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The effect of preoperative apple juice on the prevalence of hypoglycaemia in paediatric patients

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CHAPTER ONE
OVERVIEW OF THE STUDY

1.1 INTRODUCTION

In this chapter an overview of the study is provided. This includes the background to the study, the problem statement, the aim and objectives of the study, relevant definitions, the demarcation of the study field, ethical considerations, the research methodology, the significance of the study, validity and reliability, and a consideration of the potential limitations, followed by a project outline.

1.2 BACKGROUND TO THE STUDY

Children, like adults, have historically been fasted for prolonged periods preoperatively to reduce the volume and acidity of their gastric contents, in order to avoid the complication of regurgitation and pulmonary aspiration. The “nulla per os from midnight” order has been challenged by clear evidence that in healthy patients without risk factors for regurgitation and aspiration, who present for elective surgery, the risk of aspiration is not increased by eating a light meal six hours (1) or drinking clear fluids two hours prior to the induction of anaesthesia (2).

The secondary outcomes of prolonged fasting are increasingly being accepted as important. Paediatric patients are less hungry, less thirsty and less irritable if they are allowed to drink preoperatively (3, 4). The overall perioperative experience is improved for both children and their parents (5). These may seem like “soft”, subjective outcomes, but they may also be surrogates for more ominous outcomes in children who are fasted for longer periods preoperatively; these include a trend towards metabolic acidosis and lipolysis (6), impaired responsiveness to insulin

(7), a drop in blood pressure on inhalational induction with halothane, suggesting depleted intravascular volume (8), and hypoglycaemia (9).

The issues around hypoglycaemia in fasted children have been debated since a landmark study by Thomas (9) in the 1970s showed a 15.2% prevalence of hypoglycaemia (defined as a blood glucose < 2.8 mmol/l) in children following a preoperative fast. Other authors have not shown a significant prevalence of hypoglycaemia in their studied patients and the issue was, to a degree, dismissed as being unimportant, as “preoperative fasting is well tolerated in healthy preschool children, regardless of the timing of surgery” (10).

One of the reasons for these conflicting results lies in the differing definitions used for hypoglycaemia. At this point it is necessary to point out that much of the research on hypoglycaemia is performed on the diabetic population. It is debatable whether those definitions should be used in non-diabetic patients (11), but they are the currently accepted definitions. In the adult literature it is proposed that “any blood glucose equal to, or below, 3.9 mmol/l should represent hypoglycaemia, whether or not symptoms are present” (12). The traditional definition of hypoglycaemia in neonates has been a blood glucose of ≤ 2.2 mmol/l. For children, the reported cutoff values range from 2.2 - 3.3 mmol/l. Current recommendations in the paediatric diabetic literature are that hypoglycaemia should be defined as a blood glucose < 3.3 mmol/l and that values < 3.9 mmol/l should be a “cause for concern” in preschool children (13). The results of several studies that reported a very low prevalence of hypoglycaemia would be vastly different if these definitions had been used.

Hypoglycaemia is extremely difficult to diagnose clinically in children, with most children showing no signs or symptoms of a low blood glucose (14). It is more common in children under four years old or weighing less than 15.5 kg (9), those fasted for prolonged periods (14), and in those considered nutritionally “at risk” or underweight (15).

Hypoglycaemia is not innocuous. There is evidence that neurocognitive dysfunction occurs at blood glucose values of 3 mmol/l (16), even if that episode of hypoglycaemia is as acute as 30 minutes (17). Electroencephalogram (EEG) changes can be demonstrated at a blood glucose of less than 3,5 mmol/l. Neurocognitive changes may be subtle, but include impaired attention, memory deficits, delayed reaction time and slower arithmetical ability. It may take a day and a half for this function to return to normal after a single episode of hypoglycaemia (16).

Practice guidelines for preoperative fasting have been produced by a number of professional groups worldwide (18). These guidelines recommend a minimum preoperative fasting time of six hours for a light meal, infant formula or non-human milk, four hours for breast milk, and two hours for clear fluids. Clear fluids include water, fruit juices without pulp, carbonated beverages, clear tea and black coffee (19). Such liberal fasting guidelines are widely considered a level one recommendation.

The South African Society for Anaesthesiologists has issued fasting guidelines with the above recommendations in this country (20). There is no published research on the implementation of these guidelines.

A study by Fitchat (21) demonstrated that preoperative fasting instructions in our institution are inconsistently prescribed by doctors and poorly followed by both nursing staff and parents.

1.3 PROBLEM STATEMENT

Paediatric preoperative fasting instructions at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) are not standardized, do not follow national or international guidelines and, even when correctly prescribed, are often not

adhered to. As a result, children are frequently fasted for more than 12 hours before surgery. This prolonged duration of fasting predisposes children, especially younger children, to the risks of dehydration and hypoglycaemia. A recent study at CMJAH showed that 30.86% of paediatric surgical patients had a blood glucose < 4.1 mmol/l on induction of anaesthesia. Nearly 10% had a blood glucose ≤ 3 mmol/l, the level associated with potential neurocognitive dysfunction (21).

1.4 THE AIM OF THE STUDY

The aim of this study was to determine whether allowing paediatric patients to drink apple juice two hours preoperatively reduces the prevalence of hypoglycaemia at the time of surgery.

1.5 OBJECTIVES OF THE STUDY

The objectives of this study were:

- to document the prevalence of hypoglycaemia at induction of anaesthesia in children given apple juice two hours preoperatively
- to compare these results to a historical control group.

1.6 DEFINITIONS

The following definitions were applied in this study:

- **Child** - a participant in the study aged from one to five years
- **Fasting** - the period of time since an individual last ate or drank anything
- **American Society of Anesthesiologists' (ASA) classification of physical state grade I** - a healthy patient with no systemic disease (22)

- **ASA grade II** - mild to moderate systemic disease treated and not limiting patient's activities (22)
- **Hypoglycaemia** - a lower than normal blood glucose level of less than 3.5 mmol/l (23).

1.7 DEMARCATION OF STUDY FIELD

The study took place in the paediatric surgery wards and theatres of CMJAH. CMJAH is a tertiary level hospital in Gauteng, and is a referral centre for a number of smaller regional hospitals. The hospital is affiliated to the University of the Witwatersrand.

1.8 ETHICAL CONSIDERATIONS

Approval to conduct the study was obtained from the Human Research Ethics Committee (HREC) of the University of the Witwatersrand and the Postgraduate Committee of the University of the Witwatersrand.

A randomized control trial is considered the gold standard for clinical research. However, having considered the potential adverse outcomes associated with hypoglycaemia in children, and after discussion with the chairman of the HREC of the University of the Witwatersrand, a historical control trial design was used. The patient group studied by Fitchat (21) previously was used as the control group. The researcher attempted to match patients in this study as closely as possible to those in the control group for age and weight. Patients were not matched for gender as this has not been shown to affect the development of hypoglycaemia in the paediatric population.

The researcher obtained informed consent from a parent or caregiver for each participant in the study. An information document detailing the purpose and

methods of the study was provided in English (Appendix D), with a translator available when necessary.

Research was conducted according to the principles of the Declaration of Helsinki (24).

1.9 RESEARCH METHODOLOGY

1.9.1 RESEARCH DESIGN

A prospective, contextual, comparative study design was used.

1.9.2 STUDY POPULATION

The study population comprised paediatric patients aged from one to five years presenting for elective procedures requiring anaesthesia at CMJAH.

1.9.3 STUDY SAMPLE

Sample size

The sample size was determined in consultation with a biostatistician. In this single arm study a minimum study sample of 67 patients was determined to have 90% power to detect a change in the percentage of hypoglycaemic children from 30% (in the historical control group) to 15% when testing at the 0.05 level of significance.

Sample method

A nonrandom, consecutive, convenience, quota sampling method was used in this study.

Criteria for the study

Inclusion criteria

The following patients were included in the study:

- paediatric patients presenting for elective surgery;
- patients from one to five years of age;
- paediatric patients of ASA status I and II;
- patients for whom consent was obtained.

Exclusion criteria

The following patients were excluded from the study:

- paediatric patients presenting for emergency surgery;
- patients who do not fulfill the appropriate preoperative fasting criteria, i.e. who have a “full stomach”;
- patients with comorbid diseases that classify the patient as ASA status III or greater;
- patients with comorbid diseases or conditions that increase the risk of delayed gastric emptying, gastric regurgitation and pulmonary aspiration;
- patients with intravenous access, receiving intravenous fluids prior to surgery;
- patients refusing apple juice.

1.9.4 METHODOLOGY

The researcher assessed all patients on the morning of surgery. The parent or guardian of any child who met the inclusion criteria was informed about the study Appendix D) and asked for consent to include the child in the study (Appendix E).

Each child enrolled in the study was offered a 200 ml carton of commercially available apple juice. Additional juice was given if requested by the child. The volume and time of the juice consumed were documented, along with the child's demographic data (height, weight, sex), fasting duration, and ASA status (Appendix F). The child's height and weight for age were plotted on standard paediatric growth charts.

Anaesthesia and surgery proceeded a minimum of two hours after the apple juice was consumed. The researcher induced inhalational anaesthesia in all patients, administering oxygen, nitrous oxide and sevoflurane via a face mask and standard circuit. Standard monitoring was used in all cases. Once an adequate depth of anaesthesia was reached, the researcher inserted an intravenous cannula. A drop of blood from the cannula was analysed using a glucometer. The result was recorded on the data collection form, along with any treatment given for hypoglycaemia (Appendix F).

The glucometer was only used for research purposes. The same glucometer used for research in the control group was used in this study. The glucose testing strips were stored and used according to the manufacturer's recommendations. Protocols for the management of hypoglycaemia and hyperglycaemia were designed and followed.

1.9.5 DATA ANALYSIS

Data were entered anonymously on an Excel spreadsheet and analysed in consultation with a biostatistician. Results have been presented as mean ± SD or median (range) for continuous variables with normal or non-normal distribution respectively.

The groups were compared for the variables of age, weight and fasting duration. The distributions of the variables in this study were tested for normality using the Shapiro-Wilk test.

Where data were normally distributed, the means of the groups were compared using Analysis of Variance (ANOVA). The Kruskal-Wallis test was used to compare the groups where the data was not normally distributed. The ANOVA and Kruskal-Wallis tests tested for a significant difference between the two groups for the variables of weight, age and fasting duration.

Statistical modeling was then undertaken to assess the influence of the treatment. An Analysis of Covariance (ANCOVA) was conducted in order to account for the possible influence of covariates like weight and fasting duration.

The data were subsequently analysed using regression analysis to determine the extent to which there was a linear relationship between glucose concentration (dependent variable) and the independent variables in the study.

A Chi-Square test tested for the association between being in the treatment group (i.e. receiving apple juice) and blood glucose concentration. Probabilities, odds, and odds ratios were calculated from the data on the contingency table.

1.10 SIGNIFICANCE OF THE STUDY

The current preoperative fasting regimes at CMJAH put children at risk of hypoglycaemia, with its attendant adverse effects. The aim of the research was to demonstrate a reduction in the incidence of hypoglycaemia with the introduction of a simple, safe and cost-effective intervention. The aim was for this study to be the first step towards changing practice at CMJAH with the development and

institution of a standardized preoperative fasting protocol, which will contribute to the safety and wellbeing of patients.

1.11 VALIDITY AND RELIABILITY

Members of nursing staff who could communicate with parents in their mother tongue assisted the researcher when necessary. This contributed to obtaining accurate data.

One researcher performed data collection to improve consistency.

A single glucometer was used for this study. It was the same glucometer used for the control group. The glucometer and test sticks were used and stored according to the manufacturer's instructions. Whilst the glucometer used does not require formal calibration, each batch of test sticks was used with the corresponding electronic module, as per the manufacturer's instructions. This improved the quality, accuracy and consistency of the research data.

The glucose and energy content of the apple juice was standardized and known, as one brand of juice was used.

1.12 POTENTIAL LIMITATIONS

This study was contextual and its scope was limited to a certain patient population. While results obtained may not be applicable across all patient groups, it addresses a current problem experienced at CMJAH.

Due to the dynamic nature of a busy paediatric surgical operating list and the unpredictable duration of some operations, children cannot be anaesthetised exactly two hours after drinking their juice. While this is a potential limitation it is a

realistic reflection of a routine operating list. The duration of preoperative fasting was documented in the data collection form.

The limitation of the study design was accepted as it was considered ethically appropriate.

