were based on a power calculation of having a 90% chance of detecting a difference at the 5% significance level ($1 - \beta = 0.9$, $\alpha = 0.05$).

Central to the sample size calculation was the detection of a difference between the two treatment groups which was deemed to be of clinical significance. A difference in time to full feeds and post-operative length of stay of 12 hours was considered to

be clinically significant. Data from a retrospective study (Hall et al., 2004a) suggested that 70 infants in each group would be required to detect this difference. Data from a meta-analysis (Hall et al., 2004b) suggested that 30 per group would be required to detect this difference.

The two most clinically important complications are incomplete pyloromyotomy and mucosal perforation. In order to detect a difference in the complication rates between the two approaches more infants would be required. For instance to detect a 5% increase in the incidence of mucosal perforation would have required more than 200 infants per group. However to detect a 5% increase in the incidence of incomplete pyloromyotomy would have required 70 infants per group based on data from the retrospective study and 100 infants per group based on data from the meta-analysis.

Based on the data available, a sample size of 200 infants (100 per group) were expected to detect a difference of 12 hours in time to full feeds and post-operative length of stay (if actually present) and a 5% increase in the incidence of incomplete pyloromyotomy. The proposed sample size for this trial was 100 infants in each arm. Therefore a total of 200 infants were initially planned to be required.

7.3.4 Treatment Schedule

Infants were randomised to undergo either OP or LP. As far as possible all other aspects of treatment were standardised to minimise the effect of confounding variables and potential bias. All infants underwent routine pre-, peri- and post-operative monitoring.

7.3.5 Resuscitation and Pre-Operative Assessment

Following admission with a suspected clinical diagnosis of PS, the infant was commenced on standard resuscitation fluids (0.45% saline and 5% dextrose with 10 mmol KCl added to each 500 ml bag) at 150 ml/kg/day and had a naso-gastric tube inserted and enteral feeds withdrawn. Following confirmation of the diagnosis the trial was discussed with the parents and consent sought. Once consent was obtained randomisation was performed. The parents were not informed of the treatment assigned until the baby was ready for discharge. No staff member other than the operating surgeon was informed of the assigned treatment in order to ensure blinding of other health professionals. The infant were assessed by the anaesthetist and once biochemical normality was achieved, surgery was performed.

7.3.6 Anaesthesia

In order to standardise treatment between groups and centres, an anaesthesia protocol was derived and anaesthetists at each centre requested to follow this for all infants. All infants underwent an identical anaesthetic regime regardless of treatment assignment with Sevoflurane with O₂/air at induction, Isoflurane with O₂/air and Atracurium for maintenance. Peri-operative analgesia was obtained with rectal paracetamol at start of procedure, Fentanyl (1 – 2 mcg/kg), Morphine if required (10 mcg/kg) and wound infiltration (0.25% bupivacaine 0.8 ml/kg).

7.3.7 Surgery and Immediate Post-Operative Period

All infants received prophylactic intravenous antibiotics at induction of anaesthesia in the form of flucloxacillin (25 mg/kg i.v.). All wounds were infiltrated with local anaesthetic (bupivacaine 0.25% 0.8 ml/kg) before incision or following closure. Patients randomised to OP underwent a standard pyloromyotomy via a supra-umbilical incision using the technique described by Tan and Bianchi (Tan et al., 1986). The pyloric 'tumour' was delivered through the wound and a longitudinal incision made in the seromuscular layer of the pylorus. LP was performed based on the technique reported by Najmaldin and Tan (Najmaldin et al., 1995) and described in Chapter 1. All procedures were performed by a trainee under direct supervision or by a non-trainee only when the operative experience of the trainee was inadequate. This was the case when an infant was assigned to the laparoscopic pyloromyotomy group and the trainee surgeon had completed fewer than 5 laparoscopic procedures. Following wound closure, plasters were placed over wounds in a pattern identical to that used following laparoscopic pyloromyotomy. A large dressing occluded the umbilicus and surrounding area and 2 small dressings were applied over the laparoscopic 'stab' wounds or in an identical place if the open procedure was performed (Figure 7.1). The naso-gastric tube was removed at the end of the procedure.

Figure 7.1 – Opaque dressings used for all infants following either open or laparoscopic pyloromyotomy.



7.3.8 Recovery and Post-Operative Assessment

All infants returned to the ward and underwent routine clinical monitoring. Ward nurses and parents were blinded to the treatment assignment by the presence of the opaque dressings. Post-operative fluids (10% dextrose with 0.45% saline and 10 mmol KCl added to each 500 ml bag) were given at a rate of 60 ml/kg/24hrs and continued until one full feed was tolerated without significant vomiting. All infants underwent pain assessment and analgesia administration according to the standardised protocol.

7.3.9 Post-Operative Pain Assessment and Analgesia

Pain assessment and administration of appropriate analgesia was carried out by ward nurses blinded to the procedure performed. The FLACC behavioural pain scale (Merkel et al., 1997) was used to assess pain every 4 hours. Pain scores were recorded and compared at individual time points between the laparoscopic and open groups.

Paracetamol formed the basis of the post-operative analgesic regime. For infants with moderate pain the combination of paracetamol and codeine was used.

