A COMPARISON OF PLAIN RINGER’S LACTATE AND LOW GLUCOSE ADDED INTO PLAIN RINGER’S LACTATE SOLUTION USED AS A MAINTENANCE SOLUTION INTRA-OPERATIVELY TO MAINTAIN NORMOGLYCAEMIA IN CHILDREN AT DR GEORGE MUKHARI ACADEMIC HOSPITAL, SOUTH AFRICA.

By

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DECLARATION

I, Dr Siyabonga Kala hereby declare that the work appearing in this research is based on original work, except where acknowledgement indicate otherwise and neither the whole work nor any part of it has been or is to be submitted for another degree at this or any other institution (university)

My research protocol was approved by Research Ethics and Publication Committee, Faculty of medicine, at Sefako Makgatho health Science University.

The clearance certificate number: MREC/M/363/2014: PG.

Full names: Dr Siyabonga Kala Date
Signature…………………………

Student number: 210121464
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6. My colleagues in Anaesthesiology department at Dr George Mukhari academic hospital.

7. Main theatre and surgical ward nursing staff at Dr George Mukhari academic hospital.
DEDICATION

I dedicate this work to the people I value the most in my life; my mother, Nomsa, my brother, Thamsanqa and my wife, Nombulelo. Without your support I wouldn't have managed to complete this task. Enkosi!!!
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### ACRONYMS AND ABBREVIATIONS

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<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>APA</td>
<td>Association of Paediatric Anaesthetists</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anaesthesiologists</td>
</tr>
<tr>
<td>BG</td>
<td>Blood glucose</td>
</tr>
<tr>
<td>ENT</td>
<td>Ear, Nose and Throat (Otorhinolaryngology)</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>mmol/L</td>
<td>Millimoles per litre</td>
</tr>
<tr>
<td>SNS</td>
<td>Sympathetic Nervous System</td>
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<td>TNF</td>
<td>Tumour Necrosis Factor</td>
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A COMPARISON OF PLAIN RINGER’S LACTATE AND LOW GLUCOSE ADDED INTO PLAIN RINGER’S LACTATE SOLUTION USED AS A MAINTENANCE SOLUTION INTRA-OPERATIVELY TO MAINTAIN NORMOGLYCAEMIA IN CHILDREN AT DR GEORGE MUKHARI ACADEMIC HOSPITAL, SOUTH AFRICA.

ABSTRACT:

BACKGROUND:
Peri-operative incidence of hypoglycaemia in paediatrics is a serious concern that can result in serious morbidity or even mortality. Despite the incidence reported as being low by various studies, its complications can be very devastating.

There are various factors that can affect the incidence of peri-operative hypoglycaemia as highlighted by various authors, ranging from prematurity, small for gestational age, pre-operative prolonged fasting, critically ill, to the use of glucose-free solutions intra-operatively in long duration surgical procedures especially in high risk patient group.

Vigilance of the opposite extreme of hypoglycaemia, hyperglycaemia also need not be underestimated as it is also accompanied by varying complications of its own.

The purpose of this study was to compare plain Ringer’s lactate and 1% dextrose Ringer’s lactate solutions in the maintenance of normoglycaemia when used as maintenance fluid intra-operatively in paediatric patients aged 2 to 11 years at Dr George Mukhari Academic Hospital.
METHOD:

This was a randomised prospective study that was conducted in the operating theatre in Dr George Mukhari Academic Hospital.

A sample size of 201 ASA I – II paediatric patients aged between 2 and 11 years booked for elective minor or intermediate surgery from various surgical disciplines were recruited into the study.

The sample size was randomly divided into 2 groups based on which solution was administered intravenously as a maintenance fluid intra-operatively:

- **Group A** (plain Ringer’s lactate), n=101 and
- **Group B** (1% dextrose Ringer’s lactate), n=100.

The blood glucose tests were done twice. One was done during the induction of general anaesthesia by the anaesthetist, prior to the insertion of intravenous line and the other done within 1 minute after the conclusion of surgery, during the reversal of anaesthesia.

RESULTS:

**Pre-operatively**

From 201 patients that were recruited into the study, hypoglycaemia incidence pre-operatively was almost equal in both groups: Group A (plain Ringer’s lactate), n=2 (1.9%) and Group B (1% dextrose Ringer’s lactate), n=1 (1%).

Normoglycaemia pre-operatively was observed in 85% and 98 % for Group A and Group B respectively.

The difference between the two groups pre-operatively was not statistically significant with p-value of 0.456.

**Post-operatively**

In both groups A and B, there were no hypoglycaemic patients found post-operatively after the intravenous transfusion of either of the two maintenance solutions.
Blood glucose levels that were found to be within the normoglycaemic ranges were almost equal in both groups: Group A, n=99 (98%) and Group B, n =99 (99%) with no statistical significant difference.

However, the post-operative mean blood glucose levels (mmol/L) in Group A was $5.90 \pm 0.8$ standard deviation and in Group B it was $6.53 \pm 0.5$ standard deviation, which were statistically significant with p-value of 0.000.

The comparison of mean blood glucose levels taken pre-operatively and post-operatively in both groups were statistically significant, at a p-value of 0.000.

The mean duration of pre-operative fasting in hours was similar in both groups, $8.8 \pm 0.8$ standard deviation. There was no statistical significant difference between the two groups.

CONCLUSION:

This study showed that plain Ringer’s lactate was capable of maintaining normoglycaemia which was observed in 98% of the patients that were given plain Ringer’s lactate solution as a maintenance fluid.

There was a significant increase from the base line blood glucose levels after the transfusion of plain Ringer’s solution. This increase from the base line was maintained within the normoglycaemic ranges.