1.13 PROJECT OUTLINE

This study will be presented as follows:

- Chapter 1: Overview of the study
- Chapter 2: Literature review
  In this chapter, a review of the literature relevant to the various aspects of this study is covered.
- Chapter 3: Research methodology
  The study design, sample selection, eligibility criteria, and data collection process are described and discussed. The statistical tests used for data analysis are presented and discussed.
- Chapter 4: Data analysis and discussion of results
  In this chapter the results of the study are presented and discussed.
- Chapter 5: Summary, conclusions, limitations and recommendations
  A summary and conclusions from the main findings are presented. The limitations of the study are considered and recommendations for clinical practice and further research are discussed.

1.14 SUMMARY

In this chapter an overview of the study has been presented. This has included the background to the study, the problem statement, the aim and objectives of the study, relevant definitions, the demarcation of the study field, ethical considerations, the research methodology, the significance of the study, validity

and reliability, and a consideration of the potential limitations, followed by a project outline.

A single arm prospective, contextual study was designed to assess the effect of preoperative apple juice on the prevalence of hypoglycaemia in paediatric patients.

In the following chapter a review of the literature relevant to the various aspects of this study will be presented.

CHAPTER TWO
LITERATURE REVIEW AND BACKGROUND

2.1 INTRODUCTION

In this chapter the literature relevant to this study will be reviewed. A brief history of the nil per os order will be followed by a review of the physiology of gastric emptying, the pathophysiology of regurgitation and pulmonary aspiration of gastric contents, and the evidence of their occurrence and outcomes in children. The physiology of fasting and glucose control and the adverse effects of prolonged fasting will be reviewed, with a focus on hypoglycaemia: its causes and effects, clinical presentation, and the evidence for its occurrence in the paediatric population perioperatively.

2.2 HISTORY OF THE "NIL PER OS FROM MIDNIGHT" ORDER

Sir Joseph Lister (1827 - 1912) is best known to medical history as the father of antiseptic surgery. After reading the works of Semelweiss and Pasteur, he made the link between poor hygiene and infection. By introducing carbolic acid to sterilize surgical instruments and to make antiseptic dressings, and by insisting his staff wash their hands before surgery and before and after seeing patients, Lister dramatically reduced the postoperative mortality of his patients (25).

What is less well known is that Lister published the first documented fasting guidelines. In 1883 he wrote: "While it is desirable that there should be no solid matter in the stomach when chloroform is administered, it will be found very salutary to give a cup of tea or beef-tea about two hours previously" (25). With this statement he made the distinction between food and clear liquids and these, or similar, guidelines were recommended for many years.

The “NPO after midnight” order for healthy elective patients started to appear in the 1960s, and made no distinction between clear liquids and solids. The reasons behind this are not clear but were likely in response to Mendelson’s report of 66 cases of aspiration of gastric contents under general anaesthesia in obstetric patients, published in 1946. In 1974 Roberts and Shirley instilled acid into the right main bronchus of rhesus monkeys and, by extrapolating that data, defined values (by their admission, arbitrary) for gastric volume (0.4 ml/kg, or 25 ml in a female adult) and pH (< 2.5) which would put humans at risk of gastric regurgitation and pulmonary aspiration (25). As salivary secretions contribute approximately 1 ml/kg/hr and gastric secretions approximately 0.6 ml/kg/hr to gastric volume in the fasting state (26), many patients were theoretically at risk for regurgitation and aspiration, and prolonged fasting periods were adopted.

The calls for a change to this prolonged period of starvation started in the 1980s and 1990s, as evidence emerged that in healthy patients with no risk factors for gastric regurgitation and subsequent pulmonary aspiration, presenting for elective surgery, a six hour fast for solids was appropriate and that clear liquids could be taken up to two hours preoperatively (19). This shorter period of fasting has been shown to be both safe and beneficial to patients, and has been adopted by numerous professional groups internationally – more than one hundred years since Lister’s recommendations.

2.3 PHYSIOLOGY OF GASTRIC EMPTYING

The rate of gastric emptying is carefully regulated by a combination of physical, metabolic, neural and hormonal influences (27).

The main function of the stomach is to act as a reservoir for ingested food until it can be emptied into the duodenum at an appropriate rate for digestion and absorption. When food enters the stomach the fundus and body relax and expand

significantly to accommodate the increase in volume with little increase in pressure (27).

Pacesetter cells in the upper fundus trigger peristaltic contractions which move rhythmically from the fundus towards the antrum, moving food towards the pylorus where it is broken up and mixed with gastric secretions to form chyme.
The motility of the stomach and small bowel is at its greatest 30 minutes after a meal, and lasts for about four hours. In this period of “fed motility” liquids, semi-liquid contents, and small particles (less than 1-2 mm in size) are emptied from the stomach into the duodenum (27).

The activity of the migrating motor complex dominates the subsequent period of “fasting motility”, causing larger particles (larger than 1-2mm) to be emptied from the stomach (28).

Rates of gastric emptying can be measured by the aspiration of residual gastric volume (RGV), by ultrasound, by using scintigraphy to measure residual activity of radio-labelled meals, and by measuring the fraction of radio-labelled C-Octanoic acid in exhaled breath. Gamma scintigraphy has been considered the gold standard (29-31), but has the disadvantage of exposing children to radiation. Gastric emptying parameters of normal healthy children had thus not been studied until recently, when noninvasive ultrasonographic techniques were shown to provide acceptable results. Studies measuring gastric emptying report their results as either the half-emptying time (t½), the percentage of feed or radioactivity remaining in the stomach at an hour, or as the percentage emptied by an hour (or at a specified time point).

There is a marked difference in the emptying of liquids and solids from the stomach. As early as 1833 an American military surgeon called Beaumont noted a difference in the rate of emptying for fluids and solids by observing the rate at which various components came out of a gastrocutaneous fistula in an injured soldier (25).

2.3.1 LIQUIDS

Liquids empty from the stomach by a first order exponential process, such that the rate of emptying is proportional to the volume present in the stomach. The half-emptying time (t½) of non-caloric clear liquids is 12 - 20 minutes; the stomach can thus be assumed to be empty of liquid after five half-lives, i.e. after 60 - 100 minutes. Several researchers who have used ultrasound to measure gastric antral area or who have aspirated and measured RGV have confirmed that clear fluids are emptied from the stomach within two hours of intake (2-4, 32-36). A recent study using serial magnetic resonance imaging to investigate gastric emptying after clear fluid ingestion in healthy school children confirmed a median gastric emptying half-time of 23.6 (range 17.9 – 47.8) minutes, confirmed the exponential nature of the gastric emptying of clear liquids, and demonstrated that after two hours, the median gastric fluid volume was 0.32 (0.04 – 1.13) ml/kg (37).

The impact of carbonated drinks on gastric emptying in children has not been reported. Most studies in adults conclude that the carbonation of a drink per se does not alter gastric emptying, but that the intake of a flavoured or carbohydrate-containing carbonated drink may delay gastric emptying, probably due to the altered osmolality of the drink, and not the carbonation (38-42).

Gastric emptying of fruit juices is determined by the volume, osmolality and caloric content of the juice ingested. Fructose-containing liquids empty at a similar rate to water, which is faster than liquids containing sucrose or glucose (43).

2.3.2 MILK

There has been debate about the gastric emptying rates of human breast milk, infant formula and cow's milk. Many studies of gastric emptying of milk and milk products have been performed on neonates and premature infants and may not be

applicable to older children, as an age-related rate of emptying has been suggested (30).

Cow's milk

Cow's milk separates into a liquid and a solid phase on ingestion. Casein makes up 82% of the 3.3% total protein contained in milk. It contains phosphorus, and coagulates and precipitates at a pH of 4.6. Whey proteins comprise the other 18%. They are dissolved, do not contain phosphorus, and remain in solution at a pH of 4.6 (44). The curdled casein protein acts as a solid, delaying gastric emptying.

Full cream milk has been shown to have a median t½ of 86 - 87 minutes in infants and children (30, 45), slower than that of low fat milk (32).

Infant formula

Whilst infant formula is designed to be a substitute for human breast milk, the protein source is usually derived from purified cow's milk (or soy protein for the lactose intolerant). The cow's milk needs to be processed to alter the whey and casein ratio to better approximate human milk, making it more easily digestible by the human infant.

Despite a theoretical concern that casein-predominant formulas lead to delayed gastric emptying compared with whey-based formulas, this has not been shown to be the case (46,47). A gastric emptying half-time of approximately 60 minutes has been demonstrated for infant formula (48-51).

Gastroduodenal motility is delayed in infants fed formula compared to those fed breast milk, and may be part of the reason for the difference in gastric emptying between breast milk and formula (52).

Breast milk

Human breast milk has a casein : whey ratio of ± 40 : 60 (44), and thus empties from the stomach faster than formula milk, with t½s ranging from 36 - 48 minutes (48, 51-53).

2.3.3 SOLIDS

Gastric emptying of solids shows a biphasic pattern (28). Solids are broken down into smaller particles in the “lag phase”. These pass through the pylorus during the “linear emptying phase”, a process governed by zero-order kinetics. A constant rate of delivery of nutrients from the pylorus to the duodenum is maintained by a negative feedback mechanism controlled largely through the action of cholecystokinin. Glucagon-like peptide-I, peptide YY, motilin and ghrelin also play a role in regulating gastric emptying (28).

There are several other factors that influence the rate of gastric emptying.

- The volume of chyme.
- The composition of the chyme: both the particle size and viscosity of a meal affect gastric emptying (54).
- The composition and energy content of a meal: emptying of lipids is slowest, that of protein the fastest, with intermediate emptying of carbohydrate (27, 55). The greater the energy content of a meal, the longer the t½, with an increased variability in gastric emptying seen as the caloric content increases (45).
- The osmolality of a meal: the greater the osmolality, the slower its gastric emptying (55).
- The pH of gastric contents: unneutralized acid inactivates pancreatic digestive enzymes, inhibiting further chyme emptying from the stomach (55).
- The child’s position: emptying is slower in the supine versus the upright position (56).
- The temperature of the meal (57).

The mean gastric emptying t½ of solid meals in children is around 110 minutes (30, 32, 58).

A significantly increased RGV has been shown in children who chew chewing gum preoperatively compared with fasted controls (59). The clinical relevance of these findings is unclear though, and at this point no recommendations about the preoperative chewing of gum have been issued.

The effects of emotions on gastric emptying are not always predictable. Emotions such as fear tend to decrease gastric motility via autonomic neural action. Intense pain causes increased sympathetic activity, which may inhibit motility (55).

Several drugs may affect gastrointestinal motility. The opioid analgesics reduce gastric motility, gastric tone and the amplitude of small bowel non-propulsive contractions while increasing pyloric tone, delaying gastric emptying (60). In fasted patients, however, preoperative administration of morphine does not increase RGV at induction of anaesthesia compared with controls (61). Sedative premedication with midazolam, ketamine or clonidine has not been shown to increase RGV (62-64).

2.4 PATHOPHYSIOLOGY OF REGURGITATION

Regurgitation occurs when gastric contents flow passively from the stomach into the oesophagus (65). This gastro-oesophageal reflux (GOR) is normally prevented by the lower oesophageal sphincter (LOS), which maintains a high resting tone. The oesophageal muscle at the junction with the stomach is more prominent than in the rest of the oesophagus, and is surrounded by the crural muscles of the diaphragm, which aid in maintaining a higher pressure than that in the stomach. The LOS relaxes in response to swallowing (65).

For regurgitation to occur the intragastric pressure must overcome that of the LOS. As the stomach is extremely distensible, large gastric volumes are required to overcome the LOS tone. A study in cats (whose LOS is similar to that in humans) showed a mean gastric volume of 20.8 ml/kg was required for this (66). The presence of other factors that increase the intragastric pressure or volume increase the risk of perioperative regurgitation; these include obesity, gastrointestinal obstruction or atresia, ascites, large intra-abdominal tumours, emergency surgery, autonomic neuropathy, and the use of the prone or Trendelenburg positions (65).

An incompetent LOS can also predispose to regurgitation, and is the reason regurgitation is common in infants, who have a relative lack of an intra-abdominal oesophagus. Prematurity increases the risk of perioperative GOR, as does the presence of dyspnoea (65).

Anaesthesia may contribute to GOR in infants. Inadequate face mask ventilation can cause gastric inflation with air, increasing intragastric pressure. This may also occur in the event of an undiagnosed oesophageal intubation. Excessive anterior angulation of the larynx during laryngoscopy may also predispose to GOR (65).

Most described cases of perioperative regurgitation and pulmonary aspiration in children occur during induction of anaesthesia, usually during airway instrumentation in an inadequate plane of anaesthesia with no or insufficient muscle paralysis to prevent a gag or cough (67).

The true incidence of GOR in children under anaesthesia is not known.