7.3.10 Post-Operative Feeding Regime

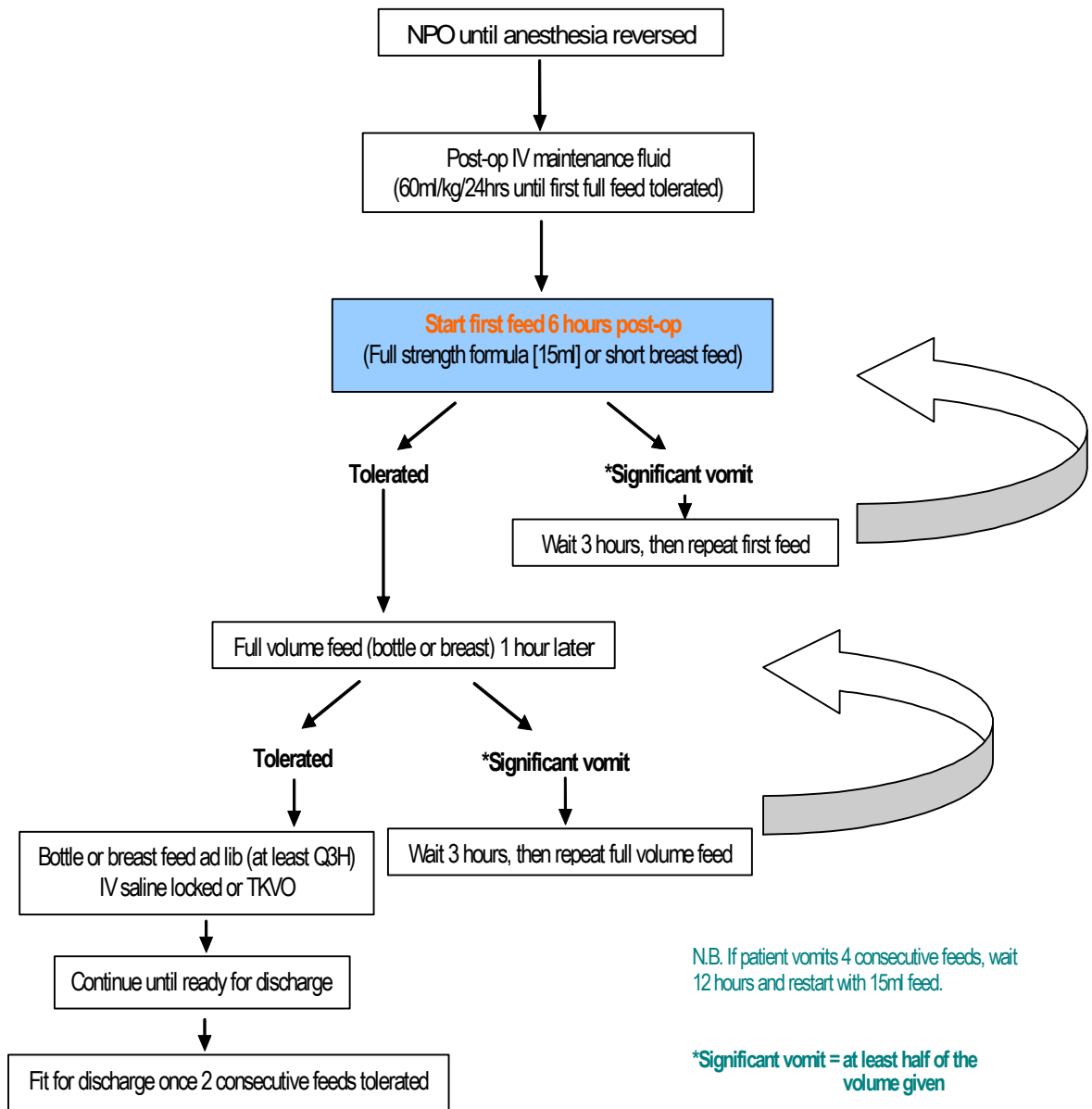
Typically feeding regimes following pyloromyotomy have been complex and conservative. They are all based on the assumption that the gradual advancement of feed volume and strength reduces post-operative emesis. Enteral feeds may be withheld for 12 or even 18 hours following pyloromyotomy. The rationale for this is, at least in part, based on an old post-operative motility study (Scharli et al., 1968) and there is actually little clinical evidence to support this theory. Recently, these complex post-operative feeding regimes have been compared with an *ad libitum* protocol by a number of authors (Garza et al., 2002; Puapong et al., 2002). The *ad libitum* regimes have been found to reduce time to full feeds, post-operative length of stay and hospital costs. Despite a slight non-significant increase in the number of infants with emesis there was no increase in re-admission rates and the investigators

concluded that *ad libitum* regimes were safe, cost-effective and indicated following OP.

In order to minimise differences which may affect outcome measures between the OP and LP groups it was necessary to use a post-operative feeding regime suitable for all infants. A recent meta-analysis (Hall et al., 2004b) found that post-operative recovery times were significantly shorter following LP but none of the studies analysed used an identical feeding protocol for all infants. In general, there was a trend for earlier introduction of feeds following LP and this may in part be responsible for the shorter recovery and discharge times. An *ad libitum* feeding regime appeared to be suitable following OP and therefore formed the basis of the regime used in this trial.

All infants were entered into the post-operative feeding protocol as per Figure 7.2.

Figure 7.2 - Pyloromyotomy trial feeding regime for all infants (NPO: nil per os)



The first post-operative feed was given 6 hours following recovery from anaesthesia of either 15 ml full strength formula or a short breast feed (5 minutes). If tolerated, a full volume feed was offered 1 hour later. Subsequent feeds (formula or breast) were given on demand or at a maximum interval of 3 hours. If during the course of a feed the infant had a significant emesis (at least half of the volume given), then the remainder of that feed was withheld and the next feed given after a period of 3 hours. If an infant vomited every feed for 4 consecutive feeds then the feeding was stopped for a period of 12 hours and then restarted. Each episode of significant vomiting (at least half of volume given) was documented.

Intravenous fluids were continued until the first full feed was tolerated.

The time at which the first full feed (150 ml/kg/8) was tolerated without significant vomiting was recorded as the time at which full feeds were achieved. The time at which the infant was ready for discharge was defined as the time at which 2 consecutive full feeds were tolerated without significant vomiting. The time at which the patient was actually discharged was documented.

The time at which the infant achieved full enteral feeding, the time at which the decision to discharge was made and the actual time of discharge were all recorded. The dressings were not removed until after discharge. All complications were recorded prior to discharge.

