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Reduced Preoperative Fasting in Children

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Abstract

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Preoperative fasting is recommended in order to reduce the risk of perioperative pulmonary aspiration. However, preoperative fasting may have negative effects on patient wellbeing and homeostasis. In this thesis, more lenient regimens for preoperative fasting in elective paediatric patients were assessed, with the aim to further improve preoperative fasting regimens.

Paper I investigated if paediatric patients allowed to drink clear fluids until called to surgery, had an increased risk of pulmonary aspiration. The incidence of perioperative pulmonary aspiration in children allowed free clear fluids until called to surgery was 3 in 10 000, as compared to 1-10 in 10 000 in previous studies where longer fasting intervals were studied. Hence, no increase of incidence for pulmonary aspiration was found.

Paper II investigated actual fasting times for clear fluids when applying two-hour fasting for clear fluids, and zero-hour fasting for clear fluids. When applying two-hour fasting, children were fasted median four hours for clear fluids. After transitioning to zero-hour fasting, median fasting time decreased to one hour, and the incidence of children fasting for more than six hours decreased from 35 % to 6 %. Abandoning the time limit for clear fluids significantly reduced the proportion of patients fasting for extended periods.

Paper III assessed gastric content volume after a light breakfast in children scheduled for elective general anaesthesia. Patients were examined with gastric ultrasound four hours after a light breakfast. Of the 20 patients included in the study, 15 had an empty stomach, 4 had clear fluids < 0.5 ml kg⁻¹ and one had solid content in the stomach. A light breakfast preoperatively might be safe, but amount and caloric restriction is needed to avoid the risk of perioperative pulmonary aspiration.

Paper IV investigated preoperative weight loss, glucose level and ketone bodies in paediatric patients presenting for elective surgery. The outcomes were tested for correlation to preoperative fasting times. Of the 43 children enrolled in the study, three had weight loss of more than 5 %, five children presented with blood glucose level < 3.3 mmol l⁻¹, and 11 children presented with ketone bodies > 0.6 mmol l⁻¹. There was no correlation between fasting time, and the respective outcomes. Even with a lenient fasting regimen, there is risk of mild preoperative dehydration, hypoglycaemia and ketogenesis.

In conclusion, the results obtained in the present thesis supports the shift to more lenient preoperative fasting regimens for clear fluids in elective paediatric patients.

Keywords: Fasting, Children, Preoperative, Pulmonary Aspiration

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To my family

List of papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. Andersson, H., Zarén, B., Frykholm, P.
Low incidence of pulmonary aspiration in children allowed intake of clear fluids until called to the operating suite.
Paediatric Anaesthesia 2015 Aug;25(8):770-7.
- II. Andersson, H., Hellström, P. M., Frykholm, P.
Introducing the 6-4-0 fasting regimen and the incidence of prolonged preoperative fasting in children.
Paediatric Anaesthesia 2018 Jan;28(1):46-52.
- III. Andersson, H. Frykholm, P.
Gastric content assessed with gastric ultrasound in paediatric patients prescribed a light breakfast prior to general anaesthesia. A prospective observational study.
Accepted for publication in Paediatric Anaesthesia
- IV. Andersson, H., Eerola, E., Frykholm, P.
Preoperative weight loss, hypoglycaemia and ketosis in elective paediatric patients, preliminary results from a prospective observational study
In manuscript

Reprints were made with permission from the respective publishers.

List of papers not included in this thesis

Andersson, H., Schmitz, A., Frykholm, P.

Preoperative fasting guidelines in pediatric anesthesia: are we ready for a change?

Current Opinion in Anaesthesiology 2018 Jun;31(3):342-348

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Abbreviations

NPO	‘Nil per os’
ASA	American Society of Anesthesiologists
6-4-2 regimen	6 hours fasting for solids, 4 hours fasting for breast milk and formula, 2 hours fasting for clear fluids
ESA	European Society of Anaesthesiologists
6-4-0 regimen	6 hours fasting for solids, 4 hours fasting for breast milk and formula, 0 hour fasting for clear liquids
ENT	Ear Nose Throat
ENT_2 h	Oral, Plastic surgery and Ear Nose Throat Anaesthesia Department when applying the 6-4-2 fasting regimen
ENT_0h	Oral, Plastic surgery and Ear Nose Throat Anaesthesia Department when applying the 6-4-0 fasting regimen
MP_0h	Main Paediatric Anaesthesia Department applying the 6-4-0 fasting regimen
OR	Odds Ratio
CI	Confidence Interval
GAA	Gastric Antral Area
GCV	Gastric Content Volume
OPÖ	Oral-, plastik-och öronoperation

1. Background

Preprocedural fasting is recommended before elective general anaesthesia, to reduce volume of gastric contents and hence reduce risk of perioperative pulmonary aspiration. Aspiration is an uncommon, but dreaded, complication to general anaesthesia (1). However, preprocedural fasting may have negative effects on fluid balance, blood glucose and wellbeing, especially in paediatric patients (2, 3). Although preprocedural fasting has been practiced for the last century, the optimal fasting interval is still not well defined. There is a need to find a balance between avoiding the event of pulmonary aspiration, and still preserving the well-being and physiological status of the patient. This is especially important in paediatric patients who have limited energy reserves and hence are less resistant to fasting compared to adults.

1.1 Preoperative fasting

1.1.1 The history of preoperative fasting

Preoperative fasting has been recommended since the end of the 19th century. In 1883, Lister published practical fasting guidelines suggesting that there should be no solid matter in the ventricle, however, it was suggested that tea or beef-tea two hours before anaesthesia was beneficial for the patient (4). This distinction between solids and fluids was maintained until the 1960s when most institutions adopted the “nil *per os* from midnight” (NPO) fasting regimen for elective healthy patients. The NPO regimen was straightforward to follow, easy for patients to understand and, if cancellation occurred, there was no problem with operating on another patient earlier than scheduled (4).

In 1997 Søreide *et al.* published new guidelines for the Norwegian Society of Anaesthesiologists (5) allowing clear fluids up until 2 hours prior to surgery, and in 1999 the American Society of Anesthesiologists (ASA) published their modern guidelines, recommending 6 hours fasting for solids, non-human milk and infant formula, 4 hours for breast milk and 2 hours for clear fluids prior to anaesthesia (6-4-2 regimen). The ASA recommend that children should be encouraged to drink clear fluids up until two hours prior to surgery, with the purpose of attenuating potential unwanted effects of prolonged fasting (6).

1.1.2 Recently published fasting statements and guidelines

In 2018, the European Society for Paediatric Anaesthesiology, along with L'Association Des Anesthesistes-Reanimateurs Pediatriques d'Expression Francaise and the Association of Paediatric Anaesthetists of Great Britain and Ireland, published a consensus statement recommending 1-hour fasting for clear fluids in paediatric patients (7). The statement includes an amount restriction of 3 ml kg⁻¹, or 55 ml to 1-5 year olds, 140 ml to 6-12 year olds and 250 ml to patients older than 12 years (7). This was later followed by statements from the European Society of Anaesthesiology (ESA) (8), the Society for Paediatric Anaesthesia in New Zealand and Australia (9), the Canadian Pediatric Anesthesia Society (10) and centres from the United states (11) and Germany (12), all advocating 1-hour fasting for clear fluids. Some centres are also allowing a light breakfast four hours prior to surgery (12-14). Recommendations for minimum fasting time are presented in table 1.

Table 1. Minimum fasting time in different guidelines. ASA = American Society of Anesthesiologists, ESA = European society of anaesthesiology

Ingested material	ASA(6)	ESA(8)	Uppsala
Clear liquids	2 h	1 h	0 h
Breast milk	4 h	4 h	4 h
Infant formula	6 h	4-6 h	4 h
Non-human milk	6 h	6 h	4 h
Solids	6 h	6 h	6 h

At the paediatric anaesthesia unit of Uppsala University Hospital, a more liberal fasting regimen has been implemented for more than two decades, (6-4-0 regimen). Thus, children scheduled for elective procedures requiring anaesthesia can drink clear fluids until they are called to theatre. Children scheduled in the afternoon are also allowed a light breakfast of yoghurt or gruel four hours prior to procedure. Otherwise, the hospital follows the European (15) and Scandinavian (16) guidelines with 4 hours fasting for breast milk and formula and 6 h fasting for solids. More details of this fasting regimen are presented in table 2. This local routine is motivated by the lack of evidence for clear fluid fasting, and a need to reduce prolonged fasting *e.g.* when rearrangements in the surgical schedule occur.

Table 2. The 6-4-0 fasting regimen

-
- For paediatric patients, 0-16 years' old
 - Allows for clear fluids up until the patient is called to surgery.
 - Clear fluids are water, fruit punch, fruit juice without pulp, coffee or tea without milk, and ice lollies.
 - Carbonated drinks, milk or yoghurt are not clear fluids.
 - 4 hours fasting for breast milk and formula
 - A light breakfast of gruel or yoghurt four hours prior to surgery
 - Fasting for solids from midnight
 - All patients are individually assessed by a paediatric anaesthetist so that the fasting regimen can be customized if increased risk of regurgitation is suspected
-

1.1.3 Compliance to fasting regimens

The currently recommended 2-hour limit for clear fluids unfortunately results in unreasonably long fasting times of 6-9 hours, see table 3 (2, 11, 12, 14, 17-20, 22-25). This is despite that several of the cited studies made ambitious attempts to reduce fasting times.

Optimizing preoperative fasting intervals has proved to be difficult. Newton *et al.* reported several interventions to reduce unnecessary fasting. Written information was revised, education was offered to all staff and the fasting limit for clear fluids was changed from 2 to 1 hour, making it possible to offer children a drink of clear fluids upon arrival at the preoperative day ward. These interventions reduced mean fasting time for clear fluids from 6.3 hours to 3.1 hours, and increased the proportion of patients fasting for less than four hours from 19 % to 72 % (20).

Table 3. Real fasting time for clear fluids and solids when applying the 6-4-2 fasting regimen

Study	Fasting time liquids	Fasting time solids
Engelhardt 2011 (2)	8 (0-21) **	12 (1-22) **
Schmitz 2011 (17)	5.5 (1.1-15.5) **	6.7 (4-20.2) **
Cantellow 2012 (18)	5 (0.5-24) **	9.5 (3-40) **
Arun 2013 (19)	4 (2-8.3) *	9 (4.8-13.5) *
Newton 2017 (20)	6.3 ± 4.5 *	
Andersson 2017 (14)	4 (0.5-17) **	
Schmidt 2018 (21)	3.9 (2-18.3) **	
Isserman 2019 (11)	9 *	

* Mean ± SD (range)
 ** Median ± SD (range)

In a recent study, Isserman *et al.* found mean fasting time for clear fluids to be nine hours, when applying 2-hour fasting for clear fluids. After a quality improvement project, containing updated information, offering drinks in the preoperative department and allowing clear fluids up until 30 minutes prior to arrival, mean clear fluid fasting time was reduced from nine to six hours, and the fraction of children fasting for less than four hours increased from 20 % to more than 60 % (11). The second paper in this thesis describes how paediatric patients prescribed two hours fasting for clear fluids are fasting a median of four hours.