2.5 PULMONARY ASPIRATION AND PNEUMONITIS

Aspiration is defined as the entry of liquid or particulate matter into the tracheobronchial tree as a consequence of passive regurgitation or active vomiting of gastric contents in a patient with inadequate protective laryngeal reflexes (68).

The risk factors for pulmonary aspiration include all the risk factors for regurgitation mentioned above. In addition, aspiration is more likely during emergency surgery, surgery performed outside normal working hours, and when an inexperienced anaesthetist administers anaesthesia (65). A reduced level of consciousness or any other reason for impaired cough or clearing of secretions is associated with an increased risk of aspiration (65, 67).

Several pulmonary syndromes may occur after aspiration, depending on the volume and composition of the aspirate and on the host's immune response. The three pulmonary manifestations most commonly described are aspiration pneumonitis, aspiration pneumonia, and airway obstruction by aspirated particulate matter. These are defined as separate clinical entities, although some overlap often exists (69).

Following pulmonary aspiration, patients may be asymptomatic or present with a range of clinical signs including cough, tachypnoea, desaturation, bronchospasm, and the development of respiratory insufficiency requiring ventilatory support (68).

2.6 THE INCIDENCE OF PULMONARY ASPIRATION IN CHILDREN

Whilst the perioperative pulmonary aspiration of gastric contents is the fifth most common adverse event occurring during general anaesthesia (68), it is a rare occurrence. It is said to occur two to three times more often in children than in adults (68), but its incidence appears to be declining (70). The reported incidence

of perioperative pulmonary aspiration in children in the perioperative period ranges from 1:10 000 to 10:10 000 (71-77).

Risk factors for perioperative pulmonary aspiration in children include emergency surgery, a higher ASA physical status (ASA 3 - 5), and the presence of bowel obstruction (congenital or acquired) or ileus. Most incidents occur on induction of anaesthesia, during manipulation of the airway (74).

Most children who aspirate in the perioperative setting will have no significant medical sequelae. No deaths secondary to pulmonary aspiration in children were reported in the reviewed literature. In fact the majority of children suffered no pulmonary sequelae. Those who did required supplemental oxygen and or ventilation, but were all discharged. Warner and colleagues found that if no respiratory symptoms (a new cough or wheeze, a decrease in SpO2 to <90% of baseline value, or radiographic changes) occurred within two hours of the event, they did not appear to develop at all (74).

This makes the mortality of such a rare event difficult to estimate, but it has been placed at less than 1:70 000 surgical patients (78).

Adhering to published fasting guidelines of six hours for solids and cow's milk, four hours for breast milk, and two hours for clear fluids, has been shown to be safe, as it does not increase the risk of regurgitation and pulmonary aspiration of gastric contents. Many children are fasted for longer than recommended (21, 79), which may be harmful.

2.7 PHYSIOLOGY OF FASTING AND GLUCOSE CONTROL

The concentration of circulating blood glucose is tightly controlled, and usually kept in the range of 3.9 - 6 mmol/l (80). Hormonal regulation maintains glucose homeostasis. This is essential as glucose serves as the primary metabolic fuel for

the brain, and its uptake into the brain depends on the concentration of circulating glucose in the blood. As glucose intake is intermittent, the hormonal control and the synthetic and breakdown function of the liver are responsible for maintaining the circulating glucose pool within normal limits (80).

After a meal, elevated glucose concentrations trigger pancreatic secretion of insulin, which stimulates glucose uptake by tissues and storage of glucose as glycogen in the liver (80).

In the post-absorptive (fasting) state, insulin levels fall as glucose levels drop. The concentrations of the counter-regulatory hormones glucagon, growth hormone and cortisol increase, as do levels of catecholamines. These hormones act to maintain a normal blood glucose level by inhibiting glycogen production and by stimulating the processes of glycogenolysis and gluconeogenesis. Hepatic glycogen stores are rapidly broken down to release glucose into the circulation, initially maintaining blood glucose levels, but as the period of fasting increases the supply of glycogen becomes depleted and the liver starts to convert the alternative fuels of glycerol, lactate and amino acids to glucose. This process of gluconeogenesis becomes the major source of endogenous glucose production with prolonged fasting. The liver is responsible for 90% of endogenous glucose production, with the remaining 10% from the kidneys after a prolonged fast (81).

Infants and children have a higher basal metabolic rate than adults (82) and thus a higher glucose requirement. Accordingly children need a relatively high rate of endogenous glucose production. This increased requirement, along with limited glycogen stores and immature liver enzymes involved in gluconeogenesis, put younger, smaller children at risk of hypoglycaemia during prolonged fasting. Children with glycogen storage diseases and malnourished children also have limited hepatic glycogen reserves and are at risk of hypoglycaemia during prolonged fasting (80, 81).

2.8 FASTING OUTCOMES

The incidence of regurgitation and pulmonary aspiration of gastric contents has been considered the primary outcome of studies assessing preoperative fasting guidelines. Secondary outcomes have also been measured.

2.8.1 THIRST

Children who are allowed to drink clear fluid two to three hours preoperatively are significantly less thirsty than those fasted for prolonged periods (5, 37, 83, 84). A recent study has found that shorter preoperative fasting reduces thirst and hunger during the first 24 hours postoperatively too (85). In a survey of adult surgical patients, the respondents rated thirst as a major cause of discomfort perioperatively, more so than hunger or not being able to sleep, and were more worried by their thirst than by the impending surgical procedure (86). Thirst is not a “soft” secondary outcome; the physiological urge to drink water is a powerful defence against hyperosmolality, and helps to maintain plasma volume and osmolality.

2.8.2 HUNGER

Children have been shown to be less hungry if allowed to drink clear fluids two to three hours preoperatively (5). They are also reportedly less irritable, anxious and upset than controls (6, 37, 87). Parents find the overall perioperative experience better if their children drink on the morning of surgery and find the fasting instructions easier to comply with than with a longer fast (6).

2.8.3 HYPOTENSION

Prolonged fasting of more than eight hours has been associated with significant reduction in blood pressure on induction of anaesthesia with halothane in infants aged one to six months (8). Prolonged fasting is considered to produce a relative hypovolaemia that is unmasked under anaesthesia, leading to hypotension.

2.8.4 METABOLIC ACIDOSIS

A trend towards metabolic acidosis has been demonstrated in children who fast for prolonged periods (88). The degree of acidosis is more marked in younger children, and indicates a depletion of carbohydrate reserves with mobilisation of fat stores and resultant ketosis.

2.8.5 COGNITIVE FUNCTION

Experiments performed on school children have shown that children who are fasted overnight and miss breakfast do worse on tests of cognitive function than those who have a shorter fasting period (15). This is marked in children who are considered to be nutritionally “at risk”, and occurs despite having a blood glucose within normal limits. The children studied showed slower working memory, slower stimulus discrimination, and made more errors in standardized tests.

2.9 HYPOGLYCAEMIA

2.9.1 DEFINITION

The American Diabetic Association (ADA) defines hypoglycaemia as “all episodes of an abnormally low plasma glucose concentration that expose the individual to

potential harm" (12). Both the duration of hypoglycaemia and the nadir glucose concentration contribute to this potential harm.

Hypoglycaemia has traditionally been diagnosed using Whipple's triad (12):

- symptoms compatible with hypoglycaemia;
- a low plasma glucose measured at the time of the symptoms;
- resolution of the symptoms on administration of glucose.

It has been argued that as the symptoms of hypoglycaemia are idiosyncratic and nonspecific, and as such may not be recognised, especially in the paediatric population, the diagnosis of hypoglycaemia should be based solely on a low plasma glucose value (11).

The ADA defines hypoglycaemia as a measured plasma glucose concentration ≤ 3.9 mmol/l (12). Frier suggests that this is too high, and has recommended a cut off of 3.5 mmol/l as the lower limit of normal in both diabetics (11) and fasted non-diabetic children (89). Some authors feel that there is no single value that defines hypoglycaemia, as hormonal counter-regulation, symptoms and altered cognitive function can occur at different glucose concentrations both between individuals and in the same individual at different points in time (90, 91).

Reference ranges for normal fasting glucose values vary slightly between laboratories. Most laboratories have a lower limit of 3.6 mmol/l and an upper limit from 5.8 to 6.3 mmol/l, and quote a normal fasting mean value of around 4 mmol/l (23). Glucose counter-regulatory systems are triggered at a plasma glucose concentration of 3.6 - 3.9 mmol/l in non-diabetic adults (12), making 3.5 mmol/l a logical lower limit of normal. Symptomatic responses and altered cognition usually commence at a blood glucose level of around 3.2 mmol/l (11). In children, ethical considerations make this extremely difficult to study. Symptom thresholds appear to be set at higher glucose values in children than in adults. According to some authors, any glucose concentration of ≤ 3.5 mmol/l should be considered abnormal as it is at this level where counter-regulatory mechanisms start to operate and

children may become symptomatic (13, 90, 92). Glucose levels ≤ 3.2 mmol/l are associated with symptoms of neuroglycopaenia (glucose deprivation in the brain) (90).

2.9.2 PATHOPHYSIOLOGY

Hypoglycaemia can occur when any of the above-mentioned counter-regulatory mechanisms fail. Broadly, this may occur because of the over-use of glucose, the under-production of glucose (including inadequate substrate), or both (93).

Inadequate glucose stores

Sufficient energy stores in the form of glycogen, muscle and adipose tissue are required to respond to a low circulating glucose concentration. Neonates, especially those who are premature or small for gestational age, are thus particularly susceptible to hypoglycaemia (80).

Older infants and children should have adequate energy stores to meet the metabolic demand imposed by a short fast, but become hypoglycaemic and ketotic after prolonged fasting (94). Malnourished children have reduced energy stores and are at risk of hypoglycaemia after shorter fasting periods (93).

Ketotic hypoglycaemia is a common cause of hypoglycaemia in children between 18 months and five years old, and typically occurs after a prolonged fast. Whilst common, the diagnosis of ketotic hypoglycaemia should be one of exclusion. It is thought to be caused by a deficiency or defective mobilisation of alanine as a fuel for gluconeogenesis. In the presence of prolonged fasting or minor illness, the liver thus converts fat to free fatty acids and ketone bodies to be used as metabolic fuel (93).

Excessive glucose use

An excessive amount of insulin (hyperinsulinaemia) causing hypoglycaemia is most commonly seen in the setting of insulin-treated diabetes. This exogenous administration of insulin is the most common cause of hypoglycaemia in diabetic children (93).

Other causes of hyperinsulinism include insulin-secreting tumours, genetic causes such as nesidioblastosis, Beckwith-Wiedemann syndrome, and infants of diabetic mothers (93).

Disorders of metabolic or hormonal pathways

Deficiencies of enzymes involved in glycogenolysis (eg glucose-6-phosphatase) or gluconeogenesis (eg fructose-1,6-diphosphatase) are rare causes of hypoglycaemia, as are deficiencies in counter-regulatory hormones such as glucagon and cortisol (93).

2.9.3 SIGNS AND SYMPTOMS

The initial symptoms that develop as blood glucose levels fall are a result of sympatho-adrenal activation. These autonomic symptoms and signs include shakiness, weakness, hunger, sweating, tachycardia and pallor (93).

Symptoms of neuroglycopaenia may follow, and include headache, difficulty concentrating, confusion, somnolence and irritability. These are thought to occur at glucose concentrations of ≤ 3.1 mmol/l (16) in healthy non-diabetic individuals.

Some of these symptoms, such as weakness and headache, are non-specific and may go unrecognised. Behavioural disturbances may be the primary feature of hypoglycaemia in younger children (90). This poses diagnostic problems in the perioperative setting, where a child may be irritable and miserable because of other factors such as pain, hunger, thirst, separation anxiety and fear.

A hierarchy of glycaemic thresholds for counter-regulatory hormone secretion, autonomic symptoms and neuroglycopaenic symptoms has been demonstrated in non-diabetic adults (95). Secretion of glucagon, adrenalin and noradrenalin occurs at a higher glucose concentration than the onset of autonomic symptoms, which in turn occur at a higher glucose concentration than neuroglycopaenic symptoms and cerebral dysfunction. This should allow time for adults to react to their symptoms early and prevent severe hypoglycaemia.

This may be different in children, where it has been reported that the dominant symptoms of hypoglycaemia may differ between different age groups, with younger children demonstrating symptoms of neuroglycopaenia more commonly than autonomic symptoms (90).

2.9.4 THE BRAIN AND HYPOGLYCAEMIA

The brain requires glucose as its main metabolic fuel. A constant supply must be delivered from the circulation, as the brain cannot synthesize or store substantial amounts of glucose (80).