7.3.11 Follow-up

Infants were reviewed in the outpatient clinic approximately 6 weeks following discharge to assess surgical wounds, identify any post-discharge complications (e.g. wound infection, incisional hernia) and to record parental satisfaction with the cosmetic outcome. Wounds were assessed objectively by a member of the surgical team using two scoring systems which assess complications of wound healing and cosmetic appearance. The first (Hollander et al., 1995) allows 0 point for the presence and 1 point for the absence of each of the following criteria: margin separation, lack of contour integrity, border step-off, wound edge inversion, excessive distortion and overall satisfaction in appearance. The maximum score is 6 and any score below 6 was considered sub-optimal. A second more detailed wound assessment score was also used in which a point was assigned for the presence of incomplete healing, active infection, erythema, oedema, pain and increased skin temperature (Ford et al., 2005). A score of 0/6 was considered optimal. Parents were asked to report their level of satisfaction with the appearance of the surgical scars using a 5-point Likert scale and a 10 cm visual analogue scale with the words ‘least satisfied’ at one end and ‘most satisfied’ at the other.

7.4 Data Analysis

Data were collected by a designated administrator at each centre and forwarded to the trial co-ordinators. Data were entered into a specifically designed database (Microsoft

Access 2003, Microsoft Corporation®, Seattle, WA) and analysed using SPSS® v.14 (Chicago, IL) on an intention-to-treat basis. Outcome variables were analysed using multivariate linear regression analysis, ordinal regression analysis, Mann-Whitney U test and χ^2 tests as appropriate. All regression models were calculated adjusting for all minimisation criteria. Skewed continuous data were transformed to their natural logarithm in order to approximate a normal distribution prior to analysis. Data are median (IQR, range) unless otherwise stated.

7.5 Data Monitoring

A data monitoring committee (DMEC) was established. This was independent of the trial co-ordinators and those providing therapy. The committee performed an interim analysis to (i) review assumptions underlying sample size calculations and (ii) to modify or close intake to the trial.

The criteria for stopping the trial were defined as: i) a significant difference ($p < 0.01$) between the two arms in post-operative length of stay; or ii) significantly ($p < 0.01$) greater incidence of serious complications in one arm compared to the other (mucosal perforation, haemorrhage requiring transfusion, incomplete pyloromyotomy requiring re-operation), analysed both as single outcomes and as total cumulative complications. The p value was set < 0.01 as recommended for stopping trials early (Montori et al., 2005; Pocock, 2005).

Data from any infant who had a complication during surgery resulting in diversion from the standard post-operative feeding protocol (e.g. mucosal perforation, conversion from laparoscopic to open procedure) was not be included in the final between groups analysis but was be recorded and reported.

7.6 Results

Recruitment commenced in June 2004. Following the planned interim analysis of the first 100 patients the DMEC recommended that the trial continued but advised an additional interim analysis following the recruitment of a further 50 patients (150 in total). As a result of this second interim analysis, the DMEC recommended the recruitment to the trial be closed due to a statistically significant difference in primary outcome measure between the two groups. This decision was ratified by the trial steering committee as it was considered unethical to continue to randomise patients to one of two treatments when outcome following the two procedures was no longer equal and equipoise no longer existed.

7.6.1 Patients

During the period of recruitment 228 infants met the eligibility criteria of whom 48 refused consent for the study. Hence a total of 180 infants were randomised to undergo OP (87 infants) or LP (93 infants) at one of 6 centres. There were no

differences between groups in any of the demographic or clinical parameters at enrolment (Table 7.2 and 7.3).

Table 7.2 – Results of minimisation; distribution of patients in different centres
(OP = open pyloromyotomy; LP = laparoscopic pyloromyotomy).

Centre	OP (n=93)	LP(n=87)
Great Ormond Street Hospital London, UK	43	43
Children's Hospital of Pittsburgh Pittsburgh, USA	19	17
Hospital for Sick Children Toronto, Canada	19	16
Medical University of Graz Graz, Austria	5	6
University Hospital of Helsinki Helsinki, Finland	5	3
Chelsea and Westminster Hospital, London, UK	2	2

Table 7.3 – Results of minimisation; (OP = open pyloromyotomy; LP = laparoscopic pyloromyotomy).

	OP (n=93)	LP(n=87)
Age (days)		
< 28	28	26
≥ 28	65	61
Weight (kg)		
< 3.5	26	28
≥ 3.5	67	59
Birth gestation (weeks)		
< 36	4	5
≥ 36	89	82
Bicarbonate at initial presentation (mmol/L)		
< 30	49	47
≥ 30	44	40
Feeding type		
Breast	16	18
Bottle or mixed	77	69
Pre-operative duration of symptoms		
<48	2	4
≥48	91	83

7.6.2 Interventions

There was no significant difference in anaesthetic time between OP and LP but surgical time for LP was significantly shorter than for OP although only by 2 minutes (Table 7.4).

Table 7.4 – Duration of anaesthesia, surgical procedure and post-operative recovery for open (OP) and laparoscopic (LP) pyloromyotomy. Data are median (IQR, range).

	OP (n=93)	LP (n=87)	Relative reduction LP vs. OP (95%CI)	<i>p</i> *
Anaesthetic time (minutes)	85 (65-103, 32-200)	85 (70-103.5, 30-195)	1.094 (0.802-1.491)	0.571
Operative time (minutes)	32 (27-40, 17-87)	30 (23.5-36, 15-85)	0.683 (0.499-0.933)	0.017
Time to first tolerated enteral feed (hrs)	11.5 (7.1-20.9, 5.7-54.7)	10.0 (7.2-17.0, 2.4-53.8)	0.705 (0.511-0.973)	0.033
Time to full feeds (hrs)	23.9 (16.0-41.0, 8.8-107.5)	18.5 (12.3-24.0, 9.0-101.5)	0.497 (0.354-0.696)	<0.0005
Post-operative length of stay (hrs)	43.8 (25.3-55.6, 15.3-169.1)	33.6 (22.9-48.1, 13.0-259.0)	0.654 (0.477-0.895)	0.008

Complications are shown in table 7.5.