Plain Ringer’s lactate was demonstrated to be sufficient in maintaining normoglycaemia when used as a maintenance fluid intra-operatively in children of ages between 2 and 11 years of ASA I – II scheduled for minor or intermediate surgery at Dr George Mukhari Academic Hospital.
CHAPTER 1

1. INTRODUCTION

1.1 Study problem

It has been a debate for many decades to reach a general consensus concerning the intra-operative use of dextrose containing solutions in the paediatric population. However, huge strides have been seen since the early 1970’s regarding this. All these improvements came about as an attempt to improve the safety of paediatric patients peri-operatively. Despite these improvements some old habits are still seen in practice, hampering with these improvements and putting paediatric patients in harm’s way.

One of the resent guidelines from the Association of Paediatric Anaesthetists (APA)¹, in an attempt to answer the question of whether it is necessary or not to use glucose containing solutions peri-operatively in the paediatric population is some of the work in progress that is available to refer to as a guide.

One of the major challenges in paediatric management is the fact that most of the practices in paediatric management is extrapolated information based on our knowledge of physiology especially from adult group and also information extrapolated from animal studies.

The risk of developing hypoglycaemia is always there, although it is of a small estimated percentage according to the available studies.² This small risk is the major determinant and justification of one’s anaesthetic practice in deciding on whether to supplement glucose in maintenance fluid or not. Even though the incidence of hypoglycaemia might be low but lipid mobilization does occur, with generation of plasma ketone bodies and fatty acids.²

The recommendations of pre-operative fasting are not strictly followed and some places still use the old traditional prolonged fasting periods of overnight (more than 10 hours)². This can be an additional risk factor for developing hypoglycaemia in paediatric patients especially those in the high risk group.

Hypoglycaemia, depending on the severity has been found to induce or worsen brain damage by increasing the risk of hypoxic-ischaemic brain or spinal cord damage especially in the newborns.² ³
However, the risk of pre-operative hypoglycaemia has been demonstrated to be low (1-2%) in normal healthy infants and children despite prolonged fasting.\textsuperscript{4,7} This might not necessarily apply to paediatric patients under anaesthesia as this is based on pre-operative blood glucose levels post fasting. The recommended concentration of dextrose in a fluid to be transfused intra-operatively is 1 to 2.5% maximum.\textsuperscript{7}

The paediatric population at highest risk of hypoglycaemia peri-operatively includes neonates (especially the premature), children on hyper-alimentation and those with endocrinopathies in which monitoring of blood glucose levels and adjusting the rate of infusion is also recommended.\textsuperscript{2,8}

Even at low blood glucose concentration, most children remain asymptomatic although some appear lethargic or irritable.\textsuperscript{9} General anaesthesia masks the physical signs and symptoms of hypoglycaemia and this makes it more difficult to impossible to detect hypoglycaemia in the absence of blood glucose testing.\textsuperscript{9} Low blood glucose levels invoke a stress response, alters cerebral blood flow and metabolism thus can lead to permanent neurodevelopmental impairment if hypoglycaemia goes unrecognised and untreated.\textsuperscript{10}

Hyperglycaemia has also been recognized as detrimental for the central nervous system. In the presence of ischaemia or hypoxia, it is proposed that the impaired metabolism of excess glucose causes an accumulation of lactate, a decrease in intracellular pH and subsequently severely compromising cellular function that may result in cell death.\textsuperscript{10} Therefore attention should also be given to hyperglycaemia as much as it is given to hypoglycaemia in order to prevent its devastating effects.

Animal studies have further demonstrated that cerebral injury is caused not only by severe prolonged hypoglycaemia but also mild hypoglycaemia if it occurs in the presence of mild hypoxia or ischemia.\textsuperscript{11} The more recent study by Leelanukrom et al\textsuperscript{12} on this topic, estimates the incidence of pre-operative hypoglycaemia to be between 0% and 2.5% and is usually associated with fasting durations of 8 to 19 hours, which are well beyond the current American Society of Anaesthesiologists recommended guidelines.

At Dr George Mukhari Academic hospital, glucose containing solution infusion intra-operatively in children is based on an individual anaesthetist’s discretion without any guidelines or protocols available as a guide.
The research question being addressed here was very important in providing and improving understanding and knowledge on intra-operative fluid suitable for maintenance of normoglycaemia in the paediatric population. This provides evidence based justification concerning glucose use in intravenous fluids intra-operatively in children.

1.2 Purpose of the study
The purpose of this study was to compare plain Ringer’s lactate and 1% dextrose Ringer’s lactate solutions when used intra-operatively as maintenance fluid in children at Dr George Mukhari academic hospital.

1.3 Objectives of the study
i) To determine if it is necessary to add 1% glucose into Ringer’s lactate solution when used as maintenance fluid in children.

ii) To determine if plain Ringer’s lactate solution alone is sufficient in maintaining normoglycaemia when used as maintenance fluid peri-operatively in children of age between 2 and 11 years.
CHAPTER 2

Literature review

Elective surgery patients that are admitted as in-patients are usually fasted for a period ranging from 6 to 12 hours pre-operatively in Dr George Mukhari academic hospital. All this is done in an attempt to reduce the risk of aspiration, especially during induction of general anaesthesia.

The recommendations on pre-operative fasting according to the American Society of Anaesthesiologist Task force and European Society of Anaesthesiologists are however not strictly followed as some places still use the old traditional prolonged fasting periods overnight (more than 10 hours).\textsuperscript{12}

In Table 2.1 are fasting recommendations according to the American Society of Anaesthesiologist Task force and European Society of Anaesthesiologists on pre-operative fasting.\textsuperscript{13, 14}

<table>
<thead>
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<th>Ingested material</th>
<th>Minimum fasting period (hours)</th>
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<td>Clear liquids</td>
<td>2</td>
</tr>
<tr>
<td>Breast milk</td>
<td>4</td>
</tr>
<tr>
<td>Infant formula</td>
<td>6</td>
</tr>
<tr>
<td>Non-human milk</td>
<td>6</td>
</tr>
<tr>
<td>Light meal</td>
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Table 2.1 – Pre-operative fasting recommendations

These are also in keeping with the recommendations from APA guidelines on peri-operative fluid management in children published in 2007.