If the glucose concentration in the blood decreases, the supply to the brain i.e. cerebral glucose content reduces proportionally, while the energy requirement of the brain remains unchanged. This means that the brain is uniquely vulnerable to the metabolic insult of hypoglycaemia. Areas most affected include the hippocampus, the basal ganglia, and the temporal lobes. This can be seen on MRI scanning (16).

As the concentration of glucose in the brain decreases, oxaloacetate builds up in the Krebs cycle. This increased oxaloacetate leads to an increase in aspartate, a reduction in brain glutamate, and intracellular calcium influx, which precipitates neuronal death (97). This process should be considered one of energy failure. Neuronal death is a late phenomenon, occurring after EEG isoelectricity has been demonstrated, and usually only occurs in cases of severe prolonged hypoglycaemia, i.e. at blood glucose levels of ≤ 1.5 mmol/l for over 30 minutes (97). This is associated with lasting structural changes in the central nervous system. Changes of EEG wave amplitude and frequency start to occur at blood glucose levels of < 3.5 mmol/l, and are marked at glucose values of < 2 mmol/l (97).

There is no prospective systematic research on the consequence of severe acute hypoglycaemia in non-diabetic children. Data from animal studies, from diabetic children, and from both diabetic and non-diabetic adults, suggest that even a single episode of acute hypoglycaemia with a glucose level < 3.1 mmol/l, lasting for as little as 30 minutes, may be associated with cognitive dysfunction. This manifests as a slowed reaction time to complex tasks, disruption of both long and short-term memory, impaired attention, disrupted arithmetical ability, and altered mood (97-99). Cognitive function seems more sensitive to hypoglycaemia than motor function.

The restoration of normoglycaemia does not result in immediate return of cognitive function, with delays of 45 - 90 minutes or longer reported (16, 97).

There is no clear evidence about the long-term consequences of a single acute episode of hypoglycaemia in non-diabetic children. It is likely that there is no long-term impact; but a single episode of hypoglycaemia will alter energy levels in the brain and thus alter brain energy metabolism, disrupting the functional efficiency and theoretically the structural integrity of neurons and glial cells (100).

Hypoglycaemia thus has the potential to cause significant central nervous system damage, and the threshold at which this occurs is not known or fixed (16).

2.9.5 PERIOPERATIVE HYPOGLYCAEMIA IN CHILDREN

The effects of preoperative starvation in children have been studied since the 1970s. The reported definition of, prevalence of and risk factors for hypoglycaemia vary widely, making the published data difficult to interpret. The studies reviewed differ in their methodology - some researchers sample venous blood while others use capillary samples, and different methods of analysing glucose levels, from the use of laboratory analysis to bedside glucometers, have been used. Some authors have taken samples prior to induction and others after induction and or intubation. Sedative premedication is prescribed in some studies and not in others.

There are several relevant issues raised by the reviewed literature.

The prevalence of preoperative hypoglycaemia in children

The quoted prevalence of preoperative hypoglycaemia in children varies widely, from as low as zero (6, 10, 87, 101) to as high as 29% - 30% (9, 21). The prevalence may be affected by the definition of hypoglycaemia used in each study; these range from < 2.2 mmol/l to < 4.0 mmol/l.

Risk factors for the development of hypoglycaemia

The following factors have been identified as placing children at risk for developing perioperative hypoglycaemia:

- **Prolonged duration of a preoperative fast**

Gupta et al (14) demonstrated an inverse correlation between fasting duration and blood glucose level that was significant in children from the ages of two to six

years ($p = 0.027$). Other authors have not found prolonged fasting times to correlate with blood glucose levels (10, 102, 107, 108, 110).

- **Children's age and weight**

In 1974, Thomas et al (9) demonstrated that children under the age of four and who weighed less than 15.5 kg were at increased risk for developing hypoglycaemia.

Several authors have published similar findings. Mastan et al (106) studied 60 children, of whom 30 were one to four years old and 30 were from four to ten years old. Of the patients younger than five, 8% were hypoglycaemic (defined as a blood glucose of < 2.78 mmol/l), whereas none of the older children were hypoglycaemic. Bevan and Burn (88) demonstrated a correlation between children's age and their blood glucose levels after a preoperative fast, finding that their measurements showed a closer correlation to age than to body weight. Gurha et al (105) found that children's mean pre-induction blood glucose level tended to increase with age. The difference in mean blood glucose levels between children younger than three and six to eight year olds was significant (3.12 mmol/l ± 0.43 versus 3.5 ± 0.58; $p<0.05$). Allison et al (104) demonstrated an 11% prevalence of hypoglycaemia (defined as a blood glucose < 3.3 mmol/l) in 92 patients studied; this prevalence increased to 23% in the subgroup of children who were younger than four years old.

These findings are in contrast to the findings of other authors (14, 107), who have not found age to be a risk factor for the development of hypoglycaemia in children; in fact, Redfern commented that "preoperative fasting is well tolerated in healthy preschool children" (10), as none of the preschool children she studied were hypoglycaemic after a preoperative fast.

- **Patients' nutritional status**

In 1982, Allison et al (104) demonstrated that children with weights below the 25th percentile had significantly lower mean plasma glucose levels than those with

weights above the 75th percentile for age (p=0.05). The authors also found that the mean plasma alanine concentration in the group of lower weight children was lower than in those of normal weight, suggesting that these children have a shortfall in hepatic gluconeogenic substrate and are thus more prone to developing hypoglycaemia. In a study from Tygerberg Hospital, Payne and Ireland (109) reported that malnourished children with a weight below the 3rd percentile for age were at significantly increased risk of developing hypoglycaemia after a preoperative fast (p<0.05).

Poor correlation between clinical and biochemical hypoglycaemia

It is clear that hypoglycaemia is difficult to detect clinically. The children who were found to be biochemically hypoglycaemic in the reviewed studies were all asymptomatic (10, 14, 102, 105, 107-108, 111). Gupta et al (14) found that clinical signs of hypoglycaemia in children studied were unreliable, and that the presence of so called typical signs of hypoglycaemia, such as sweating, headache, and excessive crying, had a high false positive rate of 66.66% in predicting actual hypoglycaemia.

The impact of drinking a calorie-containing solution on the day of surgery

Of the studies reviewed, seven compared a control group of children who had been fasted for a minimum of eight hours, or overnight, with a group who received fluids on the day of surgery (9, 10, 87, 88, 101, 105, 108). The fluids were a calorie-containing carbohydrate drink, milk, or clear fruit juice. The fluids were given from three to six hours prior to surgery, in volumes ranging from 4 (101) to 15 ml/kg (109). Most researchers gave around 10 ml/kg, to a maximum volume of 250 – 300 ml.

- **Impact on the prevalence of hypoglycaemia in paediatric patients**

Thomas's 1974 paper (9) is considered a landmark study. He studied 62 children from 1 to 13 years old. The children in the control group (n=33) were fasted

overnight prior to surgery, for a minimum of eight hours, which was then considered standard practice. Children in the intervention group (n=29) were given milk to drink (10 ml/kg up to a maximum of 300 ml) four hours preoperatively. At induction of anaesthesia 15.2% of the children in the control group, compared with none of the children in the intervention group, were found to be hypoglycaemic (blood glucose < 2.2 mmol/l). This difference was significant (p=0.05).

Bevan and Burn's study in 1973 yielded similar results (88). They studied 243 children, aged 5 months to 10 years. There was a 29% prevalence of hypoglycaemia (defined as a blood glucose < 3.3 mmol/l) in the group fasted for over eight hours, and 13% in the group given a carbohydrate drink three to four hours preoperatively. In their discussion the authors state, "younger children have a higher metabolic rate than adults. Their energy stores are small and it could be expected that the fasting state might develop earlier and to a greater extent than in the adult".

Other authors have published conflicting results. Both Jensen et al (108) and Redfern et al (10) showed no reduction in the prevalence of hypoglycaemia when comparing a group of children fasted overnight with children fed on the day of surgery. Their results should be interpreted with caution for two reasons. The first is that the definition of hypoglycaemia used in their research was a blood glucose concentration of less than 2.2 mmol/l, a definition that would exclude many children who might have been hypoglycaemic by current definitions; indeed, a histogram in Jensen's paper suggests that 8.7% of the children in his study who were fasted overnight had a blood glucose level of less than 3.3 mmol/l. The second reason is that the groups of children who received something to eat or drink on the morning of surgery still had longer preoperative fasting times than are currently recommended (a mean fasting time of 8.8 hours after breakfast in Redfern's study, and a fasting time of six hours after fruit syrup in water in the case of Jensen's patients).

- **Impact on mean blood glucose levels in paediatric patients**

The mean blood glucose levels of children in the control and treatment groups were significantly different in several studies (9, 10, 105) but not in others (87, 88, 101).

- **Adverse outcomes**

No incidents of regurgitation or aspiration as a result of shorter fasting times were documented in the reviewed literature (6, 9, 87, 101, 108).

A 2009 study at CMJAH assessed the duration of preoperative fasts and the incidence of hypoglycaemia in 81 children from the ages of one to five years (21). The researcher found that children presenting for elective procedures were fasted for a mean of 14 h 03 min (range 5 h 24 min - 21 h 57 min). Biochemical hypoglycaemia (blood glucose < 3.5 mmol/l) was detected in 18.5% (n=15). Blood glucose values ≤ 3.0 mmol/l, the level associated with potential neurocognitive dysfunction, were demonstrated in 9.87% (n=8). A significant association between the age of the child (one and two year olds versus three to five year olds) and the likelihood of hypoglycaemia was demonstrated ($p = 0.036$).

A table summarizing the reviewed studies can be found in Appendix A.

2.10 SUMMARY

In this chapter the literature relevant to this study has been reviewed. A brief history of the nil per os order was followed by a review of the physiology of gastric emptying, the pathophysiology of regurgitation and pulmonary aspiration of gastric contents, and the evidence of their occurrence and outcomes in children. The physiology of fasting and glucose control and the adverse effects of prolonged fasting have been reviewed, with a focus on hypoglycaemia: its causes and effects, clinical presentation, and the evidence for its occurrence in the paediatric population perioperatively.

The research methodology used in this study will be presented in the following chapter.

CHAPTER 3
RESEARCH DESIGN AND RESEARCH METHODS

3.1 INTRODUCTION

In this chapter the research methodology employed for this study will be described. The problem statement, aims and objectives, ethical considerations, and the research design of the study will be reviewed. The research population and sample, the method of data collection, and the statistical tests used to analyse this data will be discussed.

3.2 PROBLEM STATEMENT

Preoperative fasting instructions at CMJAH are not standardized, do not follow national or international guidelines and, even when correctly prescribed, are often not adhered to. As a result, children are frequently fasted for more than 12 hours before surgery. This prolonged duration of fasting predisposes children, especially younger children, to the risks of dehydration and hypoglycaemia. A recent study at CMJAH showed that 30.86% of paediatric surgical patients had a blood glucose < 4.1 mmol/l on induction of anaesthesia. 19.75% had a blood glucose <3.5 mmol/l, and nearly 10% had a blood glucose ≤ 3 mmol/l, the level associated with potential neurocognitive dysfunction (21).

3.3 THE AIM OF THE STUDY

The aim of this study was to determine whether allowing paediatric patients to drink apple juice two hours preoperatively reduces the prevalence of hypoglycaemia at the time of surgery.

3.4 OBJECTIVES OF THE STUDY

The objectives of this study were:

- to document the prevalence of hypoglycaemia at induction of anaesthesia in children given apple juice two hours preoperatively
- to compare these results to a historical control group (21).

3.5 ETHICAL CONSIDERATIONS

Approval to conduct the study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand and the Postgraduate Committee of the University of the Witwatersrand.

A randomized control trial is considered the gold standard for clinical research (114). However, in light of the potential adverse outcomes associated with hypoglycaemia in children, and after discussion with the chairman of the University of the Witwatersrand's HREC, a historical control trial was performed. The patient group studied by Fitchat (21) in 2009 was used as the control group. The researcher attempted to match patients in this study as closely as possible to those in the control group for age and weight. Patients were not matched for gender as this has not been shown to impact the likelihood of developing hypoglycaemia in the paediatric population.

The researcher obtained informed consent from a parent or caregiver for each participant in the study. An information document detailing the purpose and methods of the study was provided in English (Appendix D), with a translator available when necessary.

Research was conducted according to the principles of the Declaration of Helsinki (23) and Good Clinical Practice.

3.6 RESEARCH DESIGN

A prospective, contextual, comparative study design was used.

The study was prospective in that the outcome was measured after the study intervention was performed.