Table 7.5 – Complications during open (OP) and laparoscopic (LP) pyloromyotomy.

Intra-operative	OP (n=93)	LP (n=87)	<i>p</i> *
Mucosal perforation (n)	1	2	0.611
Haemorrhage (n)	0	0	1
Other§ (n)	0	1	0.483

*Fisher's exact test; §Other - unexplained drop in oxygen saturation during anaesthesia - resolved spontaneously with no long-term sequelae

There were no conversions from LP to OP. In the OP group, 9 gastric serosal lacerations occurred during delivery of the pylorus through the umbilical wound, a well-recognised complication of this technique (St Peter et al., 2006). No treatment other than haemostasis was required. Also in the OP group 2 'buttonholes' were made in the supra-umbilical skin during the procedure, both of which were identified and managed appropriately at the time. In total, 3 mucosal perforations occurred, all of which were repaired without deviation from the assigned treatment. There were no differences in the incidence of intra-operative complications between infants who

underwent OP and those undergoing LP. The proportion of LP performed by a trainee was significantly lower ($p < 0.0001$) than the proportion of OP (LP 37% vs OP 74%). To investigate whether grade of primary surgeon was a significant determinant of primary outcome, regression analyses of these markers of post-operative recovery were repeated taking into account grade of primary surgeon. Grade of primary surgeon was not a significant predictor of time to full feeds (Relative Reduction Trainee vs Non-trainee 1.01 [0.84-1.21], $p = 0.94$) or post-operative length of stay (RR 1.08 [0.91-1.28], $p = 0.38$). There was also no significant effect of the interaction between surgeon type and treatment on the primary outcome measures. Comparisons of primary outcomes following open and laparoscopic cases failed to identify any significant differences between cases performed by trainees and non-trainees (Table 7.6).

Table 7.6 – Comparison of primary outcome measures stratified by grade of primary surgeon; OP = open pyloromyotomy, LP = laparoscopic pyloromyotomy.

	OP		LP	
	Trainee	Non-trainee	Trainee	Non-trainee
Time to full feeds (hrs)	25.5 ^{\$} (16.6-40.1, 8.9-107.5)	20.0 (14.7-41.1, 8.8-57.8)	18.6 ^{\$} (14.1-21, 9-48.3)	18.5 (11.9-29.5, 9.5-101.5)
Post-operative length of stay (hrs)	43.6 ^{\$} (26.1-56.3, 15.3-169.1)	44.8 (23.3-50.8, 16.9-94)	25.6 ^{\$} (21.1-45.9, 17.3-121.3)	41.3 (23.6-49.1, 13-239.3)

Data are median (IQR, range); ^{\$}NS (p>0.05) vs OP Non-trainee; ^{\$}NS (p>0.05) vs LP Non-trainee (Mann-Whitney U test)

The incidence of significant complications (defined as requiring additional treatment or deviation from the study protocol) was similar between cases operated by trainees and non trainees (Trainee 17/101 vs Non-trainee 15/79; $p = 0.86$). Furthermore, of the complications which may be assumed to be associated with operative experience, all mucosal perforations and 2 of the 3 incomplete pyloromyotomies were in cases performed by a consultant.

7.6.3 Post-Operative Recovery

Infants who underwent LP tolerated their first full feed sooner, achieved full enteral feeds sooner and were discharged sooner than infants undergoing OP. All these differences were highly statistically significant (Table 7.4).

These data show that following LP, infants reached full enteral feeds on average just over twice as quickly as infants undergoing OP and spent 2/3 as much time in hospital following surgery. Figure 7.3 and Figure 7.4 show the cumulative proportion of patients by treatment group regarding the primary outcomes (p-values refer to linear regression analysis taking into account all factors used for minimisation).

Figure 7.3 – Cumulative proportion of infants tolerating full enteral feeds following open (solid line) and laparoscopic (dotted line) pyloromyotomy.

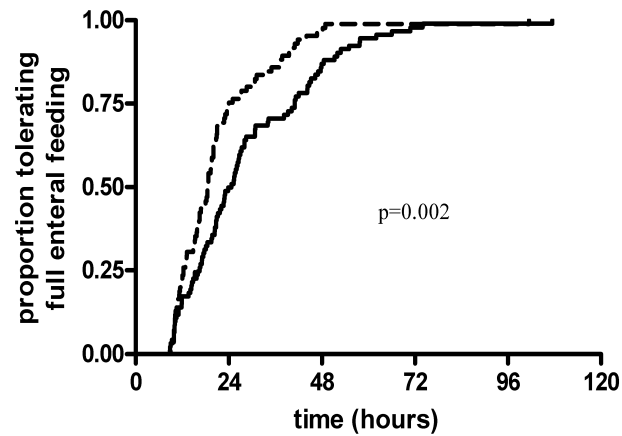
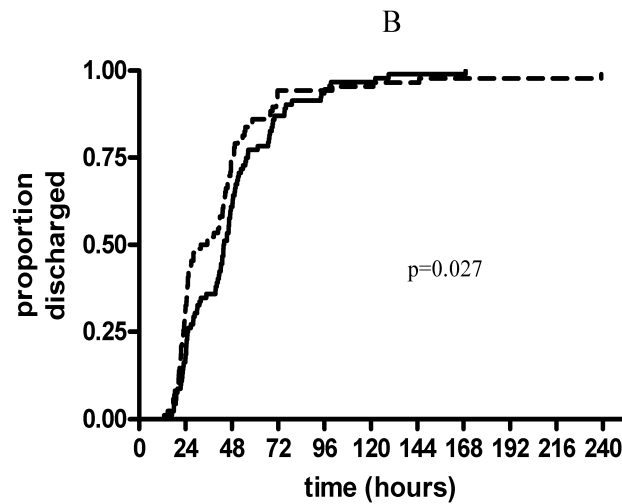


Figure 7.3 – Cumulative proportion of infants discharged following open (solid line) and laparoscopic (dotted line) pyloromyotomy.