These recommendations apply to all healthy patients of all age groups booked for elective surgical procedures but not intended for women in labour. Complete gastric emptying is however not guaranteed even when using these recommended guidelines.

The purpose of these guidelines is to reduce the severity of complications that are related to pulmonary aspiration of gastric contents, should it occur. However, fasting especially if prolonged also has some possible adverse effects of varying degrees ranging from irritability, dehydration, electrolyte imbalance, lethargy to hypoglycaemia just to name a few.
Some of these effects of prolonged fasting can have deleterious or even fatal outcomes. This can result in some of these patients developing hypoglycaemia and staying longer periods before detection especially that there is no close monitoring of “healthy” patients pre-operatively.

In some studies it is believed that even small babies are capable enough to mount a stress response secondary to anaesthesia and surgery to sustain their blood glucose levels within a normal range, therefore it is possible to manage the majority of even small paediatric patients by using glucose-free fluids without the risk of intra-operative hypoglycaemia.\(^\text{15}\)

Apart from the risk of hypoglycaemia due to prolonged fasting as some authors believe, these children also present with considerable amount of pre-operative discomfort and irritability due to hunger.\(^\text{16}\) Fear of undetected intra-operative hypoglycaemia contributes to most of paediatric anaesthetists employing the “blind” use of glucose containing solutions for intra-operative fluid maintenance in order to safeguard against this.\(^\text{16, 17}\)

The question of glucose concentration in the maintenance solution used intra-operatively was answered by Welborn\(^\text{7}\), suggesting using a maximum of 2.5% dextrose on the basis that using this solution produced a consistent increase in blood glucose but without the moderate to marked hyperglycaemia that can be seen when higher dextrose concentration solutions are given at standard maintenance rate.

Wright\(^\text{18}\) suggested that, trauma, surgical and anaesthetic induced stress results in intra-operative hyperglycaemia and advised that glucose-free solutions should be used during surgery. However, certain risk categories do exist that may lead to intra-operative or post-operative hypoglycaemia if glucose is not given and thus many paediatric anaesthetists still believe and practice that glucose containing fluids should be used routinely in order to safeguard against such a dangerous situation.\(^\text{16}\)

Stress-induced post-operative increase in blood glucose concentration is not a consistent finding. If non-glucose containing solution is used for intra-operative fluid management, intra-operative blood glucose monitoring is suggested especially if the pre-operative fasting has been prolonged. As little as 0.9% glucose may be sufficient to prevent ketosis and hypoglycaemia in children intra-operatively, while 5% glucose has been associated with development of hyperglycaemia.\(^\text{19}\) Children became hypoglycaemic when excessively fasted or if maintained with solutions which do not contain glucose.\(^\text{19, 20}\)
Other authors, however could not confirm that the duration of starvation influenced the pre-operative blood glucose concentration.\textsuperscript{21, 22}

Welborn et al\textsuperscript{5} in their study reported that the period of fasting longer than 10 hours, produced hypoglycaemia in a small number of healthy children younger than 6 years of age however, the children did not exhibit pre-anaesthetic clinical signs and symptoms of hypoglycaemia. In Welborn study, the asymptomatic hypoglycaemia was found to be a rare but ever present phenomenon in healthy children fasting for surgery.

Although all these studies collectively represent a large number of patients, caution must be exercised when comparing the results from studies that were done at different times and in various institutions.\textsuperscript{22} The differences in the methods of testing and the variable level of stress response resulting from the difference in the anaesthetic techniques and patient population in pooled studies make a meaningful comparison difficult. The possibility that hypoglycaemia may remain undetected during anaesthesia has led to many authors recommending the routine use of glucose-containing solutions during surgery.\textsuperscript{22, 23, 24}

Nilsson et al\textsuperscript{25} in their study found that limiting the starvation period and administering glucose containing solution during surgery may not be necessary as indicated by studies reporting normal blood glucose values in fasted children. Many of these studies have however involved only a small number of patients and thus may have failed to identify an episode of hypoglycaemia that might occur infrequently.

Some believe that because of the low risk (1-2\%) of developing peri-operative hypoglycaemia in “normal healthy” infants and children despite prolonged fasting, it is therefore, in vast majority of these patients it is not necessary to administer glucose containing solutions in the peri-operative period nor there is a need to monitor the blood glucose.\textsuperscript{25}

Intra-operative maintenance fluid therapy is aimed at providing basal metabolic requirements, compensating for pre-operative fasting deficits and replacing the losses from the surgical field. The ultimate goal of peri-operative fluid therapy is to maintain correct fluid and electrolyte balance thus as a consequence, normal cardiovascular stability in order to maintain adequate tissue perfusion. Incorporated to this peri-operative fluid management is the blood glucose levels which both of these should be considered as a medical prescription
of which both the volume and the composition should be adapted to the patient status, the type of surgical procedure and the expected events in the post-operative period. Blood glucose level changes during surgery is a result of different factors such as diabetes, stress, surgical trauma, injection of adrenaline-containing anaesthetics and the medications used during surgery that can alter the blood glucose levels.

However, because of hyperglycaemic response associated with surgical stress, only infants and patients receiving insulin or drugs that interfere with glucose synthesis are at risk of hypoglycaemia. According to the APA guidelines on peri-operative fluid management in children, it is suggested that the majority of children over 1 month old are capable of maintaining normoglycaemia even if given non-glucose containing fluid during surgery. They also add that children who are at risk of hypoglycaemia if non-dextrose containing solution is given are those on parenteral nutrition or a dextrose containing solution prior to surgery, children of low body weight (<3rd centile) or having surgery of more than 3 hours duration and children having extensive regional anaesthesia.