The study was contextual. It was performed at the CMJAH between June and August 2010. The data gathered was relevant to a particular group of patients, in this case children presenting for surgery to a public hospital. These patients came largely from lower income or inner city suburbs, townships and informal settlements. The use of contextual analysis implies that individuals are affected not only by their own personal characteristics, but also by those of the social group to which they belong (112). This may imply that the results would not be the same if the study was performed in, for example, a setting where resources are less limited. It was, however, necessary to perform this contextual study for two main reasons. First, a problem had been identified in our context. Secondly, most of the literature relating to preoperative fasting and hypoglycaemia in children has come from the first world, which may not be applicable in the context we have studied.

A comparative study design was used to assess two groups of patients who are similar in some respects (such as age, weight, and fasting duration) but differ in other respects (one group received apple juice on the morning of surgery). The goal of a comparative study is to determine the effect of treatment - in this case the effect of apple juice on the prevalence of hypoglycaemia.

This study used a historical control group. Traditionally the use of historical control (i.e. non-concurrent) groups has been questioned, as data in the control group is not collected specifically for comparison with the intervention group. The other difficulty with using a historical control when comparing it with prospective data is that potential selection bias may occur (113, 114). Fitchat's data (21) were

gathered from children in the same hospital presenting for similar surgery, implying that a stable population was studied, where the characteristics of the population were the same between the two time periods (114). The primary reason for using a historical control was an ethical one, as discussed. Matching was used to minimize any difference between the groups that could affect the study's conclusions.

3.7 STUDY POPULATION AND SAMPLE

3.7.1 STUDY POPULATION

The study population comprised paediatric patients aged from one to five years presenting for elective procedures requiring anaesthesia at CMJAH.

3.7.2 STUDY SAMPLE

SAMPLE SIZE

The sample size was determined in consultation with a biostatistician. In this single arm study a minimum study sample of 67 patients was determined to have 90% power to detect a change in the percentage of children with a blood glucose of less than 4.1 mmol/l from 30% in the historical control group to 15% when testing at the 0.05 level of significance.

SAMPLE METHOD

A nonrandomized, consecutive, convenience, quota sampling method was used in this study.

The randomized controlled trial is considered the gold standard in medical research for evaluating the efficacy of an intervention, as it limits bias in sampling.

Nonrandomized (nonprobability) sampling methods are often used in prospective studies as they reduce the time and cost required for the study, and show good correlation with randomized studies, but risk showing larger treatment effect (115), probably due to the way the researcher chooses the sample. This means that the results cannot be generalized to the whole population without being qualified (116).

Convenience sampling is a commonly used technique in clinical research (117). Subjects are selected because of their accessibility to the researcher, e.g. they are patients in the hospital or ward in which the researcher works. Consecutive sampling, where every available subject is selected, is the best way of doing convenience sampling, so that the whole accessible population is studied (116). In this study the researcher recruited any child who fulfilled the inclusion criteria and whose parent or guardian gave consent. Quota sampling was used in an attempt to match the ages of the children studied in the control group. This means that the population is subdivided into specified groups (in this case, based on age and weight), and proportions (or quotas) of the study sample are selected from each group. Quota sampling is nonrandom and may thus further add to sampling bias (116).

CRITERIA FOR THE STUDY

The following patients were included in the study:

- paediatric patients presenting for elective surgery;
- paediatric patients from one to five years of age;
- paediatric patients of ASA status I and II;
- patients for whom consent was obtained.

The following patients were excluded from the study:

- paediatric patients presenting for emergency surgery;

- patients who did not fulfill the appropriate preoperative fasting criteria, i.e. who have a “full stomach”;
- patients with comorbid diseases that classified them as ASA status III or greater;
- patients with comorbid diseases or conditions that increased the risk of delayed gastric emptying, gastric regurgitation and pulmonary aspiration;
- patients with intravenous access receiving intravenous fluids prior to surgery;
- patients refusing apple juice.

3.8 METHODOLOGY

The researcher assessed all patients on the morning of surgery. The parent or guardian of any child who met the inclusion criteria was informed about the study Appendix D) and asked for consent to include the child in the study (Appendix E).

Each child enrolled in the study was offered a 200 ml carton of commercially available apple juice. Additional juice was given if requested by the child. The volume and time of the juice consumed were documented, along with the child’s demographic data (height, weight, sex), fasting duration, and ASA status (Appendix F). The child’s height and weight for age were plotted on standard paediatric growth charts.

Anaesthesia and surgery proceeded a minimum of two hours after the apple juice was consumed. The researcher induced inhalational anaesthesia in all patients, administering oxygen, nitrous oxide and sevoflurane via a face mask and standard circuit. Standard monitoring was used in all cases. Once an adequate depth of anaesthesia was reached, the researcher inserted an intravenous cannula. A drop of blood from the cannula was analysed using a glucometer (Accu-Chek® Performa, Roche) prior to the infusion of any intravenous fluid. The glucose concentration was recorded (Appendix F), along with any complications related to anaesthesia and any rescue protocol followed. A solution of 1 - 2% dextrose in

Ringer's Lactate was administered intraoperatively to all children with a glucose concentration of 3.5 mmol/l or less. Protocols for the management of hypoglycaemia and hyperglycaemia were available. Ringer's Lactate was the intraoperative fluid used for normoglycaemic children.

3.8.1 QUALITY ASSURANCE

One researcher performed data collection to improve consistency.

The glucose and energy content of the apple juice was standardized and known, as one brand of juice was used.

A single glucometer was used for this study. It was the same glucometer used for the control group. The glucometer and test sticks were used and stored according to the manufacturer's instructions. Whilst the glucometer used does not require formal calibration, each batch of test sticks was used with the corresponding electronic module, as per the manufacturer's instructions. This improved the quality, accuracy and consistency of the research data.

The Roche Accu-Chek® Performa is a point of care (POC) device, designed as a glucose monitoring system for home self-testing by diabetics. It meets the International Standardization Organization (ISO) standards: glucose values > 4.1 mmol/l need to be within 20% of reference values, and those < 4.1 mmol/l need to be within 0.8 mmol/l of reference values, 95% of the time (118). POC devices have several advantages over central laboratory testing: they are less expensive, give nearly immediate results, and use a minute sample of blood (119). There are concerns, however, about their use in the critically ill, in those requiring insulin therapy for tight glycaemic control, and for clinical research (119, 120), as the ISO standards are not considered by some authors to give accurate enough results in these settings, especially in the hypoglycaemic range. A recent study of critically ill patients, however, found acceptable accuracy of the Accu-Chek® device when

tested on arterial samples, with the results falling short of the ISO requirements by 1%; the authors found the results “acceptable enough for use in intensive care” (121).

In view of the cost involved, and the fact that these children were all assessed as being of ASA status I or II, and would not be receiving insulin, the POC device was used. Any glucose levels of ≤ 3.0 mmol/l were to be checked by central laboratory testing.

Venous blood samples tested for glucose tend to report lower values than capillary samples (119, 122, 123), but this relationship is not always constant, and may vary depending on the fasting state of the patient (123). Capillary samples are more likely to give erroneously elevated readings as a result of contamination of the site, or low readings in cases of poor peripheral perfusion (122). It is thus difficult to compare results of samples tested from different sites (arterial versus venous versus capillary) and using different methods of analysis. For these reasons, the glucometer used was the same one used in the control study, and the glucose was tested in venous blood samples taken after induction of anaesthesia, as in the control group.

3.9 DATA ANALYSIS

Data were entered anonymously on an Excel spreadsheet and analysed in consultation with a biostatistician. The results were presented as mean ± SD or median (range) for continuous variables with normal or non-normal distribution respectively.

The groups were compared for the variables of age, weight and fasting duration. This is necessary to obtain comparable results when assessing the effect of treatment.

The distribution of each variable was explored on a histogram and tested for normality. It is necessary to test for normality of distribution so that the correct statistical test, parametric or nonparametric, can be applied to the results. Normality of distribution is tested using the Shapiro-Wilk test. If the p-value is larger than 0.05 the data is normally distributed.

Where data was normally distributed, the means of the groups were compared using ANOVA. ANOVA is a collection of statistical models in which observed variance is partitioned into components due to different explanatory variables (124).

Where data was not normally distributed, a nonparametric test was used to compare the two groups. In this study the Kruskal-Wallis test was used.

The ANOVA and Kruskal-Wallis tests tested if there was a significant difference between the two groups for the variables of weight, age and fasting duration. A probability value (p-value) is produced which indicates significant differences at a 95% level of confidence if the p-value is smaller than 0.05 (124).

Statistical modeling was undertaken to assess the influence of the treatment. An ANCOVA was conducted in order to account for the possible influence of covariates like weight and fasting duration.

ANCOVA tests whether it is the treatment that has an effect on the outcome variable (or dependent variable) by removing the effects of covariates (or “nuisance variables”). The interpretation of ANCOVA depends on certain assumptions about the data entered into the model. If these assumptions are not met the results obtained from the ANCOVA may be misleading, making an intervention look artificially less effective (125).

A two-way ANCOVA was conducted. The independent variable group involved two categories: control group and treatment group. The dependent variable was blood glucose level and the two covariates were weight and fasting duration.

Linear regression analysis was used to determine the extent to which there was a linear relationship between the dependent variable (glucose) and the independent variables of weight, fasting duration, and the administration of apple juice.

A Chi-Square test was used to test for the association between being in the treatment group and blood glucose level, using data presented in a 2 x 2 contingency table. In this study the Chi-Square test considers only the group the patients was in (control or treatment), and does not consider the effect of the other variables that impact on blood glucose levels, and could thus not be used as the only tool to compare the impact of the treatment (124).

From the data on the contingency table, probabilities, odds and odds ratios were calculated to assess the likelihood of children being hypoglycaemic if they do or do not receive apple juice on the morning of surgery.

Odds and probabilities are different ways of expressing the chance that an outcome may occur. The probability of an outcome is equal to the number of times the outcome is observed divided by the total observations. The odds, like in gambling, equal the probability that an outcome occurs divided by the probability that it does not occur. In other words, the odds are a ratio of probabilities. If the odds are greater than one, the event is more likely to happen than not to happen. The odds ratio is a relative measure of risk, comparing the odds for the two groups (126, 127). In this study the odds ratio equals the odds of the outcome in the control group divided by the odds of the outcome in the treatment group, the outcome being biochemical hypoglycaemia.

3.10 SUMMARY

In this chapter the research methodology employed for this study has been described. The problem statement, aims and objectives, ethical considerations, and the research design of the study have been reviewed. The research population and sample, the method of data collection, and the statistical tests used to analyse this data have been discussed.

The results of this study and a discussion of these results follow in the next chapter.

CHAPTER FOUR
DATA ANALYSIS AND DISCUSSION OF RESULTS

4.1 INTRODUCTION

In this chapter the results of this study are presented and discussed as per the research objectives. The data presented include demographic data of the study population; the prevalence of biochemical hypoglycaemia at induction of anaesthesia; and a comparison of these results with those of the control group. The findings are described and analysed using descriptive and inferential statistics.

4.2 RESULTS

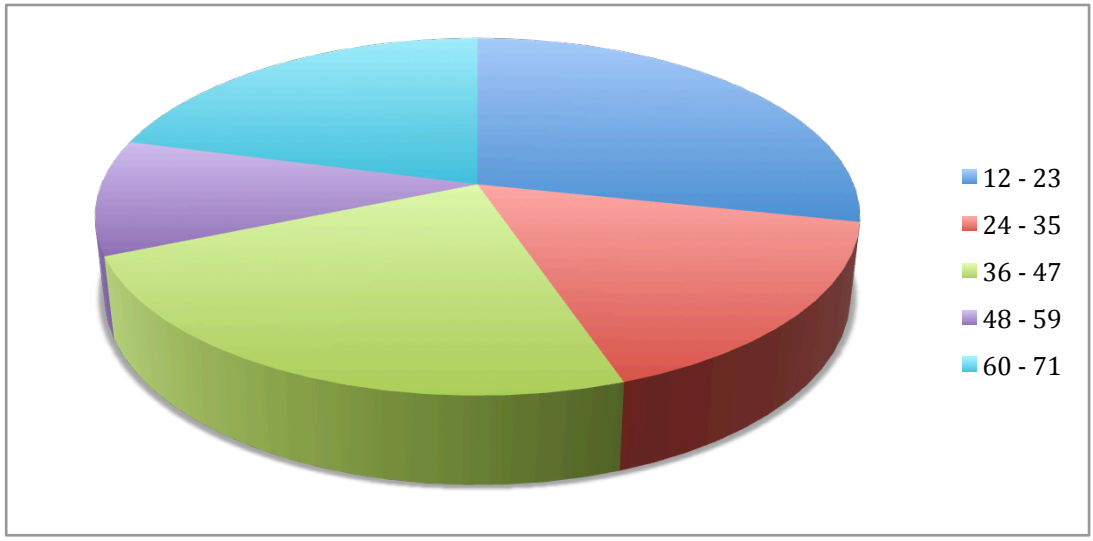
Results are presented and discussed as per the research objectives. Unless otherwise specified, data are presented as mean and ranges.