Overall 95 infants (53%) had at least one significant post-operative vomit. There were no significant differences between OP and LP in the number of infants with at least one vomit (OP 52 [56%] vs LP 43 [51%]; $p = 0.55$), those with four consecutive vomits (OP 2 [2.4%] vs LP 2 [2.2%]; $p = 1$) nor the total number of significant vomits per infant (OP 1[0 – 2, 0 – 12] vs LP 1 [0 – 2, 0 – 10]; $p = 0.26$).

7.6.4 Post-Operative Complications

Post-operative complications occurred as shown in Table 7.7.

Table 7.7 – Complications of open (OP) and laparoscopic (LP) pyloromyotomy.

Post-operative	OP (n=93)	LP (n=87)	p^*
Significant vomiting requiring investigation (n)	4	3	1
Incomplete pyloromyotomy (n)	0	3	0.111
Wound infection (n)	4	2	0.683
Other wound complication (incisional hernia,	5	4	1
Respiratory complication (n)	3	0	0.246
Other [†] (n)	1	1	1

*Fisher's exact test; [†]Other - severe hypotonia requiring neurological consultation and investigation with subsequent spontaneous resolution(1), post-operative sepsis treated with antibiotics(1); [§]Defined as requiring deviation from the study protocol or additional treatment

Of particular note 3 infants who had LP were found to have an incomplete pyloromyotomy and required repeat operation. Two of these infants never achieved full feeds during the post-operative period and had persistent vomiting. They were subsequently investigated and underwent successful OP. The third did achieve full enteral feeds but was re-admitted with persistent vomiting 18 days later. This infant underwent OP followed by re-exploration 2 days later for an unidentified mucosal perforation. This infant required further laparotomy and adhesiolysis 3 months after initial presentation. There were no differences in the incidence of any single complication or the number of patients who suffered a significant complication (18 vs 14, $p = 0.697$) between the OP and LP groups.

7.6.5 Pain and Analgesia

The relationship between FLACC score evolution and time, and the potential dependence on LP/OP, was assessed using a mixed regression model with individual patients as subjects, and time as the repeated measure. FLACC scores decreased significantly over time, but overall there was no difference in pain scores between OP and LP ($p = 0.28$). Ordinal regression analysis was used to compare number of doses of analgesia (either paracetamol or codeine) between the treatment groups. The number of doses of analgesia required by infants following LP (1 [0 – 3, 0 – 9]) was significantly lower ($p = 0.011$) than following OP (2.5 [1 – 3, 0 – 8]).

7.6.6 Follow-up

One hundred and fifty one infants (84%) attended a follow-up appointment at a median of 39 days (32 – 51, 12 – 179) following discharge. Physician assessment scores were completed for 151 infants and parental satisfaction scores for 144 infants. There was a non-significant trend ($p = 0.053$) in favour of LP for one of the physician assessment scores but not the other. Parental satisfaction of surgical scars was analysed by categorising each score into one of four categories [≤ 75 , 76 – 90, 91 – 95 and > 95], and performing ordinal logistic regression. LP was found to have a significantly higher parental satisfaction than OP ($p = 0.011$). However there was no difference in parental satisfaction between OP and LP when measured on the Likert scale using ordinal regression analysis ($p = 0.14$).

7.6.7 Costs

Costings were obtained from the three centres recruiting more than 20 infants each for the following components of the in-patient episode: cost of procedure (OP or LP) cost of operating theatre time and cost of post-operative stay in the ward. Total cost per patient was calculated and converted into US dollars (\$) at the exchange rate on the day on which the final patient was recruited into the trial. Overall there was no difference in cost of OP (median US\$ 5009 [3280 – 6101, 1080 – 9432]) and LP (median US\$ 4702 [2441 – 5913, 1108 – 8567]); $p = 0.35$ (Mann-Whitney U test).

7.7 Discussion

This trial clearly demonstrates that there is an advantage for the LP compared to the OP. The LP was first described in 1991 (Alain et al., 1991) and received a mixed initial reception based on a number of retrospective reviews (Bufo et al., 1998; Campbell et al., 2002; Ford et al., 1997; Sitsen et al., 1998). A meta-analysis of existing data reported in 2004 highlighted the lack of quality prospective data in this field (Hall et al., 2004b). More recently however, 2 such studies have been reported, both of which provide a comparison between OP with LP from single centres, one in North America (St Peter et al., 2006) and the other in France (Leclair et al., 2007). St Peter and Colleagues randomised 200 infants to either OP or LP and found no difference in length of surgery or length of recovery. They concluded however that LP was superior to OP on the basis of fewer episodes of post-operative vomiting and a lower post-operative analgesia requirement. Leclair and Colleagues studied 102 infants randomly assigned to OP or LP and concluded that OP was a superior approach based on a non-significant increase in risk of incomplete pyloromyotomy following LP.