Therefore they recommend that all these children that are at risk should be given dextrose containing solution or have their blood glucose monitored during surgery to determine if it’s necessary or not to supplement glucose.¹

In certain countries like France, there is a fluid that has a low concentration of glucose added into it called Polionique B66 which is made from lactated Ringer’s solution with 1% glucose added. This fluid gained its popularity and wide-spread acceptance in such countries following a number of deaths from hyponatraemia encephalopathy associated with hypotonic solutions used in the 1980’s.²⁶

Proven safety of Polionique B66 was demonstrated in a study by Murat et al, showing the rationale of using Ringer’s lactate solution with low dextrose concentration.²⁷ However, despite the proven safety of Polionique B66, it is still not licenced in some countries (USA, South Africa). Patients being operated under general anaesthesia, given the correct plain of anaesthesia, correct body temperature and pH, general metabolism is close to metabolism of a patient not anaesthetized and their energy requirements are close to basal metabolic rate.²⁷

The tradition of using glucose containing intravenous fluid has been done in an effort to prevent hypoglycaemia and limit protein catabolism. Iatrogenic hyperglycaemia can limit the
effectiveness of fluid resuscitation by influencing osmotic diuresis that can aggravate ischemic neurological injury. Current standard of care dictates that all “healthy” children undergoing minor surgery require no laboratory evaluation and thus can be spared the anxiety and pain of blood drawing.

The issue of fasting is of particular importance in paediatric anaesthesia as young children have smaller glycogen stores and are more likely to develop hypoglycaemia with prolonged intervals of fasting.

Intra-operative management of blood glucose is as important as managing intravascular volume and acid-base status of the patient while under anaesthesia. Autoregulation of hepatic glucose production plays an important role in the maintenance of normoglycaemia. Even though the endocrine system provides the primary response to changes in blood glucose concentration, autoregulation plays an important adjunctive role. This autoregulation like any other autoregulation in the body works within certain normal physiological limits beyond which it becomes insufficient to compensate for blood glucose concentration fluctuations.

Anaesthetist’s role is to keep this in mind, as it is known that the body’s metabolic system under the influence of anaesthesia varies widely from patient to patient, the type of anaesthesia employed and also the level of anaesthesia.

2.1 Clinical implications of hypoglycaemia

The most devastating effect of hypoglycaemia is brain damage by increasing the risk of hypoxic-ischaemic brain or spinal cord damage especially in new-borns. However, more recent studies estimates the incidence of pre-operative hypoglycaemia to be between 0% and 2.5% and is usually associated with fasting durations of 8 to 19 hours.

Is this 2.5% of possible damage to a developing brain not enough reason to warrant the prevention of hypoglycaemia? One might ask. As the answer to this question, there is a group of paediatric anaesthetists who practice and advocate for glucose containing solutions to be used intra-operatively as maintenance fluids to safeguard in those instances where a “normal healthy” patient might develop peri-operative hypoglycaemia. The factors that promote the development of hypoglycaemia in “healthy” paediatric patients peri-operatively is prolonged fasting way beyond the recommended fasting duration by the American Society of Anaesthesiologists task force on pre-operative fasting.
According to the European consensus statement for intra-operative fluid therapy in children it stipulates that “an appropriate solution for intra-operative use should have an osmolality and sodium contend close to the physiological range and addition of 1% to 2.5% glucose to avoid hypoglycaemia, lipolysis or hyperglycaemia”.\(^{13}\)

On a survey done in the United Kingdom, striking results were found confirming more than 200 anaesthetists who anaesthetised children, more than 60% of them were using hypotonic dextrose saline solution in the intra-operative period.\(^{8}\) Hypotonic solutions have been implicated in iatrogenic hyponatraemia, where death has been reported in both major and minor surgery in children, including tonsillectomy, orchidopexy, reduction of fractures and appendectomy. Therefore this practice is strongly discouraged intra-operatively.\(^{8, 30}\)

### 2.2 Clinical implications of hyperglycaemia

Anxiety, surgical and anaesthetic stress responses have been found to increase gluconeogenesis in the liver. There is also evidence suggesting a reduction in the peripheral glucose utilization.\(^{31}\) Combination of the two factors in addition to blood glucose supplementation in the intravenous fluid can further increase the risk of hyperglycaemia.

Hyperglycaemia is associated with impairment of the immune system and collagen synthesis, thus predisposing the patient to infection and hampering with normal wound healing. Hyperglycaemia can also lead to dehydration and electrolyte imbalance as a result of osmotic diuresis. These factors can predispose to an increased risk of acquiring pneumonia, systemic blood infection, urinary tract infection, skin infection and morbidity which is directly proportional to cost.\(^{32}\)

General anaesthesia compared to local or regional anaesthesia has been shown to result in higher concentration of blood glucose levels as a result of higher circulating catecholamines, cortisol and glucagon.\(^{33, 34}\) Certain anaesthetic agents used in general anaesthesia can cause an increase in blood glucose levels mainly by stimulation or sensitisation of the autonomic nervous system (sympathetic nervous system), which leads to an increase in gluconeogenesis in the liver plus a possible decrease in the peripheral utilization of glucose by the tissues.

Some common intravenous drugs that are used peri-operatively that can cause an increase in blood glucose levels: Ketamine, propofol, midazolam, adrenaline.\(^{35-37}\) Volatile anaesthetic
agents that are used to maintain general anaesthesia are believed to some extent, inhibit insulin secretion by the pancreas and increase glucose production in the liver.\textsuperscript{38, 39}

Apart from what is given to the patient under general anaesthesia, sometimes it is because of what is not given (e.g. appropriate analgesia) that can also promote gluconeogenesis and a decrease in peripheral glucose utilization plus insulin resistance. This happens as a results of light depth of anaesthesia, either directly due to pain or surgical stimulation. Therefore proper depth of anaesthesia and pain management can prevent the unwanted increase of blood glucose that when combine with supplementary exogenous glucose might lead to hyperglycaemic state.