The main reason for prolonged fasting occurring with the 6-4-2 regimen is that a two-hour limit for clear fluids demands a reliable assumption of when the procedure will start. Acute cases, rearrangements of the surgical lists and cancellations occur daily in busy surgical theatres, and inevitably lead either to multiple cancellations or long fasting intervals “just in case”. Anaesthetists need to adapt the fasting orders in case of a change in the surgical schedule or a delay. Furthermore, many children are scheduled as first case in the morning and have before this slept all night. Other reasons for extended fasting are incorrect instructions from health care personnel, and parents not understanding or not following instructions (18-20, 22). Anaesthetists, surgeons and ward nurses need to be educated about the benefits of shortened preoperative fasting and parents should be encouraged to feed children up until the last possible time.

1.2 Pulmonary aspiration

It is the fear of pulmonary aspiration of gastric contents that motivates preoperative fasting. The relationship between regurgitation, aspiration, and the life-threatening complication of aspiration pneumonitis was first described by Mendelson in the 1940's and is since also referred to as Mendelson's syndrome. Mendelson proved that the injuries of aspiration were a chemical injury, by instilling gastric aspirate into the tracheas of rabbits, which resulted in histological changes consistent with chemical pneumonitis. When the gastric acid was neutralized, the aspirate did not give any damage to the lungs of the rabbits (26). Aspiration of gastric juice immediately leads to destruction of alveolar lining and diffuse alveolar infiltration with development of interstitial pulmonary oedema. Within hours, the lungs are infiltrated by polymorphonuclear cells, and in these infiltrated parts, the lung parenchyma is destroyed. The remaining alveoli are filled with hyaline exudate and develop focal emphysema (27).

Symptoms from pulmonary aspiration can be dramatic, including tachypnoea, hypoxia, wheezing, coughing, cyanosis, pulmonary oedema and hypotension, and the syndrome may result in respiratory failure. However, fluids and mucus

are always present in the trachea and small pharyngeal aspirations occur frequently during sleep in healthy subjects, without causing any harm or danger (28). Most of aspirations occurring during general anaesthesia are silent, with neither symptoms nor sequelae (29) and in 25 % of all aspirational events, radiological findings will be initially absent (30).

1.2.1 Incidence of pulmonary aspiration

Aspiration pneumonitis is one of the most severe and fatal anaesthesia related complications, but it is rare and hence hard to study in the clinical setting. Several studies performed the past years have reported the incidence of peri-operative pulmonary aspiration in paediatric patients to be between 1 and 10 in 10 000 (31-37). For reported incidences and outcomes of pulmonary aspiration in earlier studies, see table 4.

Comparison between studies is complicated since different criteria are used to define pulmonary aspiration. Newton *et al.* defined aspiration as an unusual amount of fluid and/or vomitus, that resulted in the need for suctioning and/or lateral positioning (20). However, to be included as an aspirational event in the NAP4 project, the pulmonary aspiration had to lead to death, brain damage, the need for an emergency surgical airway, unanticipated ICU admission, or prolongation of ICU stay (38). Since definitions of outcome differ between studies, the results cannot be compared. The studies are also conducted in a wide range of settings and with diverse patient populations.

1.2.2 Outcome of pulmonary aspiration

Since the event of pulmonary aspiration is rare, the associated morbidity and mortality is hard to study. The consequences of pulmonary aspiration are divided into pneumonia due to aspiration of particulate matter, resulting in mechanical obstruction, and acid aspiration which is a chemical injury (29).

No previous studies of pulmonary aspiration in children report any mortality (1, 31-36, 39, 40). This again indicates that the incidence of pulmonary aspiration is low, and when an event occurs, the consequences are often mild. However, since reports from adult populations state that aspiration is a cause of anaesthesia-related death (38), these findings cannot be used as an excuse for frivolous airway management. Reported incidence and outcome in earlier studies are shown in table 4.

Table 4. Incidence of paediatric pulmonary aspiration and complications after aspiration. NR = not reported

Authors	Time period	Study design	Study size	Aspirational events(incidence)	Clinically significant aspiration	Need for ventilation support
Olsson <i>et al.</i> 1986 (34)	1967-1970, 1975-1983	Retrospective	NR	34 (0,06-0,09 %)	NR	NR
Tiret <i>et al.</i> 1988 (35)	1978-1982	Prospective	40 240	4 (0.01 %)	NR	NR
Borland <i>et al.</i> 1998 (32)	1988-1993	Retrospective	50 880	52 (0.10 %)	15 (0.03 %)	4 (7.7 %)
Warner <i>et al.</i> 1999 (33)	1985-1997	Prospective	56 138	24 (0.04 %)	9 (0.02 %)	6 (25 %)
Murat <i>et al.</i> 2004 (31)	2000-2002	Prospective	24 165	10 (0.04 %)	NR	NR
Walker 2013 (36)	2010-2011	Prospective	118 371	24 (0.02 %)	16 (0.01 %)	5 (20 %)
Andersson <i>et al.</i> 2015 (39)	2008-2013	Retrospective	10 015	3 (0.03 %)	2 (0.02 %)	0 (0 %)
Tan and Lee 2016 (1)	2000-2013	Prospective	102 425	22 (0.02 %)	NR	2 (9 %)
Newton <i>et al.</i> 2017 (20)	2016	Prospective	4828	2 (0.04 %)	0	0
Habre <i>et al.</i> 2017 (37)	2014-2015	Prospective	31127	29 (0.09 %)	NR	NR

1.2.3 Risk factors for pulmonary aspiration

For gastric content to reach the lung, the intragastric pressure must exceed the lower oesophageal sphincter barrier pressure, the vomitus must regurgitate via the oesophagus through the upper oesophageal sphincter, and finally pass down the trachea uninterrupted by protective airway reflexes such as laryngospasm or coughing. Risk factors for pulmonary aspiration are hence increased regurgitation (gastroesophageal reflux, strictures, decreased lower oesophageal sphincter tone), loss of protective airway reflexes (neuromuscular disorders, general anaesthesia) and increased gastric volume (inadequate fasting or delayed gastric emptying) (1). Since pulmonary aspiration is a rare event, the relationship between incidence and risk factors is hard to investigate and few studies specifically focussed on risk factors for perioperative pulmonary aspiration have been performed in the paediatric population.

1.2.3.1 Patient risk factors

The incidence of perioperative pulmonary aspiration in the paediatric population has been shown to be significantly higher than in adults (32-35). This is most likely due to a smaller ventricle, increased gastric pressure, extensive diaphragm breathing and swallowing of air during crying. Infants also tend to have a more relaxed oesophageal sphincter (41).

High ASA physical status, gastroesophageal reflux disease, dysphagia symptoms, gastrointestinal motility disorders, obesity and diabetes mellitus are all conditions that delay gastric emptying, and have been associated with increased risk of pulmonary aspiration (32, 34, 36, 37). However, pulmonary aspiration most commonly occurs in healthy ASA 1 and 2 children with no prior history (1, 40). Increased gastric content volume is prevented by prescription of preoperative fasting.

1.2.3.2 Emergency surgery

The risk for perioperative pulmonary aspiration is increased in emergency surgery (37, 40).

1.2.3.3 Anaesthesia and airway management

Most aspirations occur during induction, often associated with emergency airway management (33, 36, 38, 42). It can also occur during maintenance, usually associated with inadequate anaesthesia and an unprotected airway. Only a few of aspirational cases occur during emergence (42). Inadequate anaesthesia, both at induction and maintenance, predispose for pulmonary aspiration (36).

Not surprisingly, aspiration during the maintenance phase is more common in patients managed with laryngeal mask airway (36). Tracheal intubation allows

for a better protection of the airway. Correct assessment of risk for pulmonary aspiration and correct airway management is crucial to avoid adverse events.

Several anaesthetic drugs affect the oesophageal sphincters and the protective airway reflexes. Thiopental, inhalation anaesthetics and opioids relax the lower oesophageal sphincter, and inhalation anaesthetics, thiopental and non-depolarizing muscle relaxants relaxes the upper oesophageal sphincter. Remaining neuromuscular block at emergence increases risk for pulmonary aspiration (43-45).

Aspiration happens as a consequence of incomplete or failed assessment of the aspiration risk, or failure to modify the anaesthetic technique (38). Since previous studies have shown a higher risk for pulmonary aspiration when anaesthesia is managed by a trainee anaesthetist (38), patients with increased risk factors should be overseen by a more senior anaesthetist present in the theatre during induction.

1.2.4 Inadequate fasting as a risk factor for pulmonary aspiration

Previously, gastric fluid volume of at least 0.4 ml kg^{-1} body weight with a pH < 2.5 has been considered to be a risk factor for developing Mendelson's syndrome (46). This cut off was stipulated by Roberts and Shirley who directly instilled 0.4 ml acid into the right main-stem bronchus of one Rhesus monkey (46). Later animal studies have suggested a critical volume of 0.8 ml kg^{-1} (47). However, the authors did not establish a relationship between the volume in the stomach and what volume reaches the lungs (48).

Normal gastric fluid volume in fasted paediatric patients ranges from zero to $1.2\text{-}1.5 \text{ ml kg}^{-1}$ (49). Cook-Sather *et al.* pooled data from 611 healthy children presenting for elective surgery and found mean gastric fluid volume to be 0.4 ml kg^{-1} and 31 % of fasted healthy children having a gastric fluid volume $> 0.5 \text{ ml kg}^{-1}$ (50). Since the incidence of healthy fasting children having a gastric fluid volume $> 0.4 \text{ ml kg}^{-1}$ is over 30 % (1, 49, 51-53), it is doubtful if the early experiments can be translated to gastric volumes that will increase the risk of pulmonary aspiration in humans.

Beach *et al.* investigated the relationship between fasting and aspiration, and fasting status for liquids and solids were not found to be predictors for major complications or aspiration (54). In a recent study, Schmidt *et al.* reported 5.1 % of patients allowed clear fluids until premedication to have gastric fluid volume $> 4 \text{ ml/kg}$, compared to no patients in a 2-hour fasting group (21). If gastric content volume is a risk factor for pulmonary aspiration, children allowed liberal intake of clear fluids until premedication run a higher risk for perioperative pulmonary aspiration. A higher incidence of pulmonary aspira-

tion in centres applying more liberal fasting regimens than the currently recommended 2 hours has not been reported (20, 39). However, these regimens have only been in practice for a few years, and since the event of pulmonary aspiration is rare, further investigation is needed to provide unequivocal evidence pro or con more liberal fasting regimens.

The event of pulmonary aspiration is also dependent on other risk factors than preoperative fasting. Preventions that intend to minimize gastric content volume are not sufficient to reduce risk of pulmonary aspiration and it is important that anaesthetists are not settled with the knowledge of a long preoperative fast.

1.3 Gastric content volume

The volume and acidity of gastric content is dependent on gastric secretion, oral intake and gastric emptying.