In our study, we used the post-operative outcomes of time to achieve full enteral feeds and time to discharge as primary outcome measures since any differences in these parameters between treatment groups would be of clinical importance and may influence operative approach. The decision to analyse both is due to there being a number of factors in addition to feed tolerance that influence post-operative length of

stay such as presence of wound infection and social factors. Using a standardised post-operative feeding regimen we identified highly statistically significant reductions in these markers of post-operative recovery following LP compared with OP. Whilst these differences may seem small they should not be overlooked. Further analysis of the data reveal that, on average, the time to achieve full enteral feeds following LP is just under half that following OP and that discharge following LP is achieved in just over 2/3 of the time taken with OP. Faced with these statistics it is likely that most surgeons and parents would opt for the procedure with the shorter post-operative recovery. Furthermore the difference of over 10 hours in post-operative length of stay may have the effect of necessitating an extra day in hospital following OP. This clearly has a number of logistical implications. Neither Leclair and Colleagues nor St Peter and Colleagues observed a difference in duration of post-operative recovery between LP and OP although neither study used length of post-operative recovery as a primary outcome measure and one study prescribed that discharge should be on the third post-operative day making detection of any difference unlikely. We did not detect any difference in the incidence of post-operative vomiting between the two treatment groups. The existence of a significantly shorter post-operative recovery following LP in the absence of any difference in post-operative vomiting suggests that vomiting may be a poor marker of post-operative recovery.

Importantly, the benefit in terms of shorter post-operative recovery following LP was not associated with any increase in operative or post-operative morbidity. The

incidence of all individual complications and total complications in both treatment groups was no different. As others have reported previously (Adibe et al., 2006; Leclair et al., 2007; Yagmurlu et al., 2004), we did observe a non-significantly higher incidence of incomplete pyloromyotomy following LP although the incidence of 3% is certainly in keeping with the figure reported by other groups following both approaches (Adibe et al., 2006; Hall et al., 2004a; Hall et al., 2004b; van der Bilt et al., 2004; Yagmurlu et al., 2004). Furthermore, when all significant complications are compared together there is absolutely no difference between LP and OP.

In similarity to Leclair and Colleagues and St Peter and Colleagues we have identified a significant reduction in analgesia requirement following LP. It is interesting to note that there was no associated difference in pain scores between OP and LP and this discrepancy requires explanation. Post-operative pain scores were obtained at fixed 4-hourly intervals in order to provide consistency. Analgesia, however, was provided whenever deemed necessary by the nursing staff as it is unethical to leave infants in pain for the purpose of a clinical trial. Pain scores which triggered administration of analgesia but which fell outside the strict 4-hourly intervals were not recorded. In retrospect we feel that analgesia requirement provides a better overall measure of post-operative pain than pain scores due to the difficulties encountered in collecting and analysing pain scores over multiple different time points. This study provides the most robust evidence of differing analgesia requirements following LP and OP to date due to its blinded nature.

Very few studies of pyloromyotomy have investigated cosmetic appearance of the wounds once healed. There was no difference in objective assessment of wound healing by physicians but a significantly higher parental satisfaction score with the cosmetic appearance of the surgical wounds in this trial. However, when measured by the Likert scale, the actual effect on overall satisfaction was no different between LP and OP. The explanation for this could be related to some well-known disadvantages of the Likert scale; it is documented that using this tool, participants may base answers on feelings toward surveyor or subject and may answer according to what they feel is expected of them as participant. In this respect, all parents were extremely satisfied with the results of the surgery and “very grateful to the surgeon” because their child was completely symptoms free; the good surgical results might have influenced their perception of the cosmetic appearance and indeed, many parents commented that “they were surprised for the baby to have such small scar/scars following a big operation”, making the cosmetic appearance a non-relevant issue.

The strengths of this study are that it was carried out in a blinded fashion and across a number of centres. One potential weakness is the significant difference in grade of surgeon performing the two procedures since a higher proportion of LPs were performed by non-trainees that were OPs. However there is little evidence to suggest that this has affected the results as there was no difference in complications between LP and OP (as might be expected with less operative experience). This could be due to the fact that all procedures were strictly supervised by the consultant paediatric surgeon that was always assisting the juniors during both open and laparoscopic

pyloromyotomy. Also, whilst the difference in operative experience between LP and OP may have contributed to operative time, the difference between LP and OP was only 2 minutes and it is therefore unlikely that grade of surgeon significantly affected post-operative recovery.

7.8 Conclusions

This is the first multicentre prospective randomised controlled trial comparing LP and OP. Data reveal that both OP and LP are successful approaches with high levels of parental satisfaction. LP has a number of advantages over OP in that post-operative recovery is shorter, post-operative analgesia requirement is lower and parental satisfaction is higher. Furthermore the trial has not demonstrated any increase in complications following LP nor in-hospital costs.

Chapter 8

General discussion and Future Work

8.1 General Discussion

Laparoscopic surgery in children has secured a strong foothold over a brief period of time. However, paediatric surgeons have been slower to adopt laparoscopy, in part because the patients are smaller, the open operations are often performed with minimal incisions, and many of the conditions that require surgery are rare. Several pioneering paediatric surgeons though began to perform uncomplicated surgical procedures, demonstrating that children too, could benefit from this technique.

Nonetheless, the use of laparoscopy in children introduced additional challenges including the physiological consequences related to the insufflation of the abdomen with CO₂ (pneumoperitoneum) possibly leading to acidosis and hypercarbia. In ***Chapter 2***, I aimed to quantify the absorption of CO₂ during laparoscopy in children using a novel mass spectrometry technique. Using this technique I have documented that 10 – 20% of CO₂ eliminated during laparoscopy in children is derived from the absorption through the peritoneum. This part of my research gave me the possibility to learn a mass spectrometry technique that could have a number of potential clinical applications in the future. For example, the use of a real time analyzer based on this technique could allow quantifying the CO₂ absorption during laparoscopy in a real time mode. This could eventually help deciding if there is the need for reducing or temporarily discontinuing the pneumoperitoneum and conversion to an open procedure if haemodynamic, oxygenation, or ventilation difficulties arise during the laparoscopy because of excessive absorption of CO₂. The other chapters of this thesis

focused on the outcome of laparoscopic surgery compared to open surgery. Nowadays, an increasing number of intra-abdominal procedures such as fundoplication, splenectomy, pyloromyotomy, appendicectomy, and cholecystectomy are being commonly performed with a laparoscopic approach. Nevertheless, the effects and advantages of laparoscopic surgery in children have not been extensively investigated as in adults due to the lack of a routinely performed laparoscopic procedure such as the cholecystectomy. This thesis aimed to investigate the outcome of laparoscopy in children focusing on two of the most commonly performed surgical procedures: the Nissen fundoplication (NF) for treatment of gastro-oesophageal reflux (GOR) and the Ramstedt pyloromyotomy for pyloric stenosis.