4.2.1 DEMOGRAPHIC DATA

This study was conducted at CMJAH from June to August 2010.

There were 67 children from the ages of one to five years enrolled in the study. Of this sample, 19 (28.35%) were aged 12 – 23 months, 11 (16.42%) were aged 24 – 35 months, 16 (23.88%) were aged 36 – 47 months, 7 (10.44%) were aged 48 – 59 months, and 14 (20.89%) were aged 60 – 71 months. These data are illustrated in Figure 4.1.

Fig 4.1 Ages of children studied (months)



The mean age of the children studied was 38.85 months (range 12 – 70 months).

Forty-seven children (70.1%) were male and 20 (29.9%) were female.

The mean weight of the children studied was 14.28 kg (range 7.1 - 24.9 kg).

The ASA status of 50 children (74.63%) was assessed as being ASA status 1, and that of 17 children (25.37%) was assessed as ASA status 2.

The mean fasting duration (hh:min) for solids was 15:37 (range 06:25 – 19:45). Of the 19 children who had had a drink since their last solid meal, the time from liquid intake to surgery ranged from 03:25 to 18:15.

Each child was offered a 200 ml carton of commercially available apple juice to drink. The mean volume of juice consumed was 157.98 ml (range 20 – 200 ml). The mean volume of juice consumed in ml/kg was 11.23 ml/kg (range 1.0 - 22.2 ml/kg). Forty-two children (62.6%) drank the entire 200 ml carton.

The mean time between consumption of the apple juice and induction of anaesthesia was 04:12 (range 02:00 – 8:10).

This data is presented in Table 4.1.

Table 4.1 Demographic data of patients studied

	Mean	Range
Age (months)	38.85	12 – 70
Weight (kg)	14.28	7.1 – 24.9
Fasting duration (solids) (hh:min)	15:37	6:25 – 19:45
Volume juice (ml)	157.98	20 – 200
Volume juice (ml/kg)	11.23	1.0 – 22.2
Time from drinking juice to induction of anaesthesia (hh:min)	04:12	02:00 – 08:10

No child refused the apple juice offered.

4.2.2 THE PREVALENCE OF BIOCHEMICAL HYPOGLYCAEMIA AT INDUCTION OF ANAESTHESIA

The first objective of this study was to document the prevalence of hypoglycaemia at induction of anaesthesia in children given apple juice up to two hours preoperatively.

The mean blood glucose concentration of the sample was 4.28 mmol/l (range 3.2 - 5.7 mmol/l).

Biochemical hypoglycaemia (blood glucose less than 3.5 mmol/l) was detected in four children (5.97%).

No child had a blood glucose level below 3.2 mmol/l.

These results are presented in Table 4.2.

Table 4.2 Blood glucose values at induction of anaesthesia

Blood glucose (mmol/l)	n	%
≤ 4	19	28.35
< 3.5	4	5.97
≤ 3.0	0	0

None of the children with blood glucose values < 3.5 mmol/l displayed symptoms or signs of hypoglycaemia.

The four children presenting with hypoglycaemia will be discussed further.

1. A 35-month-old male who weighed 14 kg (between the 25th and 50th percentiles for age) and was 92 cm tall (between the 10th and 25th percentiles for age) was assessed as being of ASA class 1. His last oral intake was at 19h00 the night before surgery. He was offered apple juice at 06h50 on the morning of surgery, when he had just woken up. He had a few sips, gave the juice back, and went back to sleep. His mother commented that he wasn't used to drinking that early in the morning. He drank 20 ml of apple juice (1.43 ml/kg). His blood glucose on induction of anaesthesia at 10h30 was 3.2 mmol/l.

2. A 36-month-old male whose height (98 cm) and weight (15 kg) were both between the 50th and 75th percentiles for age was assessed as being of ASA class 1. His last oral intake was at 19h00 the night prior to surgery. He drank the 200 ml carton of apple juice (13.3 ml/kg) at 06h55. Induction of anaesthesia proceeded at 09h20, at which time his blood glucose was 3.4 mmol/l.

3. A 19-month-old male, ASA class 1, weighed 11 kg (just below the 25th percentile for age) and was 82 cm tall (between the 25th and 50th percentile for age). He had last eaten at 21h00 the night before surgery, and had drunk a mug of rooibos tea with milk at 03h00. He was offered a carton of apple juice at 08h10, and consumed

170 ml (15.45 ml/kg). At induction of anaesthesia at 11h45, his blood glucose was 3.4 mmol/l.

4. A 21-month-old male who weighed 13 kg (between the 50th and 75th percentiles for age) and was 79 cm tall (between the third and tenth percentiles for age) was assessed as being of ASA class 1. He had last eaten at 19h30 the night prior to surgery, and had had a drink at 20h00. He drank 110 ml apple juice (8.5 ml/kg) at 07h20 on the morning of surgery. Anaesthesia proceeded at 14h15, at which time his blood glucose was 3.4 mmol/l. The child complained he was hungry prior to induction.

The above data are presented in Table 4.3.

Table 4.3 Children with biochemical hypoglycaemia at anaesthetic induction

Age (months)	Weight (kg)	ASA status	Fasting duration (hh:min)	Volume juice in ml (ml/kg)	Time between juice and induction	Blood glucose (mmol/l)
35	14	1	15:30 S	20 (1.4)	3:40	3.2
36	15	1	14:20 S	200 (13.3)	2:25	3.4
19	11	1	14:45 S 08:45 L	170 (15.5)	3:35	3.4
21	13	1	18:45 S	110 (8.5)	6:55	3.4

Key: S=solids; L=liquids

There were no witnessed episodes of regurgitation or pulmonary aspiration of gastric contents. One child vomited on emergence from anaesthesia on removal of his laryngeal mask airway. No adverse sequelae were noted.

4.2.3 COMPARISON OF RESULTS WITH THE CONTROL GROUP

The second objective of this study was to compare the results of the control and treatment groups to establish the influence of the administration of apple juice.

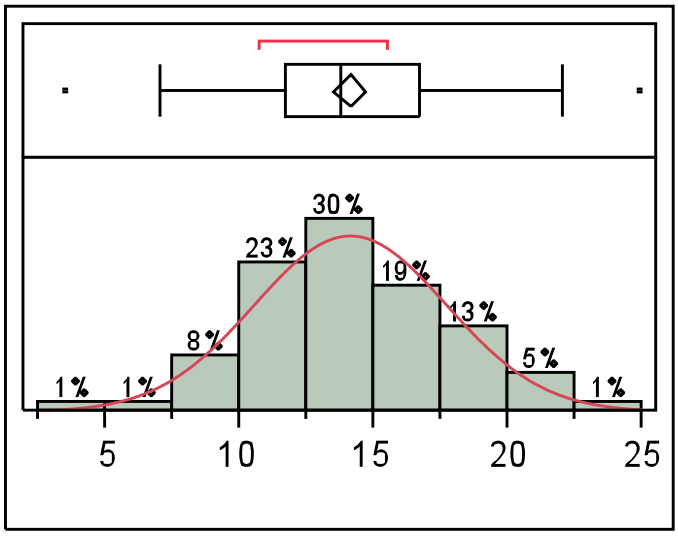
COMPARISON BETWEEN GROUPS FOR VARIABLES OF AGE, WEIGHT, AND FASTING DURATION

Before comparing the effect of the intervention, the variables of age, weight and fasting duration were compared between the two groups.

The distributions of each variable were explored via histogram and tested for normality.

The distribution of data for weight is shown in figure 4.2 below. From the histogram, it can be calculated that the data obtained for weight were normally distributed (p = 0.56).

Fig 4.2 Distribution of data for weight



p = 0.56

In the same way, the data for age, fasting duration and blood glucose concentrations were assessed. These data were not normally distributed at a 95% level of confidence, as the p values were smaller than 0.05 ($p < 0.0001$). These results are presented in Table 4.4.

Table 4.4 Shapiro-Wilk test to test for normal distribution of data

variable	Shapiro-Wilk W test	Prob < W	
Fasting time	W = 0.962955	P = 0.0005	data not normally distributed
Age	W = 0.953388	P < 0.0001	data not normally distributed
Glucose	W = 0.933833	P < 0.0001	data not normally distributed

Significant differences between the control and the treatment groups were tested for the above variables. Table 4.5 shows the means and standard deviations for the two groups.

There was no significant difference between the groups for the variables of age ($p=0.54$), weight ($p=0.58$), and fasting duration ($p=0.46$). The groups were thus comparable with respect to weight, age and fasting duration.

The mean blood glucose concentrations between the groups were not statistically different ($p=0.34$).

Table 4.5 Table of means and standard deviations

Variable	Statistics	Control group	Treatment group	p-value
Age (months)	Mean SD	40.605 16.413	38.851 18.199	p = 0.54
Weight (kg)	Mean SD	13.932 3.570	14.276 3.619	p = 0.58
Fasting duration (minutes)	Mean SD	845.346 202.015	849.552 221.183	p = 0.46
Blood glucose (mmol/l)	Mean SD	4.06 0.72	4.28 0.51	p = 0.34

TEST FOR ASSOCIATION BETWEEN BLOOD GLUCOSE LEVEL AND RECEIVING APPLE JUICE ON THE MORNING OF SURGERY

A Chi-Square test was used to test for association between being in the treatment group and the presence of biochemical hypoglycaemia at induction of anaesthesia.

Table 4.6 Contingency table to test for an association between blood glucose level and receiving apple juice on the morning of surgery

		Glucose < 3.5	Glucose ≥ 3.5	Total
Control group	count (n) total % column % row %	15 10.15 78.95 18.51	66 44.59 51.16 81.49	81
Apple juice group	count (n) total % column % row %	4 2.70 21.05 5.97	63 42.57 48.84 94.03	67
Total		19	129	148

The proportion of children with blood glucose < 3.5 mmol/l who received juice was low (4/19; 21.05%).

A significant association existed between treatment and blood glucose level at induction of anaesthesia, at a 95% level of confidence ($p = 0.023$).

From the above data, odds ratios were calculated.

The probability of biochemical hypoglycaemia occurring after the administration of apple juice was 5.97% (4 patients of 67).

The probability that blood glucose concentration at induction will be ≥ 3.5 mmol/l after the administration of apple juice was 94.03% (63 patients of 67).

The odds of biochemical hypoglycaemia occurring if apple juice was given were calculated as 0.063 (5.97/94.03).

The odds of biochemical hypoglycaemia occurring if part of the control group were calculated as 0.23 (18.51/81.49).

The odds ratio of the control group versus the treatment group was calculated thus: 0.23/0.06 = 3.83. This means that patients in the control group were 3.83 times more likely to be biochemically hypoglycaemic at induction of anaesthesia than patients in the treatment group.

MODELLING FACTORS INFLUENCING GLUCOSE LEVEL

Statistical modelling was undertaken to assess the influence of the treatment.

ANCOVA

A two-way ANCOVA was conducted in order to account for the possible influence of covariates such as weight and fasting duration. The independent variable group involved two categories: control group and treatment group. The dependent variable was blood glucose level, and the two covariates were weight and fasting duration.

The ANCOVA model was significant at a 99% level of confidence ($p < 0.001$).

The ANCOVA demonstrated that the group (control or treatment), fasting duration, weight and the interaction between fasting duration and group all had a significant influence on glucose level with p-values of: 0.047, 0.001, 0.018 and 0.007 respectively. Age was not significant in the model.

The covariates (weight and fasting duration) were linearly related to the dependent measure (blood glucose). The covariate of fasting duration was also related to the independent variable (the interaction between group and fasting duration was significant; $p < 0.01$). The assumptions for the ANCOVA were thus not met, as the covariate cannot correlate with the independent variable.

Since the assumption of the ANCOVA was not met, two separate regressions were done, a regression for each category of the independent variable, i.e. a separate regression was performed for the control group and for the treatment group.

REGRESSION

Linear regression was used to determine the extent to which there was a linear relationship between glucose and weight as well as fasting duration in both the control and treatment groups.