1.3.1 The physiology of gastric emptying

As a meal passes through the oesophagus into the stomach, the smooth muscle of the fundus relaxes and the gastric wall distends to allow storage of food without increased intragastric pressure, this is known as receptive relaxation (55). Increases in gastric volume does not increase intragastric pressure, but this is only until a threshold is reached, after which intragastric pressure rises steeply, see figure 1. Receptive relaxation is absent in new-borns, and may explain why gastroesophageal reflux is more common in new-borns than in older infants (55).

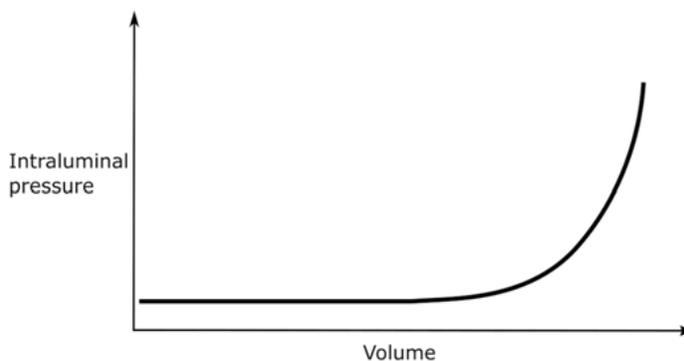


Figure 1. The relationship between gastric content volume and intraluminal gastric pressure. Due to adaptive relaxation, increased intragastric volume does not affect intragastric pressure until the volume exceeds the threshold.

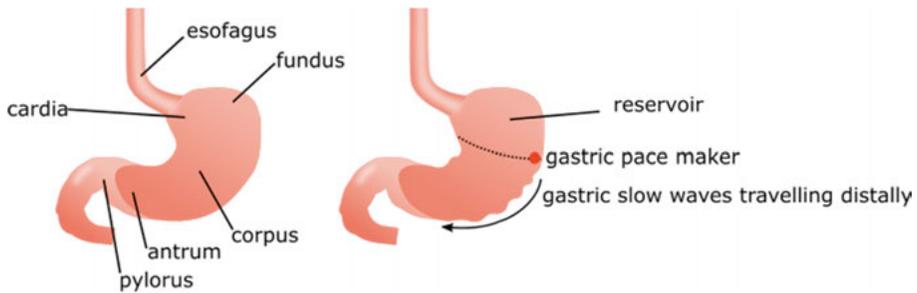


Figure 2. Stomach anatomy and related functions. The fundus and first 1/3 of the corpus serve as a reservoir for ingested food, while the distal 2/3 of the corpus and antrum, churns and mixes food with digestive juices. The pyloric sphincter regulates the outflow to the duodenum.

The ingested meal is accommodated in the fundus, which acts as a reservoir for the food and regulated forward flow. Solids are then redistributed to the distal stomach where they are ground into smaller particles that are mixed with gastric juice, see figure 2. Solids need to be broken down into pieces of 1-2 mm in diameter to be able to pass through the pylorus. During this process, there is no emptying of solids and it hence causes a lag phase in gastric solid emptying (55).

When the stomach is emptied, the migrating motor complex contracts the walls of the stomach and intestines, sweeping remaining food and indigestible products through the gastrointestinal tract. During these contractions, the pylorus is completely relaxed (56).

1.3.2 Gastric emptying rate

The rate of gastric emptying depends on what is ingested, *e.g.* caloric density, amount and temperature of the meal. Gastric emptying is thought to be slower in neonates. However, in a recently published meta-analysis, there was no correlation between age and gastric emptying, when comparing 1457 patients, from neonates to adults, albeit the authors found considerable interindividual variations in gastric emptying (57).

To ensure that all nutrients are absorbed, gastric emptying is regulated to distribute 1 to 4 kilocalories per minute to the proximal small intestine (58). Fat, proteins and carbohydrates induce the release of mediators that slow gastric emptying, reduce appetite and relax the ventricle walls (59). Gastric emptying is further affected by the blood glucose level. Hyperglycaemia is associated with a reduction in fundic tone and antral contraction, and stimulation of py-

loric contractions, which leads to slowing of gastric emptying, while hypoglycaemia accelerates gastric emptying (60). Gastric emptying rates of different entities are displayed in figure 3.

1.3.2.1 Solids

Emptying of solids start after a lag phase of approximately 20-60 minutes and then follows a linear emptying pattern, depending on the amount ingested and the caloric density of the meal (60, 61). Thus, it is necessary to contemplate both fasting time and the type of solid ingested. A light meal can be digested in 4 hours (13, 62-64), while a heavy meal takes up to 9 hours to clear (65, 66).

Indigestible solids, such as cellulose from vegetables, may not break down into pieces that are small enough. These larger parts remain until the stomach has emptied everything else and are then emptied into the duodenum during the fasting phase (56).

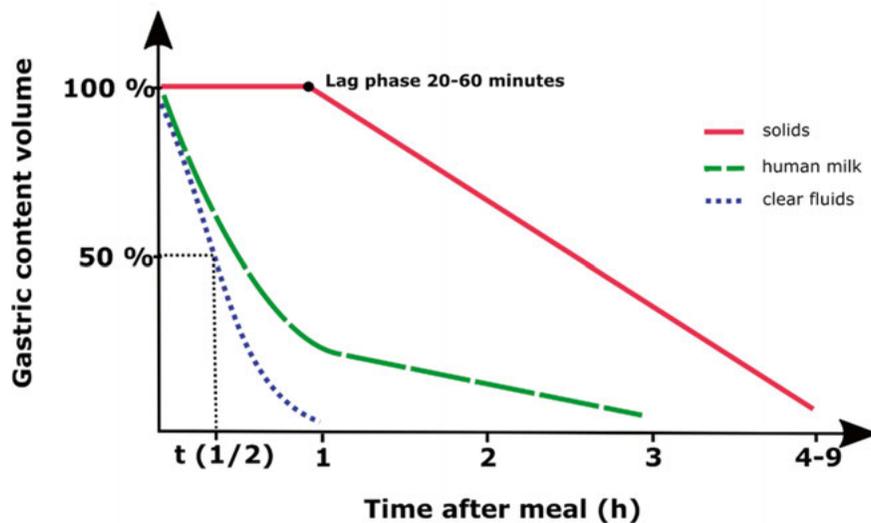


Figure. 3. Gastric emptying patterns of solids, human milk and clear fluids. Solids are emptied in a linear manner following a lag phase. Human milk empties with an initial fast phase followed by linear elimination. Emptying time for solids and milk depends on the caloric density of the meal. Clear fluids follow first order kinetics with half-life of 10-26 minutes.

1.3.2.2 Milk products and breast milk

Infants are usually fed breast milk or formula for the first months of life. Human breast milk has a bimodal emptying pattern with a rapid initial phase followed by a slower phase (67). The half-life of human breastmilk in the stomach is 25-48 minutes (68-70) and it empties in about three hours (71). Formula has a more linear emptying pattern and a half-life of 51-78 minutes (68-70). Just like with solids, the caloric content of the milk affects gastric emptying, with caloric enriched breast milk having longer gastric emptying time than regular breast milk (72).

Cow's milk is separated into clear fluid and a semi-solid curd, which is eliminated with a half-life of 46-86 minutes in healthy children (53, 66, 67, 69, 73). The emptying pattern shows an initial fast emptying, followed by a slower linear emptying phase.

Full milk is a relatively caloric rich nutrient, and the emptying time depends on the amount of calories ingested which is a function of both volume and fat content. Du *et al.* recently reported that almost 300 ml of 2% cow's milk was eliminated within 202 minutes (74).

1.3.2.3 Clear fluids

Clear fluid emptying occurs more rapidly than that of solids, and when both are present, liquids are emptied first. Liquids are emptied from the stomach without a lag phase, following first-order kinetics with a half-life of 10-26 minutes and an emptying time of less than one hour, but with considerable interindividual variation (60). Clear fluid half-life also seems dependent on the amount of fluids ingested, with half-life of 27 minutes for 7 ml kg⁻¹ syrup, and 20 minutes for 3 ml kg⁻¹ syrup (75).

Schmitz *et al.* investigated gastric content volume with MRI after an overnight fast, and then 30 minutes, 1 hour and 2 hours after drinking 7 ml kg⁻¹ syrup. Mean gastric content volume was lower two hours after drinking clear fluids, than after an overnight fast, and one hour after drinking the syrup, mean gastric content volume was 1.27 ml kg⁻¹. However, after only 30 minutes of fasting, mean gastric content volume was almost 3 ml kg⁻¹ (76).

Schmidt *et al.* (21) compared gastric content volume in children fasted for 2 hours, to children allowed clear fluids until premedication. There was no difference in mean gastric content volume, which was < 0.5 ml kg⁻¹ in both groups. However, when comparing fractions of patients with gastric fluid volume of more than 1, 2 and 4 ml kg⁻¹ respectively. The authors found a significantly higher occurrence in the liberal fasting group (21).

1.3.3 Delayed gastric emptying

The rate and pattern of gastric emptying varies between healthy individuals and is hence hard to predict with accuracy. There are some conditions that are known to delay gastric emptying and hence should prompt the anaesthetist to re-evaluate the anaesthesia plan. The most common reasons for preoperative delayed gastric emptying are medications, diabetes, obesity and emergency surgery (58, 77). In diabetes, it seems like both hyperglycaemia and hyperinsulinemia suppress the migrating motor complex and increase contractility in the pylorus (58). Gastric emptying is also delayed by pain, anxiety, stress, critical illness and trauma (78). Drugs that delay gastric emptying are muscarinic cholinergic receptor antagonists, beta-agonists, dopamine agonists, ondansetron and opioids (58), while erythromycin stimulates gastric emptying. (78) Liberal fasting do not apply for patients with gastro-oesophageal reflux, renal failure, severe cerebral palsy, enteropathies, oesophageal strictures, achalasia, diabetes, gastrointestinal motility disease or emergency surgery (8, 14).

1.3.4 When is the stomach empty?

The answer is of course: never. In the fasted state, normal fasted gastric content volume ranges from nil to 1.5 ml kg⁻¹ (49). Gastric emptying of different entities follows different emptying patterns and have great interindividual differences. It is likely that the stomach is empty four hours after a light meal, three hours after ingestion of breast milk and a little longer after ingestion of cow's milk or formula, and about one hour after ingestion of clear fluids. However, it seems like the caloric content of the ingested nutriment has a bigger effect on gastric emptying than the entity. When comparing beverages in adult patients, Okabe *et al.* found that non-human milk had same gastric emptying rate as pulp less orange juice when the milk was diluted with water to the same caloric density as the juice (79). Whether this calls for shortened fasting times for milk or longer fasting times for pulp less juice remains unresolved. Nonetheless, it certainly should encourage contemplation of caloric density, rather than just stick to set time limits for different nutriments.

Emergency surgery patients should always be considered to have a full stomach, regardless of fasting time (77). Conversely, there are also elective patients that will show up to surgery with a full stomach regardless of sufficient fasting and absence of risk factors (80). Thus, the anaesthesiologist must be aware of this variability and be prepared for the child that vomits on induction, irrespective of fasting time.