The NF has been for many years considered the procedure of choice for the surgical management of GOR in children. Nonetheless, the open procedure, performed through a midline laparotomy, carries significant morbidity especially in neurologically impaired children. The laparoscopic approach offers the advantage of decreasing the surgical trauma and has become the procedure of choice in many major centres. To test the hypothesis that the laparoscopic Nissen fundoplication (LNF) has similar results to the “classic” open approach I performed a long-term follow-up study on a randomised controlled trial including 38 children. The results are reported in *Chapter 3* and *Chapter 4*. Performing this follow-up study was a significant challenge since it involved recruiting patients randomised 4 years before and some patients had changed their contact details or, sadly, were deceased at the time of the follow-up. The results on the available 31 patients showed that the NF

improves the quality of life and controls GOR independently of the technique (open or laparoscopic); the laparoscopic technique has a lower incidence of retching at 4-year follow-up. This could be related to the fact that the laparoscopic technique seems to be associated with an improvement of gastric emptying in the immediate post-operative period as documented in *Chapter 5*. One key aspect of the follow-up study described in *Chapter 4* is the significant parental satisfaction with the results of the Nissen fundoplication, regardless of the technique. This is particularly important in families with neurologically impaired children that are totally dependent on caregivers for daily existence.

In *Chapter 5*, I have applied the mass spectrometry technique (as previously utilised in *Chapter 2*) to calculate the gastric emptying time for liquid meals using the ^{13}C -octanoic acid breath test. This non-invasive method relies on the rapid absorption (in the duodenum) and metabolism to $^{13}\text{CO}_2$ of the ^{13}C -octanoic acid (that contains a stable isotope of the carbon and thus is non-radioactive). During this test a special meal appropriate for the child's age and containing the ^{13}C -octanoic acid was given and after the meal I collected some of the air that the child was breathing out using a special tool made with a face mask connected to a syringe that I personally designed. This technique did not interfere with the child's breathing in anyway, was well tolerated in all cases and subsequently adopted in the Surgery Unit at the Institute of Child Health for other research projects.

Because the Nissen fundoplication carries a significant recurrence rate, I performed a large review on patients who underwent a second operation for recurrent GOR (redo-

Nissen fundoplication) reported in *Chapter 6*. The results showed that the redo-Nissen fundoplication has overall high failure rate but the redo-fundoplication performed after a primary laparoscopic Nissen has lower risk of failure, favouring the use of primary laparoscopy in children.

For the laparoscopic pyloromyotomy, a double blind, multicentre, international, randomized controlled study was performed enrolling 180 children and is reported in *Chapter 7*. The trial revealed that both open and laparoscopic pyloromyotomy are successful approaches with high levels of parental satisfaction. The laparoscopic approach, if performed in centres with suitable laparoscopic experience, has a number of advantages over the open one in that post-operative recovery is shorter, post-operative analgesia requirement is lower and parental satisfaction is higher. This was one of the largest randomised controlled trial (RCT) performed in paediatric surgery. RCTs are the gold standard for the evaluation of the effectiveness of clinical interventions and as demonstrated in paediatric oncology particularly, they have shown to have positive effects in clinical practice. Unfortunately, few clinical RCTs have been conducted in paediatric surgery and this could be due to a number of reasons: surgical techniques are difficult to standardise; some operations are associated with a variable learning curve (trainees were allowed to perform surgery in the pyloromyotomy trial); uncommon conditions with small patient numbers and concerns about patient choice. In this respect, the pyloromyotomy trial was a successful and remarkable collaboration between surgeons in different countries, with a very high recruitment rate (only 48 families refused to participate over the study

period) and I was privileged to co-ordinate that collaboration. This thesis has significantly contributed to the field of laparoscopic surgery in children by clearly demonstrating that laparoscopy has significant advantages over traditional open surgery in children undergoing common surgical procedure.

8.2 Future Work

Although there is a great deal of evidence suggesting that expired and/or arterial CO₂ is increased during minimally invasive procedures, there are several factors which can influence the amount of CO₂ which is eliminated. Thus far, there have been few systematic studies precisely quantifying the amount of CO₂ absorbed under different conditions and I plan to use the mass spectrometry technique used in **Chapter 2** to study the CO₂ absorption from body cavities during other minimally invasive procedures (e.g. thoracoscopy, etc.).

The follow-up study on Nissen fundoplication (**Chapters 3 and 4**) has proven that the laparoscopic technique is associated with reduced incidence of retching, but this is still a significant problem at long-term follow-up. The mechanism of retching in these children is poorly understood, likely related to abnormal gastric emptying and the results in **Chapter 5**, demonstrate that the Nissen fundoplication performed laparoscopically improves gastric emptying. This may result in fewer disturbances to gastric motility due to less extensive tissue trauma on the vagus nerves and stomach compared to the open procedure. My future work will involve investigating the

effects that the Nissen fundoplication has on gastric motility, both for solids and liquid meals, and detecting the presence of disturbed gastric electrical activity (i.e. by performing electrogastrography) secondary to vagal nerve dysfunction that may explain the different incidence of retching in the open and laparoscopic group. Finally, patients in the randomised controlled trial of **Chapter 7** represent a precious cohort that I am planning to follow-up in the future to assess the best cosmetic results between open and laparoscopic pyloromyotomy.