2.3 \textbf{Physiology of glucose management}

Essentially all the carbohydrates in the food are absorbed in the form of monosaccharides, only a small fraction are absorbed as disaccharides and almost none as larger carbohydrate compounds. By far the most abundant of the absorbed monosaccharides is glucose, usually accounting for more than 80\% of calories absorbed.

The reason for this is that glucose is the final digestion product of our most abundant carbohydrate food, the starches.\textsuperscript{40}

The final products of carbohydrate digestion in the alimentary tract are almost entirely glucose (80\%), fructose and galactose.

After absorption from the intestinal tract, much of the fructose and almost all the galactose are rapidly converted into glucose in the liver.\textsuperscript{40}
The liver releases the monosaccharide back into the blood almost (>95%) entirely in a form of glucose. This is because the liver cells contain large amounts of glucose phosphate. Before glucose can be used by the body’s cells, it must be transported through the tissue cell membrane into the cellular cytoplasm.

Glucose cannot easily diffuse through the pore of the cell membrane because of its molecular weight.40
Figure 2.2. Passage to the interior of the cell is by facilitated diffusion, using glucose carrier protein from higher concentration to lower concentration.\textsuperscript{40}

Active sodium-glucose co-transport, the active transport of sodium provides energy for absorbing glucose against a concentration gradient. When glucose is not immediately required for energy, the extra glucose that continually enters the cells is either stored as glycogen or converted into fat. Glucose is preferentially stored as glycogen until the cell has stored as much glycogen as possible (sufficient for 12-24 hours energy supply).\textsuperscript{40}
2.4 Blood glucose levels in association with pain

In the olden days it was believed that new-borns and infants could not feel any pain, this was justified by the knowledge of the time, reasoning this to be because of the immaturity and less well developed central nervous system at this age. It was then later found that the nervous system at birth actually displayed some hypersensitivity to sensory stimuli in comparison to that of adults.

This would translate to a possibility that new-borns and infants actually experience more pain than adults due to this hypersensitivity of their nervous system. Both pain and stress have been shown to induce a significant physiologic and behavioural response in children, through their capability to mount a hormonal response to the stress of their illness. This response to both pain and stress leads an increase in gluconeogenesis and decreased peripheral utilization of glucose.

Impacts of painful experience of paediatrics nervous system has significant long term effects including lower pain tolerance for months after a painful experience. Unrelieved acute pain can lead to considerable anxiety, distress and in some instances can have long-term physical and behavioural consequences. Important physiological consequence as a result of lower pain and anxiety threshold is an increase in glucose production by the liver.

With this new information, it is clear that management of blood glucose also comprise of stress and pain management even in children who are non-diabetic. Thus a multi-modal approach is advocated in pain management and may involve both pharmacologic and non-pharmacologic methods.

Children suffer post-operative pain in the same way or even more than adults. The main difference is that factors such as fear, anxiety, coping style and lack of social support can further exaggerate the physical pain in children. The analgesic requirements following surgery does not depend on the age of the patient but on the nature of the procedure and the pain threshold of the patient.

Peri-operative pain management therefore begins during the pre-operative visit by preparing both the parents and the child about the upcoming surgery and information about the type of pain that is associated with it. Knowledge regarding the different types of drugs, blocks and their effectiveness as well as the side effects must be conveyed to the parent prior to surgery.
The current trend is to provide pre-emptive regional blocks before surgery, after induction of anaesthesia, as well as post-operative local infiltration of the wound in an attempt to lessen the need for narcotics during recovery. The ideal way to provide better post-operative analgesia in children is the use of multiple analgesic with additive or synergistic effects, yet with different side effects profiles so that adequate analgesia can be provided with the least amount of side effects.\textsuperscript{42}

2.5 PHYSIOLOGICAL RESPONSE TO STRESS

Stress occurs when allostatic mechanisms are insufficient for maintaining homeostasis, thus causing the organism to significantly alter many of its functions to reduce and contain the stressful threat.\textsuperscript{43}

Table 2.2: General systemic response to surgery.\textsuperscript{43}

<table>
<thead>
<tr>
<th>Systemic response to surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic nervous system activation</td>
</tr>
<tr>
<td>Endocrine stress response</td>
</tr>
<tr>
<td>- Pituitary hormone secretion</td>
</tr>
<tr>
<td>- Insulin resistance</td>
</tr>
<tr>
<td>Immunological and haematological changes</td>
</tr>
<tr>
<td>- Cytokine production</td>
</tr>
<tr>
<td>- Acute phase reaction</td>
</tr>
<tr>
<td>- Neutrophil leucocytosis</td>
</tr>
<tr>
<td>- Lymphocyte proliferation</td>
</tr>
</tbody>
</table>

Hypothalamic activation of the sympathetic autonomic nervous system results in increased secretion of catecholamines which leads to increased sympathetic activity, causing cardiovascular effects (tachycardia and hypertension) and in addition, the function of certain visceral organs including the liver, pancreas and kidney is modified directly by efferent sympathetic stimulation plus the circulating catecholamines.\textsuperscript{43}
Growth hormone is also released as part of the endocrine stress response and apart from its major role in growth regulation it also has many actions mediated through insulin-like growth factors (IGF), notably IGF-I which is produced in the liver, muscle and other tissues. Growth hormone effects on metabolism is stimulation of protein synthesis and inhibition of protein breakdown, promotes lipolysis and has an anti-insulin effects, that is it inhibits glucose uptake and it also stimulate glycogenolysis in the liver.\textsuperscript{43}

Table 2.3: Principal hormonal responses to surgery.\textsuperscript{43}

<table>
<thead>
<tr>
<th>Endocrine gland</th>
<th>Hormones</th>
<th>Change in secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior pituitary</td>
<td>ACTH</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>Growth hormone</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>TSH</td>
<td>May increase or decrease</td>
</tr>
<tr>
<td>Posterior pituitary</td>
<td>AVP</td>
<td>Increase</td>
</tr>
<tr>
<td>Adrenal cortex</td>
<td>Cortisol</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>Aldosterone</td>
<td>Increase</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Insulin</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>Glucagon</td>
<td>Small increase</td>
</tr>
<tr>
<td>Thyroid</td>
<td>T\textsubscript{3}, T\textsubscript{4}</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

Insulin concentration may decrease after the induction of general anaesthesia and during surgery there’s a failure of insulin to match the catabolic, hyperglycaemic response.