1.3.5 Gastric pH

Gastric pH is thought to affect the severity of pulmonary aspiration. Fasted pH is usually low because of the presence of basal secretion of hydrochloric acid and the absence of food and liquid to buffer the gastric acid (81).

When comparing children fasted two-hours for clear fluids to patients allowed clear fluids until premedication, Schmidt *et al.* found no difference in gastric pH (21). Several studies comparing gastric volume and pH in paediatric patients allowed clear liquids up to 2 h before induction of anaesthesia, with patients who fasted for longer intervals, have shown no significant differences in gastric volume or pH (17, 51, 82-86). In a small pilot study, fasting times down to 20 minutes for clear fluids did not affect gastric pH, see figure 4 (Andersson, Hellström, Frykholm, unpublished).

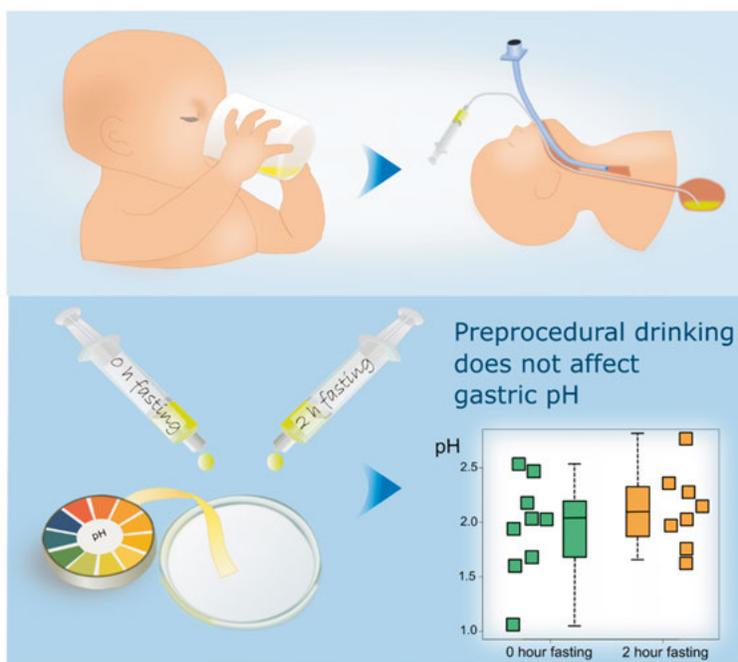


Figure 4. Showing effects of 2- vs. 0-hour fasting for clear fluids, on gastric pH at induction, in paediatric patients. Gastric acid was aspirated through an oro-gastric tube at induction. Gastric pH was measured and compared between children fasted 2 and 0-hours for clear liquids, respectively. There was no difference in gastric pH between the two groups (Andersson, Hellström, Frykholm, unpublished).

1.4 Physiological effects of fasting

1.4.1 Normal fasting metabolism

Regulation of the body's energy reserve is mainly controlled by insulin and glucagon. During fasting, glucagon acts on the liver to increase the plasma glucose level and proteins, glycogen and lipids are broken down to create substrate for gluconeogenesis and ketone bodies (87). Relative insulin resistance in skeletal muscle and adipose tissue ensures that the limited stores of glucose will be reserved for the brain (81).

1.4.2 Physiological response to surgical stress

In case of surgical stress, afferent nerves and cytokines from the injury activate the hypothalamic-pituitary-adrenal-axis and increase activity of the sympathetic nervous system (88). The aim of the response is to maintain plasma volume, increase cardiac output and mobilize energy reserves. The metabolic response to fasting and surgical stress is shown in figure 5.

Preoperative fasting exacerbates the surgical stress response (89) and debilitates important systems such as fluid homeostasis, endocrine response and gut integrity that are normally activated during stress (90). In animal models, it is beneficial to be in a fed as opposed to a starved state when facing surgical stress, such as haemorrhage. Preserved glycogen stores enable rapid glucose mobilization and provides a hyperosmolar state which is beneficial to fluid homeostasis, with increased plasma volume, improved heart function and increasing peripheral blood flow (91, 92).

1.4.2.1 Perioperative insulin resistance

The stress of surgery induces release of catecholamines, cortisol and glucagon which increases insulin resistance in skeletal muscle and adipose tissue (94-96). Fasting induces insulin resistance (97, 98), and though this may be beneficial in the state of starvation, postoperative insulin resistance is, by way of hyperglycaemia, associated with increased infectious complications and elongated postoperative length of stay (99-101).

1.4.2.2 Hypoglycaemia

Children are more sensitive to fasting than adults due to smaller stores of glycogen in liver and muscles, and the younger the child, the faster hypoglycaemia and ketogenesis will develop (102-104). Even if symptomatic hypoglycaemia is often quickly detected and corrected, asymptomatic hypoglycaemia is an existing problem in paediatric patients (104). The incidence of preoperative hypoglycaemia in elective paediatric patients ranges from 0-9 % (3, 105, 106) and shortened fasting time leads to decreased incidence of hypoglycaemia (107).

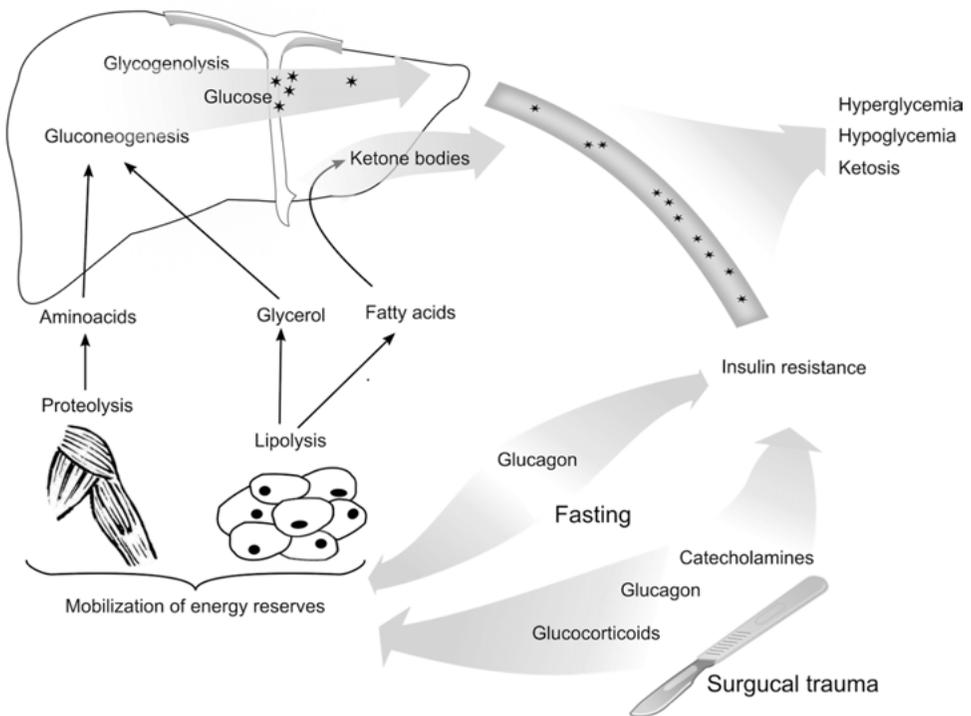


Figure 5. Showing the metabolic response to fasting and surgical stress. Fasting and surgical stress independently induce insulin resistance and mobilization of energy reserves. This leads to an initial hyperglycaemia, but as glycogen stores are consumed, hypoglycaemia and ketosis emerge.

1.4.2.3 Ketogenesis

Fasting time correlates to concentration of ketone bodies, anion gap, base excess, osmolality and bicarbonate (3), and shortened fasting times will decrease the incidence of increased ketone body concentration (107).

1.4.2.4 Haemodynamic

Shortened fasting time for clear liquids preserves intravascular volume and thus improves hemodynamic conditions (102, 107, 108). Children allowed clear liquids before surgery appear less likely to show signs of dehydration such as prolonged capillary refill, absence of tears, dry mucous membranes and unwell appearance (109). Optimized fasting intervals decrease incidence of hypotension and debilitates the drop in mean arterial pressure at induction (107).

1.4.3 Preoperative carbohydrate loading

In adults, enhanced recovery after surgery protocols recommend a preoperative carbohydrate-rich drink two hours prior to surgery (*110*). This treatment intends to alter the metabolism from a fasted to a fed state, and thereby optimise preoperative conditions. In paediatric patients, preoperative carbohydrates two hours prior to induction reduces preoperative gastric content volume and postoperative nausea, compared to fasting according the 6-4-2 regimen (*111*) or after eight hours of fasting (*112*). Preoperative carbohydrates also decrease postoperative insulin resistance in children, compared to fasting (*113*).

1.5 Psychological effects of preoperative fasting

Fasting leads to thirst, hunger and anxiety. Young children are used to eating more often than adults and it is also hard to explain to a small child why they cannot eat. Preoperative fasting may thus lead to additional anxiety and discomfort, in children already anxious because of the hospital environment and preoperative procedures. Not surprisingly, several studies show that children allowed to drink prior to surgery show less thirst, hunger and discomfort, than children that are kept fasting for longer periods (2, 21, 24, 51, 82, 86, 109, 114-117). Shortened fasting time for clear fluids also decreases postoperative pain and increases tolerance to postoperative nausea and vomiting (118). In paediatric patients, the preoperative fasting also affects the accompanying caregiver. When comparing 1 and 2 hour fasting for clear liquids, caregivers are more satisfied with the 1 hour regimen (119).

2. Aims

The overall aim of this thesis was to assess the effects of implementing a more lenient regimen for preoperative fasting in paediatric elective patients.

The specific aims were:

- I. To study if zero-hour preoperative fasting for clear liquids entails an increased risk of perioperative pulmonary aspiration, in elective paediatric patients.
- II. To study if a more lenient fasting regimen for clear fluids decreases the total fasting time, and if it can reduce the number of patients subjected to extended preoperative fasting, in elective paediatric patients.
- III. To investigate if a preoperative breakfast of semi-solids empties from the ventricle within four hours, in elective paediatric patients.
- IV. To investigate the incidence of preoperative weight loss, hypoglycaemia and increased ketone bodies in small children when the 6-4-0 regimen is implemented.

3. Materials and methods

3.1 Paper I

3.1.1 Patients and study protocol

Elective patients anaesthetised in the paediatric anaesthesia department of Uppsala University Hospital from January 2008 to December 2013 were enrolled. Inclusion criteria was age 6 months to 16 years, elective surgery and general anaesthesia. Emergency cases were excluded, as were children anaesthetized for other procedures than surgery, such as radiation therapy or radiological examinations. All anaesthesia charts were reviewed retrospectively in the electronic medical record system. In case of vomiting, regurgitation and/or aspiration, the discharge note and any available chest x-rays were retrieved and analysed.