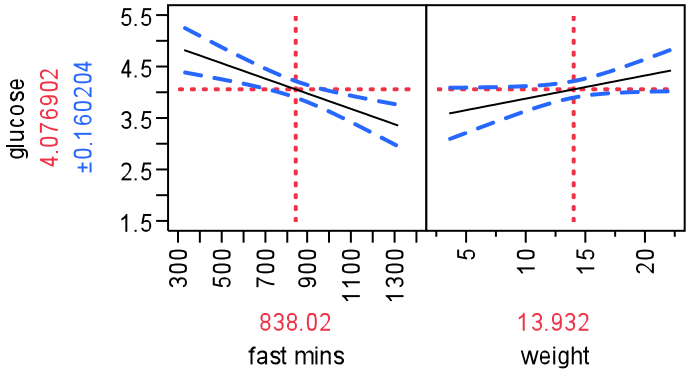
Regression for the control group

The linear regression showed a significant fit for the model at a 99% level of confidence ($p=0.0005$).

Fasting duration had a significant influence on blood glucose level at a 99% level of confidence ($p=0.0003$). Children weighing less than 15 kg were more likely to have a lower blood glucose, but the influence of patient weight was not statistically significant ($p=0.0525$).

The prediction profiler (figure 4.3) demonstrated a strong negative influence of a longer fasting duration on blood glucose level and a positive influence of weight on blood glucose level, i.e. the longer the period of fasting, the more likely it was that hypoglycaemia would occur, and the lower the child's weight, the more likely the child was to become hypoglycaemic.

Fig 4.3 Prediction Profiler for the control group



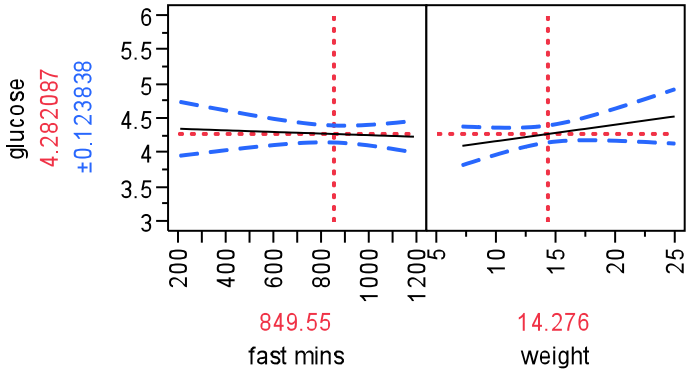
Regression for the treatment group

The linear regression showed a non-significant fit for the model at a 95% level of confidence (p=0.3982).

When apple juice was administered on the morning of surgery, fasting duration had no significant influence on glucose level at a 95% level of confidence (p=0.687). The influence of patient weight was not significant at a 95% level of confidence (p=0.18).

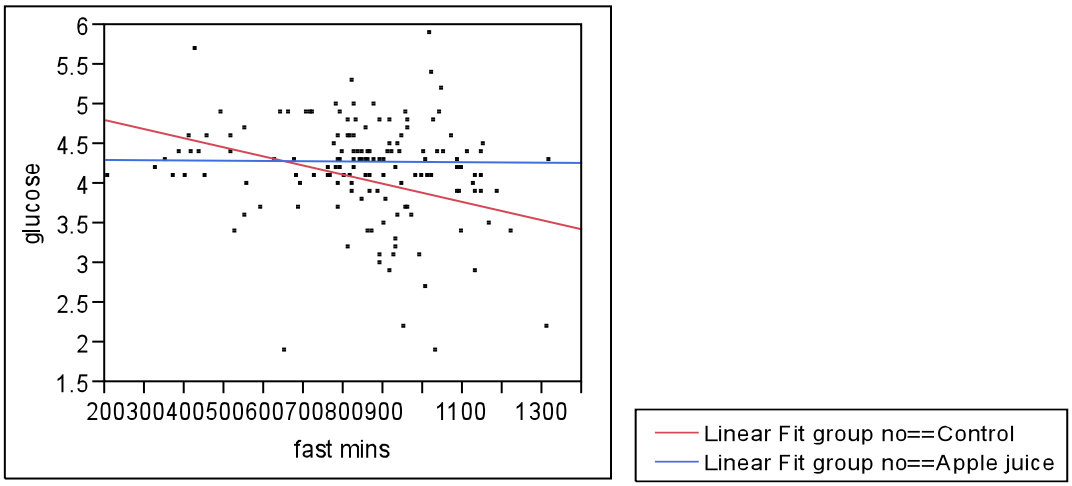
The prediction profiler (figure 4.4) demonstrated no influence of fasting duration on glucose level and a slight positive influence of weight on glucose level. This means that the duration of fasting had no effect on glucose levels when apple juice was consumed on the morning of surgery. Children weighing less than 15kg were more likely to have a lower blood glucose level, but the effect of weight was not statistically significant.

Fig 4.4 Prediction Profiler for the treatment group



This is also depicted graphically below (figure 4.5). There was a significant negative linear relationship between the fasting duration and the blood glucose level in the control group, while there was no relationship between fasting duration and blood glucose level in the treatment group.

Fig 4.5 Bivariate fit of glucose concentration by fasting duration



4.3 DISCUSSION

The decision to use a blood glucose level of < 3.5 mmol/l as the definition of biochemical hypoglycaemia was based on evidence that this is the level at which physiological counter-regulatory mechanisms start to occur, in an effort to maintain a normal glucose level. This cut-off value may, however, make the prevalence of biochemical hypoglycaemia in the control group (18.51%) seem higher than that

reported in the literature, where studies have used cut off values of as low as 2.2 mmol/l.

The administration of apple juice on the morning of surgery did not have a significant impact on the mean blood glucose levels between the control and treatment groups (4.06 mmol/l versus 4.28 mmol/l; p=0.34). This is in keeping with several studies in the literature (86, 87, 101).

The administration of apple juice on the morning of surgery did, however, significantly reduce the prevalence of hypoglycaemia in one to five year olds presenting for elective procedures from 18.51% to 5.97% (p=0.023). The effect of the apple juice was to reduce the influence of fasting duration from being significant in the fasted control group (p=0.0003) to having no significance in the treatment group (p=0.687).

The effect of age and weight on blood glucose level were not significant in this statistical model, despite the fact that the four children who were biochemically hypoglycaemic at induction of anaesthesia were all younger than four years old and weighed less than 15.5 kg, in keeping with the group of children identified by Thomas (9) and other authors (102-106) as being at increased risk of developing hypoglycaemia after a prolonged fast.

The four children who were biochemically hypoglycaemic in this study were not malnourished or underweight, either clinically or as defined by their positions on standardized CDC growth charts. The weight of one of the children was just below the 25th percentile for age, whereas the other three children all had weights greater than the 25th percentile. A single measurement of weight taken on the day of surgery was used to assess their weight, which may not be an accurate reflection of a child's overall health and nutritional status, as it does not reflect changes in weight and weight for age percentiles over time.

These findings are in contrast to those of Allison et al (104), who found that children whose weight for age was below the 25th percentile were particularly at risk for developing hypoglycaemia as they have inadequate stores of gluconeogenic substrates. Payne and Ireland (109) found this to be most pronounced in children whose weight for age fell below the third percentile, the World Health Organization's definition of underweight (128).

The children who were biochemically hypoglycaemic in this study displayed no clinical signs of hypoglycaemia, in keeping with the findings of other researchers, who have found the presence or absence of the clinical signs and symptoms of hypoglycaemia in children to be unreliable in predicting biochemical hypoglycaemia (9, 13, 102, 105, 107, 108, 111).

From the above findings, it would seem that hypoglycaemia after a prolonged fast is difficult to predict and diagnose in children, as the factor with the most significant impact is that of reducing the fasting period in line with accepted published guidelines.

The perioperative experience of both paediatric patients and their parents is increasingly used as an outcome measure in the literature. This was not an outcome measure used in this study. There were, however, many parents who commented on how grateful they were that their child was given something to drink. Several parents said that their children had been crying on the way to hospital, some that their children were "grumpy" or irritable, and that these settled after the children had had juice to drink.

4.4 CONCLUSION

The duration of a preoperative fast and being in the treatment group had a significant influence on the blood glucose level of preschool children presenting for elective surgery. The influence of weight and age were not significant. When apple

juice was not administered, fasting duration had a significant influence on glucose. Fasting duration had no influence on blood glucose when apple juice was administered up to two hours prior to surgery,

A significant association existed between treatment and the prevalence of biochemical hypoglycaemia in children between the ages of one and five years presenting for elective surgery at CMJAH.

4.5 SUMMARY

In this chapter the results of this study have been presented and discussed as per the research objectives. The data presented include demographic data of the study population; the prevalence of biochemical hypoglycaemia at induction of anaesthesia; and a comparison of these results with those of the control group. The findings have been described and analysed using descriptive and inferential statistics.

In the final chapter a summary, the limitations, recommendations and conclusions of the study are presented.

CHAPTER 5
SUMMARY, LIMITATIONS, RECOMMENDATIONS AND CONCLUSIONS

5.1 INTRODUCTION

In this chapter the aim, objectives, study design and results of this study will be briefly reviewed. The limitations of the study will be addressed, recommendations for clinical practice and further research made, and a conclusion presented.

5.2 SUMMARY OF THE STUDY

5.2.1 AIM OF THE STUDY

The aim of this study was to determine whether allowing paediatric patients to drink apple juice two hours preoperatively reduces the prevalence of hypoglycaemia at the time of surgery.

5.2.2 OBJECTIVES OF THE STUDY

The objectives of this study were:

- to document the prevalence of hypoglycaemia at induction of anaesthesia in children given apple juice two hours preoperatively;
- to compare these results to a historical control group (21).

5.2.3 SUMMARY OF THE METHODOLOGY USED IN THE STUDY

A prospective, contextual, comparative study design was used. The study population comprised paediatric patients aged from one to five years presenting for elective procedures requiring anaesthesia at CMJAH.

The sample size was determined in consultation with a biostatistician. A minimum study sample of 67 patients was calculated to have 90% power to detect a change in the percentage of hypoglycaemic children (blood glucose < 4.1 mmol/l) from 30% (in the historical control group) to 15% (i.e. halve the prevalence of hypoglycaemia) when testing at the 0.05 level of significance.

Nonrandom, consecutive, convenience, quota sampling was used.

Inclusion and exclusion criteria were defined.

All patients were assessed on the morning of surgery. Informed consent was obtained from the parent or guardian of each child who fulfilled the inclusion criteria.

Each child enrolled in the study was offered a 200 ml carton of commercially available apple juice. Additional juice was given if requested by the child. The volume of juice consumed was documented, along with the child's demographic data (height, weight, sex), fasting duration, ASA status, and the time at which the child drank the juice. The child's height and weight for age were plotted on standard paediatric growth charts.

Anaesthesia and surgery proceeded a minimum of two hours after the apple juice was consumed.

Anaesthesia was induced using an inhalational technique, using oxygen, nitrous oxide and sevoflurane. Standard monitoring was used in all cases. The researcher

administered anaesthesia to all patients. Once an adequate depth of anaesthesia was reached, the researcher inserted an intravenous cannula. A drop of blood from the cannula was analysed using a glucometer. The result was recorded on the data form, along with any treatment given for hypoglycaemia.

Protocols for the management of hypoglycaemia and hyperglycaemia were designed and followed.

5.3 MAIN FINDINGS OF THE STUDY

While the mean blood glucose levels of the two groups were not significantly different, the prevalence of biochemical hypoglycaemia, defined as a blood glucose value of less than 3.5 mmol/l, was significantly reduced in the group of children who drank apple juice on the morning of surgery ($p = 0.016$).

Linear regression analysis demonstrated that fasting duration and drinking apple juice had a significant influence on blood glucose levels, while the influence of age and weight of the patients was not significant.

No child given apple juice had a blood glucose value less than 3.2 mmol/l.

One child vomited on emergence from anaesthesia, likely due to airway manipulation in a light plane of anaesthesia. He was able to protect his airway and did not aspirate. No episodes of regurgitation or aspiration of gastric content were observed.

Many parents were grateful that their children were able to drink juice on the morning of surgery, saying that their children had been complaining of thirst. Several commented on their child's improved behaviour after drinking the juice, and were interested in both the study's results and impact on practice. Many

members of the nursing staff were supportive of the research and said they hoped it would change practice at CMJAH.

5.4 LIMITATIONS OF THE STUDY

The main limitations of this study lie in its design and sampling method.
This study was contextual and its scope was thus limited to a certain patient population. While results obtained may not be applicable across all patient groups, it addressed a problem experienced at CMJAH.