This may be caused partly by alpha-adrenergic inhibition of beta-cell secretion. In addition there is a failure of the usual cellular response to insulin, the so-called “insulin resistance” which occurs in the peri-operative period.\textsuperscript{43}

Glucagon effects are to promote hepatic glycogenolysis and also increase gluconeogenesis from amino acids in the liver plus lipolytic activity. Cortisol and catecholamines facilitate glucose production as a result of increased hepatic glycogenolysis and gluconeogenesis. This is in addition to the decreased peripheral utilization of glucose.\textsuperscript{43}

All these mechanisms promote and encourage an increase in blood glucose levels.
**Figure 2.3.** Mechanisms that initiate the stress response. Afferent neutral input plus cytokines such as IL-6 and IL-1 stimulate the hypothalamic-pituitary axis leading secretion of ACTH and activation of the SNS. Cytokines and growth factors act locally in the area of the wound and some also have endocrine effects.⁴⁴

Diagram from Miller's anaesthesia, 7th edition.⁴⁴
2.6 EFFECTS OF ANAESTHESIA ON THE STRESS RESPONSE TO SURGERY

**General anaesthesia**

Opioids suppress the hypothalamic and pituitary hormone secretion.

Etomidate interferes with the production of steroids in the adrenal cortex by reversible inhibition of the 11-beta-hydroxylase and cholesterol side chain cleavage enzyme, this leads to blockage of synthesis of both aldosterone and cortisol.

Benzodiazepines also inhibit cortisol production and could also have inhibitory effects on steroid production.

Ketamine can be used to treat pain thus inhibiting the pathway of increasing gluconeogenesis by pain or it could influence an increase in blood glucose levels by stimulating the sympathetic nervous system thus increasing gluconeogenesis in the liver. This is just a few of the drugs administered in anaesthesia that may have an influence on blood glucose concentration.

**Regional anaesthesia**

Regional anaesthesia using local anaesthetic agents is generally known to inhibit the stress response to surgery and can also influence post-operative outcome by beneficial effects on organ function.\(^{43}\) Regional anaesthesia causes a lesser release of catecholamines, cortisol and glucagon compared to general anaesthesia and as a result lower blood glucose concentration in regional anaesthesia.\(^{33, 34, 45}\)
CHAPTER 3

3. RESEARCH METHOD

3.1 Study design

Randomised prospective study.

3.2 Study setting

The study was conducted in the main operating theatre at Dr George Mukhari Academic Hospital in Gauteng, South Africa.

3.3 Study population

Patients that were included were all ASA I and ASA II paediatric patients of ages between 2 and 11 years that were booked for minor and intermediate surgery from different surgical departments (ENT, Plastic surgery, Urology, orthopaedics, Paediatric surgery and ophthalmology).

3.4 Sampling method

Sample selection was based on age, ASA classification and surgical procedure classification.

3.5 Inclusion criteria

a) ASA I and ASA II paediatric patients.

b) Age 2 to 11 years, both males and females.

c) Minor and intermediate surgical procedures.

d) Pre-operatively fasted for 6 to 12 hours.
3.6 Exclusion criteria

a) ASA III-IV and emergency cases.

d) Ages below 2 years or above 11 years.

c) Major surgery.

e) Pre-operatively fasted for less than 6 hours or more than 12 hours.

d) Intravenous fluid administration during the fasting period pre-operatively.

e) History of medical condition(s) that could have an influence on blood glucose levels e.g. Diabetes mellitus, metabolic syndrome.

f) Use of anaesthetic drugs that are known to have an influence on blood glucose levels (e.g. Ketamine, Adrenaline).

3.7 Data collection

A randomised prospective study conducted in the main operating theatre at Dr George Mukhari academic hospital.

Only the researcher knew which fluid was administered.

Two hundred and one ASA I and ASA II paediatric patients aged between 2 and 11 years scheduled for elective minor or intermediate surgery in these respective surgical departments were recruited into the study: paediatric surgery, ophthalmology, urology, orthopaedics and otorhinolaryngology.

Intermediate surgery is described in NICE guidelines (pre-operative tests for elective surgery) as Grade 2, giving these as examples: primary repair of inguinal hernia, excision of varicose vein(s) of leg, tonsillectomy/adenotonsillectomy, knee arthroscopy. 46

The sample size was randomly divided into two separate groups depending on which fluid type that was given intra-operatively: Group A (plain ringer’s lactate) n = 101 and Group B (1% dextrose added into plain ringer’s lactate), n = 100.

All these patients were booked for elective surgery after pre-operative fasting of 6 to 12 hours.

The data collected was recorded on the data collection sheet, Appendix B.
3.8 Material apparatus and instruments

50% dextrose solution

1% dextrose Ringer’s lactate (prepared by adding 4mls of 50% dextrose in 200mls of plain Ringer’s lactate).

Plain Ringer’s lactate.

Intravenous cannula, needle (22G and 25G) and intravenous line.

Sterile water plus gauze/cotton wool.

Data collection sheet

Accu-Chek active: A trademark of Roche.

The machine is used for rapid blood glucose testing (the approximate measuring time is 5 seconds).

The machine delivers accurate results that meet internationally recognized standards.

Blood volume required is 1-2 microliters. Requires capillary, venous or arterial blood.