3.1.2 Definition of outcome

The outcome measurement of this study was categorical, the patients either had or had not aspirated. The main outcome, pulmonary aspiration, was defined as children vomiting during anaesthesia with observations of gastric contents in the airway and/or radiological findings consistent with aspiration and/or symptoms of respiratory distress during the postoperative period. This outcome was clinically relevant and used the same definition of pulmonary aspiration as many previous studies, which made comparison of incidence possible. The secondary outcome, suspected pulmonary aspiration, was defined as children vomiting during anaesthesia and showing transient respiratory symptoms, but lacking observation of gastric contents in the airway, lacking postoperative symptoms of respiratory distress and not showing any findings in postoperative x-rays. This secondary outcome was added due to the risk that the strict requirements for the primary outcome would result in cases of pulmonary aspiration not being included. Timing for the event was limited to the operating room.

3.1.3 Statistics

Only descriptive statistics were used. The data were presented with sum and percentages.

A power analysis was performed. The risk for pulmonary aspiration in the elective paediatric population was assessed, from former studies of incidence, to be 4 in 10 000. A randomized controlled trial would demand 70 200 participants in each group to detect an increase from 0.04 % to 0.05 %, with a significance level of 0.05 and power of 80 %. However, this was an observational study and the results were planned to be compared to other studies. Several different scenarios were calculated. An increase from 0.04 % to 0.07 % would demand about 9 000 patients, which was feasible in our department during a ten-year period.

3.2 Paper II

3.2.1 Patients and study protocol

Time from last drink to induction was measured in elective paediatric patients aged six months to 17 years. Emergency cases and children already intubated on arrival to theatre were excluded.

Three groups of patients were investigated. The first group (ENT_2h) consisted of paediatric patients scheduled for elective procedures in the oral surgery, plastic surgery or ear-nose-throat anaesthesia department when applying two hours fasting for clear fluids (6-4-2 fasting regimen). The second group, (ENT_0h) were assessed at the same department, one year after changing pre-operative fasting practice into allowing free clear fluids until called to surgery (6-4-0 fasting regimen). A third group (MP_0h) was recruited from the main paediatric operation unit where the 6-4-0 fasting regimen have been implemented since 1999.

When arriving at the operating theatre, patients and caregivers were asked when the child last ate or drank, and the reported respective times were documented. A few sips of water with the premedication did not count as if the patient had had a drink.

The main outcome was mean fasting times for clear fluids in the three groups. As a secondary outcome, fasting for more than 4, 6 and 12 hours for clear fluids was analysed. Children under 36 months of age was analysed as a subgroup.

3.2.2 Statistics

When designing the study, a power analysis concluded that 18 patients in each group were needed to detect a difference in mean fasting time of 4.5 hours, with a significance level of 0.05 and power of 80 %. The 4.5-hour difference was chosen from the results of a pilot study, showing a difference in mean

fasting times of 4.5 hours when comparing children fasted according to the 6-4-2 and 6-4-0 fasting regimens.

Fasting times were presented as median values with 95 % confidence intervals. Due to unequal variance, comparison of total fasting times between groups was performed using Kruskal-Wallis ANOVA. Frequencies of patients fasting for extended times were reported as percentages. Comparisons between groups were initially planned to be done with chi-square-test. However, during the submission process, this was changed to using binary logistic regression to produce odds ratios with 95 % confidence intervals. The effect of the predictors “group”, “age”, “time of day for surgery”, and “in/out patient status” on the outcome “fasting six hours or more” were quantified by binary logistic regression analyses. In crude analyses, the effect of each predictor was separately evaluated against the outcome. Adjusted analysis was not performed, due to the small sample size. Odds ratios (OR) and their 95% confidence intervals (CI) are presented. The level of significance was set to $\alpha = 0.05$.

3.3 Paper III

3.3.1 Patients and study protocol

Children aged 1-6 years prescribed of a light breakfast at the preoperative assessment were enrolled in this observational cohort study. The main outcome of the study was binary, either a full or an empty stomach, derived from the clinical algorithm suggested by van de Putte and Perlas (see figure 6) (120).

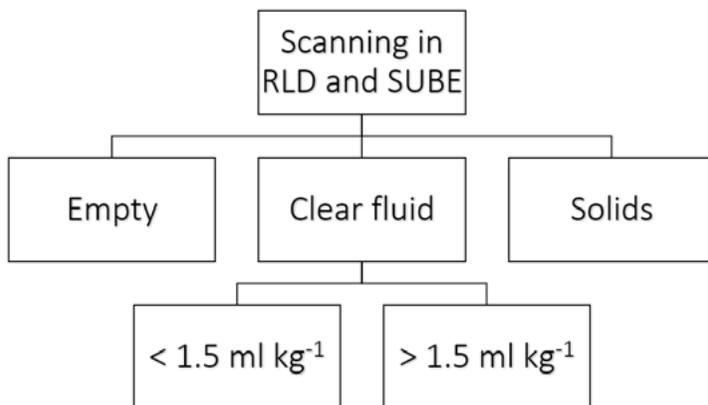


Figure 6. Diagram showing a clinical algorithm for gastric ultrasound and aspiration risk assessment suggested by Van de Putte and Perlas (120). An empty stomach or clear fluids $< 1.5 \text{ ml kg}^{-1}$ suggest low risk for pulmonary aspiration. Solids or clear fluids $> 1.5 \text{ ml kg}^{-1}$ suggests a high risk for pulmonary aspiration.

Ultrasonic visualisations of the gastric antrum were made. If an empty stomach was visualised in the right lateral decubitus position, no further measurements were made. If there were solids or clear fluids, two orthogonal diameters were measured, two times in two different pictures. The biggest diameter was used to calculate gastric antral area (GAA). Gastric content volume was then calculated using the formula by Schmitz: $GCV = 0.0093 \times GAA \text{ (sq-mm)} - 0.96$ (121).

3.3.2 Gastric ultrasound

The gastric ultrasound examinations were made using the method described by van de Putte and Perlas (120). In short, the patient is placed in the right lateral decubitus position and the gastric antrum is visualized between the left lobe of the liver and the pancreas in a sagittal plane in the epigastrium. To standardise the scanning plane through the antrum one could either use the superior mesenteric vein or artery (120). It is possible to determine the type of content in the ventricle using ultrasound, see figure 7. Clear fluids appear hypoechoic. Milk, thick fluids or suspensions have increased echogenicity. After a solid meal, a frosted-glass pattern appears, caused by the substantial amount of air mixed with the food. The small fractions of air create artefacts which typically blur the posterior wall of the antrum (122, 123). The empty antrum is flat with juxtaposed walls, in the sagittal plane, it is round and looks like a bull's eye (122, 123).

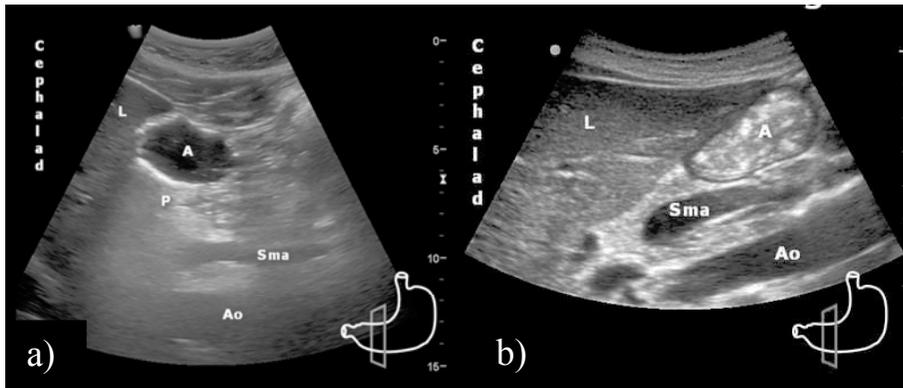


Figure 7. Ultrasound images showing the gastric antrum. a) Gastric antrum containing clear fluid, hypoechoic content. b) Gastric antrum with solid content. A-antrum, L-liver, P-pancreas, Ao-aorta, SMA-superior mesenteric artery.

Figures from www.gastricultrasound.org ©gastricultrasound, All Rights Reserved, with permission.

3.3.3 Statistics

Patients characteristics were presented as mean with 95 % confidence intervals. The main outcome was reported as percentage with 95 % confidence interval.

The material was considered too small for binary logistic regression. The results were hence only presented using descriptive statistics.

No power analysis was performed. Previous studies performed in healthy volunteers had not found any children with a full stomach four hours after a light breakfast. Twenty patients were judged to be sufficient for this first observational study of a light breakfast in clinical practice.

3.4 Paper IV

3.4.1 Patients and study protocol

Paediatric patients aged 0-6 years, scheduled for elective surgery under general anaesthesia were enrolled in this prospective, observational cohort study. Children undergoing multiple procedures were only included once. Since this was a study of preoperative metabolism in fasted patients, children who received parenteral nutrition, intravenous fluids, were admitted to critical care or had metabolic disorders were not included.

The main outcome was weight change prior to anaesthesia. Secondary outcomes were ketone bodies and blood glucose level at induction. Weight loss of 5 % was set as clinically significant since this is the grade of dehydration when distinguishable clinical symptoms emerge in paediatric patients. Moderate hypoglycaemia was defined as blood glucose concentration ≤ 2.8 mmol l⁻¹ and mild hypoglycaemia as glucose 2.9-3.3 mmol l⁻¹. Ketone bodies were considered deviating if ≥ 0.6 mmol l⁻¹.

The patients were weighed at 7 pm in the evening prior to surgery, and at 7 am the next morning. If the induction was later than 8:30 am, an additional weight was collected before the patient left the ward to go to theatre. Blood glucose level and ketone bodies were measured at induction and the blood sample was collected in conjunction with iv. cannulation.

3.4.2 Statistics

Sample size calculation using G*Power 3.0 using A priori, indicate that a sample size of 82 children would allow the detection of a 0.3 correlation coefficient between fasting times and ketone body concentration, with 80 % power

and 5 % alfa error. The 0.3 correlation coefficient was taken from Dennhardt *et al* (3).

The outcome measurements were analysed using multiple linear regression for each outcome with age and fasting time as explanatory variables. Age was treated as a categorical variable with age groups 1-2 months, 3-12 months, and > 12 months. The shortest fasting time for clear fluids, breast milk and solids was used as explanatory variable for weight loss. The shortest fasting time for breast milk and solids was used as explanatory variable for ketone bodies and blood glucose level.

3.5 Ethical considerations

Paper I, II, III and IV have been approved by the local ethics committee in Uppsala, Sweden (Dnr. 2013/450, Dnr. 2014/487/1, Dnr 2017/294 and Dnr. 2016/433, respectively).

In the first paper, informed consent by study participants and caregivers were waived, whilst in the second, third and fourth paper, oral and written informed consents, respectively, were collected from caregivers.

4. Results

4.1 Paper I

11 535 procedures, dating from January 2008 to December 2013, were enrolled in the study. Of these, 1520 patients were excluded, and in all, 10 015 procedures on 9 889 patients were included, consort diagram in figure 8.