A minimum study sample of 67 patients was determined to have 90% power to detect a change in the percentage of children with a blood glucose of less than 4.1 mmol/l from 30% in the historical control group to 15% when testing at the 0.05 level of significance. The cut off value of 4.1 mmol/l was used as it was the definition used in Fitchat's study (21). A cut off glucose concentration of 3.5 mmol/l was subsequently considered to be more appropriate, as this is the level associated with sympatho-adrenal activation. The administration of apple juice has made a statistically significant difference to the prevalence of this level of biochemical hypoglycaemia, but is not what this study was designed to detect. In a subsequent consultation with a biostatistician, it was determined that a study designed to show a 50% reduction in the prevalence of hypoglycaemia defined as ≤ 3.5 mmol/l with 80% power would require 199 patients in each group (more if 90% power was used). This is beyond the scope of this research report and would require enrolling further children into a control group, which would not be ethically acceptable.

The use of convenience sampling, which may have contributed to bias in this study, was minimized by the use of quota sampling in an attempt to match patients with the control group. The use of a historical control group has also been considered to contribute to sampling bias; this limitation of the study design was accepted after consultation with the HREC of the University of the Witwatersrand.

The dynamic nature of a busy paediatric surgical operating list, and the unpredictable duration of some operations, means that some children cannot be anaesthetised exactly two hours after drinking their juice. While this was a potential limitation it is a realistic reflection of a routine operating list. The duration of preoperative fasting was documented in the data collection form.

5.5 RECOMMENDATIONS FROM THE STUDY

5.5.1 RECOMMENDATIONS FOR CLINICAL PRACTICE

The ASA recommended fasting guidelines do not increase the risk of regurgitation and aspiration of gastric contents, and are thus safe to implement. It is also clear that implementation of these guidelines is beneficial as it significantly reduces the prevalence of hypoglycaemia in preschool children. It is thus recommended that the ASA guidelines are introduced and implemented across the paediatric surgical departments at CMJAH. This will involve discussion with, and education of, nursing staff, medical colleagues and parents, in both inpatient and outpatient settings.

5.5.2 RECOMMENDATIONS FOR FURTHER RESEARCH

Should the ASA fasting guidelines be introduced at CMJAH, it is recommended that their implementation and impact be followed up.

The prevalence of prolonged fasting and hypoglycaemia in children less than a year of age has not been studied at CMJAH. While age was not significantly associated with the development of hypoglycaemia in this study, it has been identified as a risk factor in the literature, and is thus recommended as a focus for further research.

5.6 CONCLUSION

Drinking clear apple juice a minimum of two hours before surgery reduces the prevalence of biochemical hypoglycaemia in preschool children.

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APPENDIX A: TABLE

PERIOPERATIVE HYPOGLYCAEMIA IN CHILDREN

Year	Author	no and age of patients	mean fasting time (hrs)	definition of hypoglycaemia (mmol/l)	Prevalence of hypoglycaemia	findings / comments
1972	Watson (102)	n = 80 22 m - 15 y	10.5 (range 3 – 18)	≤ 2.2	10% (n=8)	Patients with low blood glucose tended to be younger (4.25 ± 3.3 y vs 6.45 ± 3.7 y); result not statistically significant
1973	Bevan, Burn (88)	n = 243 5 m - 10 y	"starved" group (n=142) ≥ 8hrs "fed" group (n=101) given high calorie carbohydrate drink 3 - 4 hrs preoperatively	< 3.3	"starved" group 29% "fed" group 13%	Mean glucose tended to be higher in "fed" group, but not statistically significant (no p values given). Capillary blood sample tested Trend towards metabolic acidosis in patients in "starved" group
1974	Thomas (9)	n = 62 1 – 13 y	fasted group (n=33) ≥ 8 hrs "fed" group (n=29) given milk (10ml/kg up to 300 ml) 4 hrs preoperatively	< 2.2	15% in fasted group; 0% in fed group (p=0.05) 28% of children in fasted group who were <4y and <15.5 kg	Mean glucose levels statistically significantly lower in fasted group (2.96 mmol/l vs 3.69 mmol/l, p < 0.0005) All hypoglycaemic children were < 4 y and < 15.5 kg
1976	Ffoulkes-Crabbe et al (103)	n = 28	14 (range 8.15 - 19)	< 2.5	7.1% (n=2)	Trend towards lower glucose if ≤ 2 y and < 13 kg

Year	Author	no and age of patients	mean fasting time (hrs)	definition of hypoglycaemia (mmol/l)	Prevalence of hypoglycaemia	findings / comments
1979	Graham et al (110)	n = 31 < 5 y	range 6 - 17 hrs	< 3.3	13% (n=4)	No correlation between fasting duration and glucose concentration
1982	Jensen et al (108)	n = 128 6 m – 9 y	Group 1 (n=92) overnight fast Group 2 (n=36) fed fruit syrup 7.5 ml/kg 6 hrs preoperatively	≤ 2.2	1/128	Histogram suggests that 8.7% (8/92) children had glucose < 3.3 mmol/l
1982	Allison et al (104)	n = 92 8 m - 8 y	overnight fast	< 3.3	11% (n=10) 23% (7/30) in children < 4 y	Children < 4 y and < 25th percentile for weight particularly at risk (p=0.05)
1984	Payne, Ireland (109)	n = 100 < 5 y and < 20 kg	7.5 (range 5 – 12) 5% dextrose water orally 4 (range 1 – 8) hrs preoperatively	< 3.0	8% (n=8) All 8 children < 3rd percentile for weight (8/32)	Underweight children at risk. Statistically significant in children > 1 y (p<0.05)

Year	Author	no and age of patients	mean fasting time (hrs)	definition of hypoglycaemia (mmol/l)	Prevalence of hypoglycaemia	findings / comments
1986	Redfern et al (10)	n = 54 1 - 5 y	Control group: 14.9 h (range 9.4 – 18.8) breakfast group 8.8 h (range 6.7 – 20.6)	< 2.2	0	Mean glucose levels significantly different between groups (fasted 4.8 mmol/l, fed 4.4 mmol/l; $p < 0.05$) Author's comment: "Preoperative fasting is well tolerated in healthy preschool children"
1986	Welborn et al (111)	n = 446 1 m – 6 y	NPO for solids from midnight. Children > 1 y allowed to drink up to 6 h (range 4 – 19) preoperatively	< 2.78	2/446	Ranges of glucose levels suggest that more children had a glucose < 3.5 mmol/l but no breakdown at these values given
1988	Gurha et al (105)	n = 90 6 m – 8 y	Control group (n=60): overnight fast Intervention group (n=30) drank milk 10ml/kg up to 300ml 6h preoperatively	< 2.2	2.2% (n=2)	Mean glucose levels significantly lower in fasted group (3.13 vs 3.57, $p < 0.001$) Mean glucose levels increased with increasing age; mean glucose levels in children under 3 years was 3.12 ± 0.43 Both hypoglycaemic children were underweight for age
1989	O'Flynn et al (107)	n = 34 11 m - 8 y	14h (9.5 - 17)	< 3.0	8.8% (n=3)	Mean glucose 4.16 (range 2.3 – 5.4) No correlation between fasting duration, age or weight and glucose concentration

Year	Author	no and age of patients	mean fasting time (hrs)	definition of hypoglycaemia (mmol/l)	Prevalence of hypoglycaemia	findings / comments
1990	Mastan et al (106)	n = 60 Group 1 (n=30) 1 - 4y Group 2 (n=30) 4 - 10y	8 - 10 h	< 2.78	8% of the younger age group (2/30)	All hypoglycaemic children were < 5y old
1993	Maekawa et al (6)	n = 105 1 - 14 y (mean 4.5 y)	Apple juice 10ml/kg 2, 4 or 12 h preoperatively	< 2.8	0	Mean blood glucose levels higher in group fasted for 2 hours but not statistically significant Concentrations of ketone bodies and fatty acids statistically significantly elevated in those fasted for longer than 2 hours
2001	Moyao-Garcia et al (101)	N = 40 3 – 12 y (mean 5.6 y)	“fasted” group ≥ 8 h (overnight fast) “fed” = 4ml/kg clear liquid (containing 20g glucose/l) 3 h preoperatively	< 2.2	0 No patient had a blood glucose < 3.3	RGV less and gastric pH higher in fed group No difference in mean blood glucose levels between groups

Year	Author	no and age of patients	mean fasting time (hrs)	definition of hypoglycaemia (mmol/l)	Prevalence of hypoglycaemia	findings / comments
2004	Gupta et al (14)	N = 56 2 m – 13 y (median 4 y)	12 (range 6 – 19)	< 3.3	3.6% (n=2)	No significant correlation between glucose and age (p = 0.83) or weight (p = 0.53) Correlation between fasting duration and glucose significant from 2 - 6 yrs of age Poor correlation between signs of hypoglycaemia and biochemical hypoglycaemia
2005	Castillo-Zamora et al (87)	N = 100 6.1 – 7.0 ± 4.4 y	"fasted" group (n=50) fasted overnight "fed" group (n=50) given apple juice (≥ 10 ml/kg to max 250 ml) on morning of surgery	< 2.7	0	Glucose measurement prior to induction No difference in mean blood glucose levels between groups
2009	Fitchat et al (21)	N = 81 1 - 5 y	14:05 (range 5:24 - 21:57)	< 4.0	30.86% (n= 25)	19.75% (n=16) had blood glucose ≤ 3.5

APPENDIX B

PERMISSION FROM POSTGRADUATE COMMITTEE

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011) 717-2745

Reference: Ms Tania Van Leeve
E-mail: tania.vanleeve@wits.ac.za
24 June 2010
Person No: 9301902M
PAG

Dr CP Lee
11 5th Street
Parkhurst
2193
South Africa

Dear Dr Lee

Master of Medicine (in the specialty Anaesthesia): Approval of Title

We have pleasure in advising that your proposal entitled "*The effect of preoperative apple juice on the prevalence of hypoglycaemia in paediatric patients*" has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX C

PERMISSION FROM ETHICS COMMITTEE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Clover Ann Lee

CLEARANCE CERTIFICATE	**M10509**
PROJECT	The Effect of Preoperative Apple Juice on the Prevalence of Hypoglycaemia in Pediatric Patients
INVESTIGATORS	Dr Clover Ann Lee.
DEPARTMENT	Department of Anaesthesiology
DATE CONSIDERED	28/05/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 27/08/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Mrs J Scribante

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX D: PATIENT INFORMATION LETTER

Dear Parent

My name is Clover-Ann Lee. I am a doctor in the University of the Witwatersrand department of Anaesthesiology. This means that I look after your children when they have an operation. I give them medicine to make them sleep, I make sure that they don't have pain, and that they are comfortable at the end of the operation.

For your child's anaesthetic to be safe, he/she needs to have an empty stomach before he/she has an operation. But if his/her stomach is empty for too long that can be unsafe because the level of sugar in his/her blood can get too low.

I am trying to see if we can keep your child's stomach empty but not let his/her sugar level become low. To do this I would like to give your child some apple juice to drink a few hours before the operation. This is a safe thing to do. I will make your child sleep for the operation by giving him/her gases to breathe through a mask. All children having an operation have a drip put in when they are already asleep so that we can give them fluids and medicines during the operation to prevent pain and infection. When I put your child's drip in, I will take one drop of blood and test the sugar level. Your child will not feel any pain and will not have any extra pricks from a needle - the drop will come from the drip.

If the sugar level in that drop of blood is too low or too high I will give medicine to treat it and check again to see that the sugar level comes to normal.

I hope that this study will improve they way we care for the children in our hospital. I would be very grateful for your participation.

Your participation is completely voluntary. If you do not want your child to be part of this study, that is your choice, and will not affect the care and treatment your child gets. You can choose to withdraw from the study at any time.

All information will be kept anonymously. This means nobody not involved in the study will know your child's results.

If you have any questions about this study, please call me on 082 557 0083 during working hours (07h30 - 17h00).

This study has been approved by the University of the Witwatersrand's Human Research Ethics Committee. If you have any questions about letting your child be a part of the study you can Call them on 011 717 1234 (office hours).

If you agree to take part in this study, please sign the attached form.

Thank you.

Clover-Ann Lee 082 557 0083

APPENDIX E: CONSENT FORM

PAEDIATRIC HYPOGLYCAEMIA STUDY

I, _____, give my consent that my child's blood can be tested for its sugar level when s/he is asleep before his / her operation.

Name	
Signature	
Date	

Researcher's name	
Signature	
Date	

Witness	
Signature	
Date	

APPENDIX F: DATA COLLECTION FORM

Study number		Date	

Age	
Height	
Weight	
Gender	

ASA	
Comorbid disease/s	

Time apple juice consumed	
Time of induction of anaesthesia	
Fasting duration: solids	
Fasting duration: liquids	
Volume of apple juice	mls:
	ml/kg:

Rescue protocol used	Yes / No
Describe rescue protocol	