Chapter 9

Publications and Presentations Arising From the Thesis

9.1 Publications

1. Pacilli M, Pierro A, Kingsley C, Herod J, Curry JI, Eaton S. **Absorption of carbon dioxide during laparoscopy in children measured using a novel mass spectrometric technique.** *British Journal of Anaesthesia* 2006; 97: 215-219.
2. Pacilli M, Eaton S, Maritsi D, Lopez PJ, Spitz L, Kiely EM, Drake DP, Curry JI, Pierro A. **Factors predicting failure of redo Nissen fundoplication in children.** *Pediatric Surgery International* 2007; 23: 499-503.
3. Eaton S, Pacilli M, Wood J, McHoney M, Corizia L, Kingsley C, Curry JI, Herod J, Cohen R, Pierro A. **Factors affecting (13)C-natural abundance measurement of breath carbon dioxide during surgery: absorption of carbon dioxide during endoscopic procedures.** *Rapid Communication in Mass Spectrometry* 2008; 22: 1759-1762.
4. Pacilli M, Pierro A, Lindley KJ, Curry JI, Eaton S. **Gastric Emptying is Accelerated following Laparoscopic Nissen Fundoplication.** *European Journal of Pediatric Surgery* 2008; 18: 1-2.
5. Hall NJ, Pacilli M, Eaton S, Reblock K, Gaines BA, Pastor A, Langer JC, Koivusalo AI, Pakarinen MP, Stroedter L, Beyerlein S, Haddad M, Clarke S, Ford H, Pierro A. **Recovery after open versus laparoscopic pyloromyotomy for pyloric stenosis: a double-blind multicentre randomised controlled trial.** *Lancet*. 2009; 373: 390-8.

6. Eaton S, McHoney M, Giacomello L, Pacilli M, Bishay M, De Coppi P, Wood J, Cohen R, Pierro A. **Carbon dioxide absorption and elimination in breath during minimally invasive surgery.** *Journal of Breath Research.* 2009; 3: 047005 (4pp).

9.2 Presentations

1. **Absorption of carbon dioxide during laparoscopy in children.** Pacilli M, Pierro A, Kingsley C, Herod J, Curry JI, Eaton S. 52nd Annual International Congress of the British Association of Paediatric Surgeons. Dublin, Ireland. July 12th – 15th, 2005.
2. **Redo fundoplication in children for recurrent gastro-oesophageal reflux: high failure rate.** Pacilli M, Lopez PJ, Maritsi D, Spitz L, Kiely EM, Drake DP, Curry JI, Eaton S, Pierro A. 2005 American Academy of Pediatrics National Conference and Exhibition. Section on Surgery. Washington, DC, USA. October 8th – 11th, 2005.
3. **Factors predicting failure of redo-Nissen fundoplication in children.** Pacilli M, Eaton S, Spitz L, Kiely EM, Drake DP, Curry JI, Maritsi D, Lopez PJ, Pierro A. 19th International Symposium of Paediatric Surgical Research. Florence, Italy. October 26th-28th, 2006.
4. **¹³C-natural abundance measurement of carbon dioxide absorbed during keyhole surgery in children.** Pacilli M, Pierro A, Kingsley C, Herod J, Curry JI, Eaton S. 2007 Conference of Stable Isotope Mass Spectrometry User Group. Newcastle, England. June 20th – 22nd, 2007.
5. **Quality of life improves after open and laparoscopic fundoplication: follow-up of an randomized controlled trial.** Pacilli M, Eaton S, McHoney M, Kiely EM, Drake DP, Curry JI, Lindley KJ, Pierro A. Peter Paul Rickman Prize Section

of the 54th Annual International Congress of the British Association of Paediatric Surgeons. Edinburgh, Scotland. July 17th – 20th, 2007.

6. **Gastric emptying is accelerated following laparoscopic Nissen fundoplication.** Pacilli M, Eaton S, Lindley KJ, Curry JI, Pierro A. 9th European Paediatric Surgeons' Association Conference. Istanbul, Turkey. June 18th – 21st, 2008.
7. **Laparoscopy shortens post-operative recovery following pyloromyotomy.** Hall NJ, Pacilli M, Eaton S, Reblock K, Gaines B, Pastor A, Langer JC, Koivusalo AI, Pakarinen MP, Stroedter L, Beyerlein S, Haddad M, Clarke S, Ford H, Pierro A. 9th European Paediatric Surgeons' Association Conference. Istanbul, Turkey. June 18th – 21st, 2008.
8. **Results of open and laparoscopic Nissen fundoplication: 4 year follow-up of a randomized controlled trial.** Pacilli M, Eaton S, McHoney M, Kiely EM, Drake DP, Curry JI, Lindley KJ, Pierro A. Peter Paul Rickham Prize Section of the 55th Annual International Congress of the British Association of Paediatric Surgeons. Salamanca, Spain. July 2nd – 5th, 2008.
9. **Laparoscopic pyloromyotomy is cheaper than open pyloromyotomy: economic analysis of a randomised controlled trial.** Carrington EV, Eaton S, Hall NJ, Pacilli M, Drake DP, Curry JI, Kiely EM, De Coppi P, Pierro A. 40th Annual Meeting of the American Pediatric Surgical Association. Fajardo, Puerto Rico. May 28th – 30th, 2009.

10. Effect of clinical characteristics at presentation on post-operative recovery following pyloromyotomy. Hall NJ, Pacilli M, Eaton S, Reblock K, Gaines B, Pastor A, Langer JC, Koivusalo AI, Pakarinen MP, Stroedter L, Beyerlein S, Haddad M, Clarke S, Ford H, Pierro A. 10th European Paediatric Surgeons' Association Conference and the 56th Annual Congress of the British Association of Paediatric Surgeons Joint Meeting. Graz, Austria. June 17th - June 20th, 2009.

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