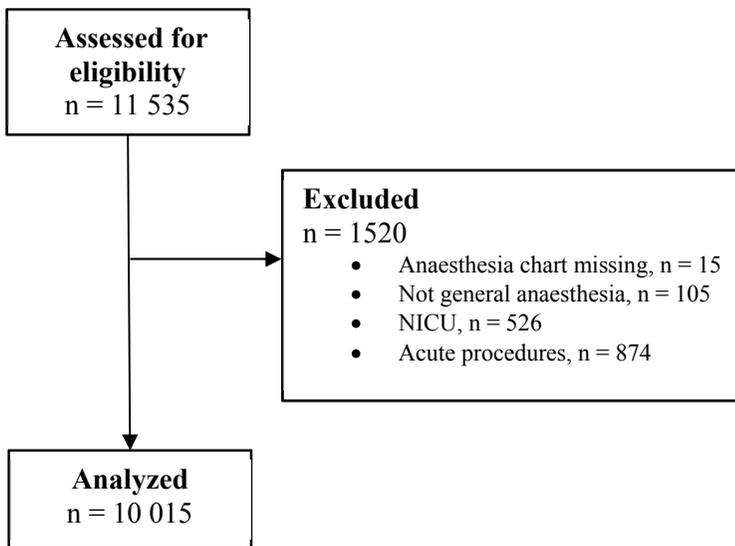


Figure 8. Enrolment and exclusion of patients.

Age ranged from 0 to 16 years (mean \pm SD; 6,5 \pm 5,2). Induction was intravenous in 87 % of procedures and inhaled in 13 % of procedures. For airway control, laryngeal mask was used in 54 % of procedures and intubation in 38 % of procedures. The remaining 8 % were other methods of airway management e.g. spontaneous breathing, mask ventilation or tracheostomy.

Three cases of pulmonary aspiration were found, giving an incidence of 0.03 %. These patients vomited during anaesthesia and showed radiological findings consistent with aspiration postoperatively. Two of them also presented with postoperative respiratory symptoms. Neither of the patients needed mechanical ventilation or intensive care. Both patients who developed symptoms were free from symptoms the day after surgery.

The first case was a 16-year-old girl, ASA classification II, admitted for gastroscopy due to epigastralgia, weight loss and vomiting. Immediately after the endoscopist found the fundus full of green liquid (approximately 1 L), the patient vomited and was intubated. No symptoms of respiratory distress during anaesthesia were noted. Postoperatively, the patient had chest ache, diminished breath sounds and SpO₂ was reduced to 91-92 %. A chest x-ray showed radiological findings consistent with pulmonary aspiration. The patient was already treated with antibiotics and no further treatment was initiated. The day after gastroscopy, the child did no longer have any symptoms. A gastrointestinal transit time exam later showed a duodenal stenosis, probably due to Crohn's disease.

The second case was a six-year-old girl, ASA classification II, admitted for urological surgery. At induction, the child vomited and desaturated for a short while. A chest x-ray was performed the same day, showing signs consistent with pulmonary aspiration. The patient did not show any postoperative symptoms of respiratory distress or fever but was treated with systemic antibiotics. No symptoms developed and she was discharged the next day.

The third case was a healthy five-year-old boy admitted for day care surgery of a hydrocele. During maintenance, the boy vomited and was intubated. No signs of respiratory distress were noted at the event, but postoperatively the child developed a fever, and when examined, rales over the right lung. An x-ray performed the same day as the procedure showed radiological signs of pulmonary aspiration. The boy was treated with systemic antibiotics. He was observed in the surgical ward for one night, the symptoms diminished, and he was discharged the next day.

Fourteen patients showed transient symptoms of respiratory distress immediately after vomiting, but no gastric contents were observed in the trachea, endotracheal tube or laryngeal mask and the patients did not show any signs of respiratory distress postoperatively. In the two cases where chest x-ray was performed, no signs of pulmonary aspiration could be seen. These fourteen cases were thence defined as suspected pulmonary aspiration, giving an incidence of 0.14 %. See the original article (Paper I) for closer description of all events of suspected pulmonary aspiration.

There were no cases needing ventilation support or intensive care, there was no mortality and no procedures were cancelled due to aspirational events.

4.2 Paper II

Two-hundred and three patients were included. In the oral, plastic surgery and ear, nose, throat anaesthesia department, patients fasting according to the 6-4-

2 fasting regimen (ENT_2h) (n = 66) had a median fasting time for clear fluids of 4 hours (95 % CI 3.1 – 4.5 hours). After shifting to the 6-4-0 fasting regimen (ENT_0h) (n = 64), median fasting time for clear liquids was reduced to one hour (95 % CI 0.9 – 1.5 hours), (p<0.0001).

In the main paediatric anaesthesia unit (MP_0h) (n = 73), median fasting time was 2.3 hours (95 % CI 1.7 – 3.0 hours). The median fasting time was significantly shorter than when the 6-4-2 fasting regimen was applied in the ENT (p < 0.001), but also significantly longer than when the ENT changed to the 6-4-0 fasting regimen (p < 0.01). The distribution of fluid fasting duration in all three groups are shown in figure 9.

Cut-offs for extended fasting were set at 4, 6 and 12 hours. After shifting fasting regimen in the ENT unit, from two to zero-hour fasting, patients fasting four hours or more decreased from 56.1 % to 18.8 % (OR=0.18, 95 % CI: 0.08-0.39, p<0.001), patients fasting six hours or more decreased from 34.8 % to 6.2 % (OR=0.13, 95% CI: 0.03-0.35, p<0.001), and patients fasting 12 hours or more decreased from 15.2 % to 3.1 % (OR=0.18, 95 % CI: 0.03-0.72, p=0.032), table 5 and 6.

Table 5. Fractions of patients fasting more than 4, 6 and 12 hours when applying different fasting regimens

	ENT_2h (1) n = 66 p (95 % CI)	ENT_0h (2) n = 64 p (95 % CI)	MP_0h (3) n = 73 p (95 % CI)
Fasting ≥ 4 hours	n = 37 56.1 % (44.1 %:67.4 %)	n = 12 18.8 % (11.1%:30.0%)	n = 25 34.3 % (24.4%:45.7%)
Fasting ≥ 6 hours	n = 23 34.8 % (24.5 %:46.9 %)	n = 4 6.3 % (2.5 %:15.0 %)	n = 17 23.3 % (15.1%:34.2%)
Fasting ≥12 hours	n = 10 15.2 % (8.4 %:25.7 %)	n = 2 3.1 % (0.9 %:10.7 %)	n = 6 8.2 % (3.8%:16.8%)

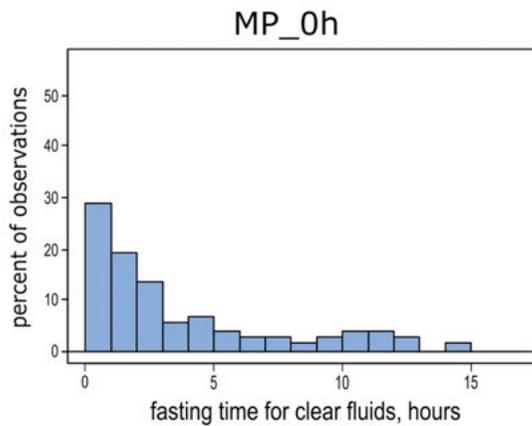
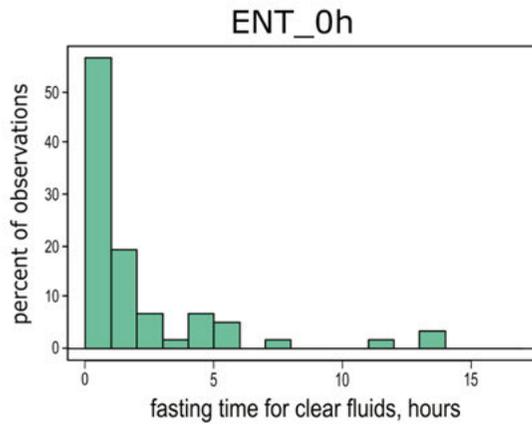
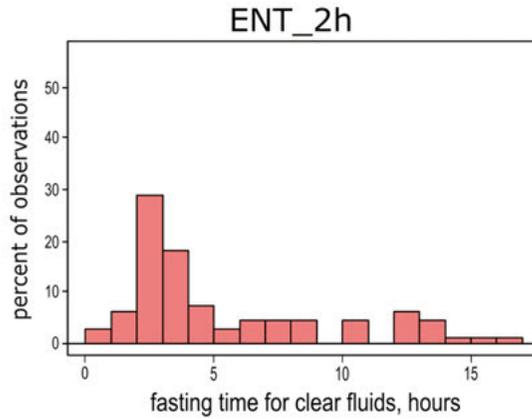


Figure 9. Histograms showing distribution of actual fasting time for clear fluids when fasting 2 or 0 hours for clear fluids. ENT_2h = the ENT department when applying 2-hour fasting for clear fluids, ENT_0h = the ENT department when applying 0-hour fasting for clear fluids, MP_0h = the main paediatric department when applying 0-hour fasting for clear fluids.

The incidence of prolonged fasting was lower in the main paediatric anaesthesia unit, compared to the ENT unit before the transition, with 34.2 % of children fasting four hours or more (OR=0.41, 95 % CI: 0.20-0.80, p=0.01), 23.3 % fasting six hours or more (OR=0.57, 95 % CI: 0.27-1.19, p=0.135). and 8.2 % of children fasting 12 hours or more (OR=0.5, 95 % CI: 0.16-1.44, p=0.207), table 5 and 6.

Table 6. Group, age, time of surgery and in/out-patient status in relation to the outcome fasting \geq six hours. Results from crude regression analysis¹

	OR ²	95% CI ³	p
Group			
ENT_2h (1)	reference		
ENT_0h (2)	0.13	0.03-0.35	<0.001
MP_0h (3)	0.57	0.27-1.19	0.135
Age			
< 3 years	reference		
3-6 years	0.52	0.23-1.15	0.109
> 6 years	0.39	0.17-0.91	0.031
Time of surgery			
First case	reference		
Morning	0.50	0.30-0.81	0.014
Afternoon	0.31	0.11-0.79	0.020
In/out-patient status			
Inpatients	reference		
Outpatients	0.79	0.40-1.57	0.488

¹. Logistic regression analyses with each predictor at a time against the outcome.

². Odds ratio

³. 95% confidence interval for odds ratio

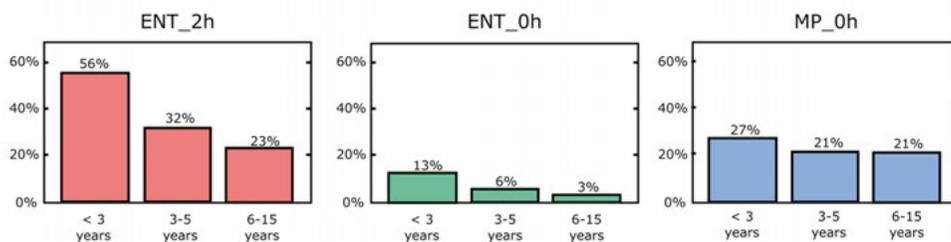


Figure 10. Frequency of fasting > 6 hours for clear fluids in different age groups when applying 2-or 0-hour fasting for clear fluids.