Measuring rage in 0.6 to 33.3 mmol/L.

The result of the measured blood glucose is displayed on LCD screen.

Standard monitoring: Non-invasive blood pressure monitor at 2.5 minutes intervals.

Electrocardiogram.

Capnography.

Pulse oximetry

3.9 Data collection process

A drop of blood was collected by the researcher at the time of gas induction by the researcher with assistance from the anaesthetic nurse.

Induction of anaesthesia was done using sevoflurane done before the insertion of an intravenous line.
The drop of blood was tested for the blood glucose concentration level using a rapid blood glucose machine (Accu-Chek active).

During the surgical procedure, a specific fluid (either plain ringer’s lactate or 1% dextrose ringer’s lactate) was administered as a maintenance fluid intra-operatively.

At about one minute after the conclusion of the surgery another blood glucose test was done using the rapid blood glucose machine (Accu-Chek active).

No intra-operative blood glucose test was done.

3.10 **Statistical considerations and sample size**

Patients were randomized into Group A and Group B.

A sample of 201 “healthy” ASA I and ASA II paediatric patients, aged between 2 and 11 years presenting to theatre for elective minor or intermediate surgical procedure.

**Group A** = 101 patients were given plain ringers lactate.
**Group B** = 100 patients were given 1% dextrose ringer’s lactate.

With a sample size of 201 patients (group A = 101, group B = 100) there was 84% power to detect a difference of 20% between the percentages of patients with normal blood glucose levels post operatively, using a two group Fisher Exact test at a 0.05 significance level, assuming 60% patients in one group and 80% patients in the other group (odds ratio of 2.667).

Demographics of the patients included in this study were summarised descriptively according to the sample size, mean, standard deviation, frequency and percentage calculated as appropriate of gender, age, fasting duration and duration of surgery.

The percentage of patients with normal blood glucose levels post-surgery were compared between group A and B, using the Fisher Exact test.

All the statistical procedures were performed on Microsoft windows using IBM SPSS statistics 23 for a personal computer. Statistical testing was two-sided and the P-values < 0.05 was considered to be significant.
3.11 Reliability and validity of the study

**Reliability:** The extent to which results are consistent over time and an accurate representation of the total population under study is referred to as reliable and if the results of a study can be reproduced under a similar methodology, then the research instrument is considered to be reliable.\(^{47}\)

**Validity:** Validity determines whether the research truly means that which it was intended to measure or how truthful the research results are.\(^ {47}\)

To ensure reliability and validity, there was a randomization of patients into the study, the Accu-Chek Active glucose machine for checking rapid blood glucose was regularly calibrated, and test strips checked for the expiry date and the blood samples were taken from the second or third toe in all the patients.

The results found during testing were entered in the data collection sheet: Appendix B.

3.12 Bias

Refers to any tendency which prevents unprejudiced considerations of a question.\(^ {48}\)

In research, bias occurs when “systemic error(s) introduced into sampling or testing by selecting or encouraging one outcome or answer over other”.\(^ {48}\)

To minimise selection bias, a large sample size from different backgrounds, different surgical disciplines and broader inclusion criteria were used in this study.

Both genders were considered without choosing one over the other.

3.13 Limitations

This refers to elements over which the researcher has no control over.

a) Certain patients estimated body weights were used due to inability to measure their body weight (e.g. patients with tibia/fibula and/or femur fractures), this was due to no other means available at the institution where the study was done to measure body weight of the studied age group except for the weight-scale that requires a patient to be standing upright. Therefore weight estimation using a the formula, weight (Kg) = 3(age) + 7.\(^ {49}\)
b) Some of the body weights and measurements done pre-operatively might not have been a “true” patient body weight due to certain factors like in orthopaedic patients who were in casts (POP, back slabs/splints) during the weigh in process.

c) As a result of inadequate pain therapy employed pre-operatively and intra-operatively, this might also have had an influence on the blood glucose levels.

d) Some patients could be having metabolic condition(s) otherwise not yet diagnosed, thus influencing the blood glucose concentrations.

3.14 Ethical considerations related to data collection

The permission to conduct this study was requested and approved by the clinical superinternant of Dr George Mukhari academic hospital and Head of department of anaesthesiology.

Informed consent was obtained from the parents/guardians of patients after providing full information about the study, the purpose of the study, the benefits and potential risks associated with the study: Appendix A.

Parents/guardians were informed of their rights to make a voluntary decision for their children to be included in the study, their right to refuse and their right to withdraw from the study.

No high risk methods of blood collection that could cause bodily harm was used (e.g. femoral blood collection, jugular vein blood collection).

Approval for the conduction of the study was obtained from the Medunsa Research Ethics Committee (MREC/m/363/2014: PG) prior to conduction of this study: Appendix C.

Patient confidentiality was maintained by the exclusion of the patient’s name and hospital number on the data collection form.
CHAPTER 4

RESULTS

All the data was collected inside the operating theatre at Dr George Mukhari academic hospital.

The first blood sample for glucose check was taken during the gas induction of anaesthesia by the researcher, before the insertion of intravenous line. This sample of blood was used as a baseline and the second one was taken and tested approximately 1 minute after the completion of the surgical procedure. From the two values, a change from baseline whether there was an increase, decrease or stayed the same was noted and documented.

The computer software use for the statistical data analysis was IBM SPSS Statistic 23, using Fisher Exact test, running index Microsoft windows for a personal computer.