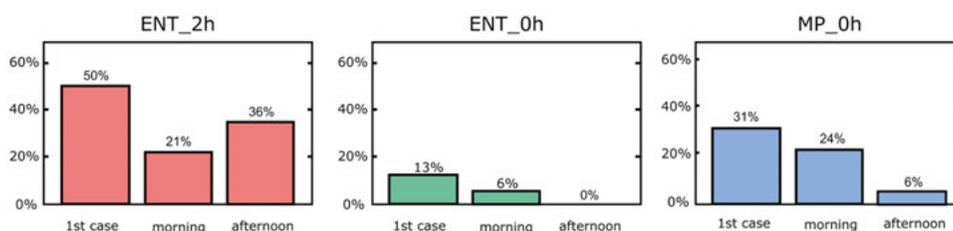


Figure 11. Frequency of fasting > 6 hours for clear fluids for patients scheduled in different times of the day when applying 2-or 0-hour fasting for clear fluids.

Older children had a lower risk of fasting six hours or more, compared to children under three years of age (children aged 3-5 years: OR=0.52, 95 % CI: 0.23-1.15, $p=0.135$; children over 6 years: OR=0.39, 95 % CI 0.17-0.91, $p=0.031$), see table 6. The proportions of children fasting for more than six hours stratified by age and group are displayed in figure 10.

Children scheduled in the morning or afternoon had lower risk of fasting six hours or more, compared to children scheduled as first case (morning patients OR =0.50, 95 % CI 0.30-0.81, $p = 0.014$) (afternoon patients OR=0.31, 95 % CI 0.11-0.79, $p=0.020$), see table 6. The proportions of children fasting for more than six hours stratified by the time of day for surgery and group are displayed in figure 11.

4.3 Paper III

A total of 36 patients were identified to meet inclusion criteria. However, 16 patients had to be excluded due to no common language (n = 2), declined participation (n = 3) and fasted since midnight (n = 11), see figure 12.

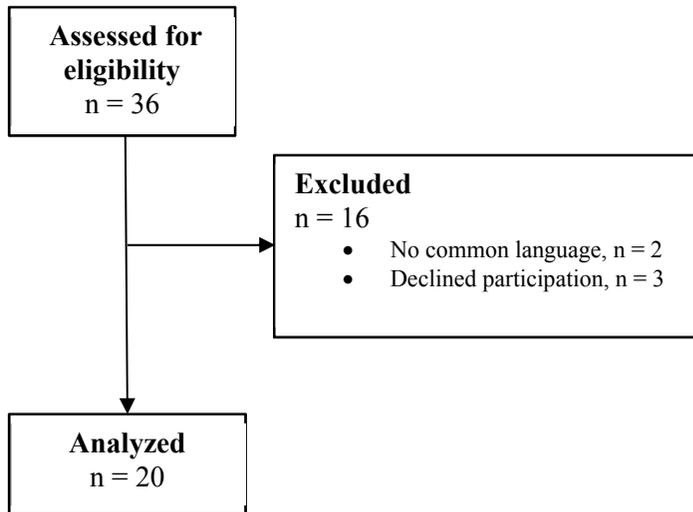


Figure 12. Inclusion of patients

The most common breakfast was yoghurt or gruel, but one patient had soured milk and one had regular cow's milk. The ingested amount differed between 2.5 – 25 ml kg⁻¹.

Gastric ultrasound examination was performed 3-5.5 hours after ingestion of a light breakfast in the superior with upper body elevated (n = 8) and/or right lateral decubitus (n = 20) position. No patients were examined before breakfast.

15 patients had an empty stomach with juxtaposed walls at examination, and no further measurements were made. In four patients, clear fluids were visualised. When calculating gastric content volume, three of these patients had a calculated gastric content volume of 0 ml kg⁻¹, and one patient had gastric content volume of 0.46 ml kg⁻¹. The stomach was defined as empty in all the 19 cases mentioned above. One patient had a full stomach with solids and a gastric content volume calculated to 2.1 ml kg⁻¹, see figure 13.

The patient with a full stomach had ingested a total of 25 ml kg⁻¹ of gruel. The ingested amount of breakfast in all patients are displayed in figure 14.

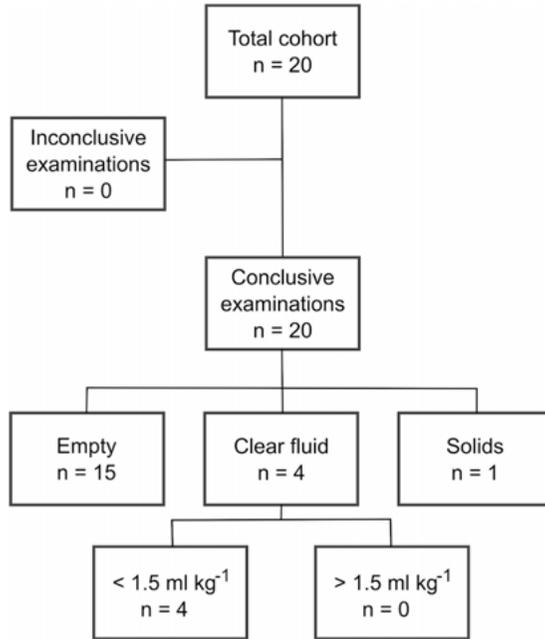


Figure 13. Primary outcome. Fifteen children had an empty stomach with juxtaposed walls, four had clear fluid content $< 1.5 \text{ ml kg}^{-1}$, and one child had solid content present in the stomach four hours after breakfast.

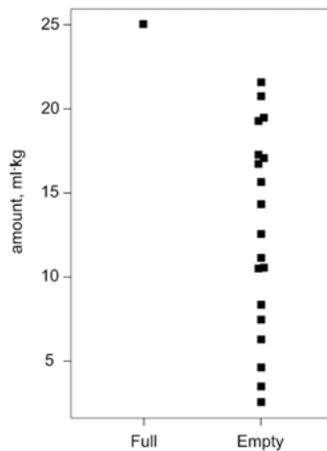


Figure 14. Ingested amount (ml kg^{-1}) of breakfast four hours prior to examination, for one child with a full stomach and 19 children with empty stomachs.

4.4 Paper IV

A total of 42 patients aged 0-72 months were included. Median fasting times for solids, breast milk and clear fluids were 15.5, 5.6 and 2.1 hours respectively. Mean preoperative weight change was -0.6 % and mean preoperative blood glucose level and ketone bodies were 4.4 mmol/l and 0.2 mmol/l, respectively.

Three out of 42 children (7 %, 95 % CI: -1 % to 15 %) presented with weight loss ≥ 5 %. Multiple linear regression did not show correlation between fasting time and age group, and the outcome weight change.

Five out of 42 children (12 %, 95 % CI: 2 % to 22 %) presented with glucose level ≤ 3.3 mmol l⁻¹ at induction and one child had preoperative glucose of ≤ 2.8 mmol l⁻¹. Multiple regression analysis did not indicate a correlation between fasting time and age, and the outcome preoperative blood glucose.

Eleven out of 42 patients (26 %, 95 % CI: 13 % to 39 %) presented with preoperative blood ketone bodies ≥ 0.6 mmol l⁻¹. Multiple regression analysis indicated no correlation between fasting time and age, and the outcome preoperative ketone bodies.

Table 7. Multiple linear regression results. Outcome variables “weight change”, “blood glucose” and “ketone bodies”. Explanatory variables “age group” and “total fasting time” for weight change, and “age group” and “fasting time for solids/semi-solids” for blood glucose and ketone bodies.

Outcome	Variable	Beta	t-value	p-value
Weight change	Intercept	-0.0109	-1.0180	0.3150
	“3-12 months”	0.0068	0.5860	0.5610
	“>12 months”	-0.0042	-0.3830	0.7040
	Total fasting time	0.0009	0.8630	0.3930
Blood glucose	Intercept	4.8775	13.6870	4.7e-16
	“3-12 months”	-0.4396	-1.1690	0.2500
	“>12 months”	-0.3044	-0.7840	0.4380
	Total solid fasting	-0.0285	-0.8200	0.4170
Ketone bodies	Intercept	0.1668	0.9030	0.3725
	“3-12 months”	0.3446	1.7680	0.0853
	“>12 months”	0.1736	0.8630	0.3940
	Total solid fasting	0.0033	0.1810	0.8571

5. Discussion

Preoperative fasting is necessary to avoid pulmonary aspiration and current fasting regimens intend to minimize gastric volume by prohibiting ingestion of food and drink before anaesthesia. It is a common conception that the longer the fast, the safer it is and many patients are fasted for longer than necessary, leading to physical and psychological suffering. The studies included in this thesis, and new knowledge of gastric emptying, have contributed to a new consensus statement, recommending 1-hour fasting for clear fluids (7).

In paper I, no increase in incidence of pulmonary aspiration was found when allowing free clear fluids up until surgery. There were three clinically significant cases of pulmonary aspiration in 10 000 patients, albeit neither of them needed mechanical ventilation or intensive care. Both patients who developed symptoms, were free from symptoms the day after surgery. These results are in line with previous studies reporting the incidence of perioperative pulmonary aspiration to be 1-10 in 10 000 (31-35). However, due to differences in study design and definitions of the outcome pulmonary aspiration, the reported incidences in previous studies are hard to compare. In the current study, there were no cases needing intensive care or even experiencing symptoms on the day after surgery. More lenient fasting regimens for clear fluids would improve preoperative comfort and facilitate logistics. The implication is that application of a zero-hour fasting regimen may be as safe as traditional fasting regimens and hence shortened fasting times for clear fluids are possible.

In the second paper, the transition from two to zero-hour fasting for clear liquids reduced median fasting time, and the proportion of patients fasting for an extended time. The high incidence of extended fasting in the 2-hour fasting group is not due to healthcare personnel's unwillingness to adhere to guidelines, but rather due to the difficulty to adapt to a continuously changing surgical schedule. Allowing clear fluids until premedication avoids much of the information problem for the anaesthetist trying to work a smooth surgical list while avoiding prolonged fasting times. It does not demand for a set time of surgery. When cancellations, rearrangements and acute cases appear in the schedule, these organisational and logistic problems do not have to have the same effect on the preoperative patients. It also reduces the need for constantly updating fasting orders according to the current surgical procedure. This has the possibility to attenuate prolonged preoperative fasting and hence improve

preoperative experience for patients and care givers. In departments that choose to apply set time limits for preoperative fasting, the recommendation would probably be easier to follow if the anaesthetist prescribes the patients food and drink at specific times, rather than just a time limit of 2, 4 or 6 hours for clear fluids, breast milk and solids, respectively. The differences in fasting times between the ENT department and the main paediatric surgical department, suggests that compliance to a new fasting regimen is higher one year after the shift. Although, the difference may also be due to different patient clientele.

In paper III, a light breakfast four hours prior to induction resulted in a full stomach in one out of 20 patients. Due to the small material, these results should be interpreted with caution. Previous studies of gastric emptying of light meals in young children have also revealed outliers with slower gastric emptying time (64). However, in the current study, the event may well have been caused by an excessive intake of food. Gastric emptying depends on the caloric density of the food and low caloric nutrients are hence emptied in a higher pace than nutrients with a high caloric density (60, 61). Nevertheless, after eating a big amount of low caloric nutrients, everything still needs to be emptied through the pylorus, and the intestines requires a slow but steady pace to ensure all calories can be absorbed. Allowing a light breakfast four hours prior to surgery has been implemented in our clinical practice for two decades and have also been reported by other centres (12-14). Still, no increase in peri-operative pulmonary aspiration was found in paper I. Gastric content volume is frequently used as a surrogate marker for the risk of pulmonary aspiration. However, there is no evidence to support the existence of a dose-response relationship between the quantity of gastric fluid volume and the risk for pulmonary aspiration (124).

In paper IV, preoperative fasting time did not affect preoperative weight loss, blood glucose or ketone bodies in young children undergoing general anaesthesia. Of the 42 children, three children had a preoperative weight loss of $\geq 5\%$, five had low blood glucose levels and eleven had high ketone bodies at induction. This implies that dehydration and metabolic derangements occur in the preoperative period even when implementing lenient fasting regimens. However, the cause of these outcomes remains unknown and further patient recruitment is planned before publishing the results of this study.

Finally, assuring the stomach is empty is not just about fasting time. The anaesthetist has to ask what the patient has eaten and how much. A small amount of low caloric food will empty faster than a heavy meal, and clear fluids empty within an hour. We must not forget that even after an overnight fast, it is normal for a child to have fluids in the stomach.

6. Conclusions

This thesis concludes that more liberal preoperative fasting rules for children reduces the risk of prolonged fasting without seeming to increase the risk of pulmonary aspiration.

- I. The 6-4-0 fasting regimen does not seem to entail an increased risk of perioperative pulmonary aspiration in the studied material.
- II. The 6-4-0 fasting regimen enables shortened preoperative fasting times and reduced incidence of extended fasting.
- III. A light breakfast empties from the stomach within four hours in most children. Therefore, a light breakfast four hours prior to induction is possible, but volume restrictions are essential.
- IV. Preoperative weight loss and metabolic changes are uncommon with the 6-4-0 fasting regimen, but mild weight loss and hypoglycaemia still occur in some children.

7. Future perspectives

Since publication of the first paper in this thesis, other centres have started to reduce fasting times for clear fluids. However, there are still no proof these fasting regimens are safe and updated evidence-based guidelines considering new physiological and clinical data are needed.

As more centres are reducing fasting times, the incidence of perioperative pulmonary aspiration must be registered, preferably in a large multicentre study where centres applying different fasting regimens for clear fluids can be compared. In such a study, there will be many confounding factors and differences between centres that may affect the incidence of perioperative pulmonary aspiration, such known confounders must be registered and corrected for.

There is a problem with extended fasting in paediatric patients, leading to dehydration, catabolism, and decreased preoperative wellbeing. Awareness of non-compliance to fasting regimens must be raised. Health care personnel are often aware of the crucial effects of not fasting, but not everyone perceives prolonged fasting as a clinical problem. Registration of actual fasting times prior to induction, and education of doctors, nurses and care givers on the potentially harmful effect of elongated fasting may improve compliance to recommended fasting times.

The use of gastric ultrasound in anaesthesia might be useful in case of deviation from fasting regimen or choice of induction technique in acute case surgery. Hopefully, the technique will develop even more with smaller and updated machines which further improve the use in clinical practice.

Postoperative insulin resistance occurs also in paediatric patients. It has been showed that a commercial preoperative carbohydrate rich drink diminishes both postoperative nausea and insulin resistance. Most studies compare these carbohydrate enriched drinks to fasting from midnight or according to the 6-4-2 fasting regimen. It should be studied if improvement of fasting times with 0-1 hour fasting for clear fluids, allowing a light breakfast and encouraging both care givers and health care personnel to shorten preoperative fasting, could have the same positive effects as the preoperative drinks.

Gastric contents after a light breakfast should be investigated in a blinded randomized clinical trial, comparing gastric content volume in children fasted overnight and children allowed a light breakfast four hours prior to induction.

8. Sammanfattning på Svenska

I denna avhandling har vi undersökt möjligheten för kortare preoperativ fasta för barn. Barn som ska sövas är ofta oroliga eftersom de hamnar i en okänd miljö där de utsätts för olika undersökningar som skapar stress, oro och ibland även smärta. En stor orsak till obehag är kravet att barnen måste fasta innan sövningen.

I dagens sjukvård är det allmänt accepterat att patienter ska fasta innan sövning för att undvika kräkning. Vid narkos är medvetandet och flertalet reflexer i kroppen utslagna vilket gör att det finns risk för att mag-innehåll rinner ned i lungorna om man kräks. Detta kallas pulmonell aspiration och är den vanligaste orsaken till anestesirelaterad död hos vuxna patienter. Aspirationen kan orsaka ett luftvägsstopp, när fasta partiklar täpper till luftvägen, eller en kemisk skada, när den sura magsyran fräter sönder lungvävnad.

Idag rekommenderas två timmars fasta för klara drycker såsom vatten, saft och kaffe, och sex timmars fasta för allt som innehåller fasta partiklar, såsom mat, juice med fruktkött och mjölk. Samma regler gäller för både barn och vuxna, förutom för spädbarn som tillåts dricka bröstmjölk fram till fyra timmar innan operation.

Det är inte farligt för små barn att fasta två timmar för klar dryck, fyra timmar för bröstmjölk och sex timmar för mat, men tyvärr är dessa fasteregler mycket svåra att följa. Om ett barn som ska opereras måste sluta dricka vatten minst två timmar innan operationen, kräver det att föräldrar och vårdpersonal vet exakt när operationen ska börja. I dagens sjukvård med höga produktionskrav opereras flera patienter efter varandra på samma operationssal. Starttiden för operationen kan endast meddelas för den första patienten. Övriga patienter får ungefärliga tider beroende på var i turordningen de står. Detta leder till att många barn i praktiken fastar mycket längre än vad som är rekommenderat. Studier där man tittar på hur länge barn är fastar innan operation har visat att barn i genomsnitt fastar 13 timmar för mat och 9 timmar för klara drycker.

För små barn som behöver äta ofta får dessa långa fastetider både fysiska och psykiska konsekvenser. Barn har mindre energidepåer än vuxna och riskerar att bli uttorkade, få lågt blodsocker och gå in i svältmetabolism om de fastar för länge. En operation kan jämföras med ett idrottslopp och kroppen klarar

av påfrestningarna bättre om den har fulla depåer. Fastan leder även till törst, hunger och oro, vilket har större påverkan på barn än vuxna.

På Akademiska Sjukhusets barnoperationsavdelning noterade man i slutet av 90-talet att många barn kom till operation hungriga och uttorkade. Efter en genomgång av den aktuella forskningen konstaterades att det inte finns någon vetenskaplig evidens för att barn ska fasta två timmar för klara drycker. Vatten rinner rakt igenom magsäcken och ut i tarmen, och 30 minuter efter att man druckit ett glas vatten är magsäcken tom igen. Sedan 1999 har barn som ska sövas på Akademiska Barnsjukhusets barnoperationsavdelning därför tillåtits att dricka vatten och saft, samt äta isglass, fram till att dom ska åka från sin avdelning till operationssalen. Barn som inte opereras direkt på morgonen får även äta en lätt frukost bestående av välling eller yoghurt, fyra timmar innan sövning.

Det första arbetet i denna avhandling undersökte om en så pass frikostiga fasteregim som den som används i Uppsala verkligen är säker. För att ta reda på detta undersöktes förekomsten av pulmonell aspiration på barnoperationsavdelningen i Uppsala. I studien inkluderades 10 000 patienter och förekomsten av pulmonell aspiration var 3 på 10 000, eller 0,03 %, vilket kan jämföras med en förekomst på 1-10 på 10 000, eller 0,01-0,1 % på andra sjukhus i världen. Denna studie kunde således konstatera att fritt intag av klara drycker fram till operation inte verkade leda till ökad risk för pulmonell aspiration hos det undersökta materialet.

I det andra arbetet undersöktes hur länge barn egentligen fastar före operation. Tre olika grupper undersöktes. Den första gruppen bestod av barn som opererades på oral-, plastik- och öronoperation (OPÖ) på Akademiska sjukhuset, när denna operationsavdelning rekommenderade två timmars fasta för klar dryck. Den andra gruppen inkluderades på OPÖ ett år efter att man bytt fasteregim till att tillåta klara drycker fram till operation. Den tredje gruppen inkluderades på barnoperation där barn tillåtits dricka klara drycker fram till operation sedan 1999. Barn som blev ordinerade två timmars fasta för klar dryck på OPÖ fastade i genomsnitt fyra timmar och 35 % av barnen fastade längre än sex timmar. Barn som tilläts dricka fram till operation fastade i genomsnitt en timma på OPÖ och två timmar på barnoperation. Endast 6 % av barnen på OPÖ och 23 % av barnen på barnoperation fastade längre än sex timmar. Studien visar att barn fastar längre tid än nödvändigt, men att man kan minska onödigt långa fastetider genom mer tillåtande rekommendationer för klar dryck.

I det tredje delarbetet undersöktes om en lätt frukost innan sövning hinner tömma sig ur magsäcken på fyra timmar. Barn som blivit ordinerade en lätt frukost undersöktes med ultraljud av magsäcken fyra timmar efter att de ätit.

Totalt 20 barn undersöktes och av dessa hade 19 en tom mage, men ett barn hade välling kvar i magsäcken efter fyra timmar. Hos de flesta barn hinner alltså frukosten tömma sig ur magsäcken, men inte hos alla. Det barn som hade mat kvar i magsäcken var det barn som ätit mest. Det är bevisat att ju mer man äter, desto längre tid tar det innan magsäcken blir tom. I nuläget finns ingen mängdbegränsning för den frukost som erbjuds, men efter detta fynd måste en begränsning av intaget diskuteras.

I det fjärde delarbetet undersöktes om det finns barn som påverkas negativt av att fasta innan sövning. De utfallsmått som undersöktes var preoperativ vikt-förändring, lågt blodsocker och förekomst av ketonkroppar. Av de 43 barn som inkluderades i studien var det tre som tappade 5 % i vikt, fem som fick lågt blodsocker, och 11 som fick ketonkroppar. När dessa resultat jämfördes med hur länge barnen fastat kunde man inte se något samband mellan fastetid och vikt-förändring, blodsocker eller ketonkroppar. Även med mycket tillå-tande fasteregler förekommer det alltså att barn tappar i vikt, får lågt blod-socker och ketonkroppar innan de ska sövas.

Resultaten från denna avhandling styrker att mer tillåtande fasteregler för barn är möjliga. Den europeiska specialistföreningen har tagit till sig denna forsk-ning och rekommenderar nu en timmas fasta för klar dryck för barn. Även på Nya Zeeland, i Australien, Brasilien och USA har man börjat försöka korta ned fastetiden för små barn. Detta kommer förhoppningsvis att underlätta tim-marna innan operation för både barn, vårdnadshavare och vårdpersonal.

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