Statistical testing was two-sided and the P-values < 0.05 was considered to be significant.
**PATIENTS DEMOGRAPHICS**

**Table 4.1:** Gender distribution percentage

<table>
<thead>
<tr>
<th>Gender</th>
<th>Group A frequency(percentage)</th>
<th>Group B frequency(percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>101</td>
<td>100</td>
</tr>
<tr>
<td>Female</td>
<td>31(30.7)</td>
<td>35(35)</td>
</tr>
<tr>
<td>Male</td>
<td>70(69.3)</td>
<td>65(65)</td>
</tr>
</tbody>
</table>

**Table 4.2:** mean-SD of Age, fasting hours, operation duration.

<table>
<thead>
<tr>
<th></th>
<th>Group A mean ± SD</th>
<th>Group B mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>101</td>
<td>100</td>
</tr>
<tr>
<td>Age (years)</td>
<td>5.8 ± 2.5</td>
<td>5.9 ± 2.5</td>
</tr>
<tr>
<td>Fasting (hours)</td>
<td>8.8 ± 0.8</td>
<td>8.8 ± 0.8</td>
</tr>
<tr>
<td>Surgery duration (minutes)</td>
<td>80.3 ± 52.7</td>
<td>72.1 ± 43.6</td>
</tr>
</tbody>
</table>
Table 4.3: Frequency distribution of patients according to surgical departments

<table>
<thead>
<tr>
<th>Surgical department</th>
<th>Group A frequency(percentage)</th>
<th>Group B frequency(percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>101</td>
<td>100</td>
</tr>
<tr>
<td>ENT</td>
<td>18(17.8)</td>
<td>13(13.0)</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>1(1.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>12(11.9)</td>
<td>16(16.0)</td>
</tr>
<tr>
<td>Orthopaedics</td>
<td>50(49.5)</td>
<td>56(56.0)</td>
</tr>
<tr>
<td>Paediatric surgery</td>
<td>8(7.9)</td>
<td>2(2.0)</td>
</tr>
<tr>
<td>Plastics</td>
<td>4(4.0)</td>
<td>3(3.0)</td>
</tr>
<tr>
<td>Urology</td>
<td>8(7.9)</td>
<td>10(10.0)</td>
</tr>
</tbody>
</table>

Table 4.3 indicates the wide distribution of patients according to surgical departments, with majority of patients being orthopaedic patients in both groups.

Table 4.4: Frequency of pre-operative blood glucose in mmol/L, percentages in brackets.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>BG &lt; 3.8</th>
<th>BG = 3.8-5.5</th>
<th>BG &gt; 5.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>101</td>
<td>2(1.9)</td>
<td>89(88.1)</td>
<td>10(9.9)</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>1(1)</td>
<td>97(97)</td>
<td>2(2)</td>
</tr>
</tbody>
</table>

Pre-operatively it was observed in the data collected that the incidence of blood glucose levels that were below normal was 1.9% in group A and 1% in group B, Table 4.4.

This was in accordance with the American diabetes association criteria definition of hypoglycaemia post fasting.54

The blood glucose levels that were within the normal ranges (3.8 – 5.5 mmol/L) were found to be 88% and 97% for group A and Group B respectively, Table 4.4.

The Levels above the normal fasting blood glucose ranges was 10% and 2% for group A and group B respectively, Table 4.4.
Table 4.5: Blood glucose levels comparison pre-operatively

<table>
<thead>
<tr>
<th>Group</th>
<th>BG (mmol/L) (Mean ± SD)</th>
<th>p-value</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4.94 ± 0.6</td>
<td>0.456</td>
<td>0.746</td>
</tr>
<tr>
<td>B</td>
<td>4.99 ± 0.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The pre-operative mean blood glucose levels (mmol/L) in group A and group B were 4.94 ± 0.6 and 4.99 ± 0.3 respectively. The difference between the two groups was not statistically significant.

Table 4.6: Post-operative blood glucose levels in mmol/L

<table>
<thead>
<tr>
<th>Group A frequency(percentage)</th>
<th>N</th>
<th>BG &lt; 3.8</th>
<th>BG = 3.8 – 7.7</th>
<th>BG &gt;7.7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>101</td>
<td>0</td>
<td>99(98)</td>
<td>2(1.9)</td>
</tr>
<tr>
<td>Group B frequency(percentage)</td>
<td>100</td>
<td>0</td>
<td>99(99)</td>
<td>1(1)</td>
</tr>
</tbody>
</table>

Post-operatively, there was no blood glucose levels found to be below the normal range (<3.8mmol/L) in both groups, 98% of patients had a normal blood glucose in group A and 99% of patients in group B. Those above normal were 2% in group A and 1% in group B.

The blood glucose level ranges used on this table are the postprandial values used by American diabetes association.⁵⁴

Table 4.7: Blood glucose levels comparison post-operatively

<table>
<thead>
<tr>
<th>Group</th>
<th>BG (mmol/L) (Mean ± SD)</th>
<th>p-value</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5.90 ± 0.8</td>
<td>0.000</td>
<td>6.687</td>
</tr>
<tr>
<td>B</td>
<td>6.53 ± 0.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The post-operative mean blood glucose levels (mmol/L) in group A and group B were 5.90 ± 0.8 and 6.53 ± 0.5 respectively. The difference between the two groups was statistically significant.
Table 4.8: Comparing BG levels, pre- and post-operatively in group A and B

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-op BG (mmol/L) (mean ± SD)</th>
<th>Post-op BG (mmol/L) (Mean ± SD)</th>
<th>p-value</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4.94 ± 0.6</td>
<td>5.90 ± 0.8</td>
<td>0.000</td>
<td>-9.648</td>
</tr>
<tr>
<td>B</td>
<td>4.99 ± 0.3</td>
<td>6.53 ± 0.5</td>
<td>0.000</td>
<td>-26.411</td>
</tr>
</tbody>
</table>

The comparison of mean blood glucose levels taken pre-operatively during induction of anaesthesia with blood glucose levels taken post-operatively in group A and group B were statistically significant.
5.1 DISCUSSION

Pre-operative fasting forms an integral part of pre-operative preparation of patients that are booked for elective surgery. The main reason for this fasting practice is to reduce the risk of pulmonary aspiration. Generally in the practice of medicine, benefit has to always out-weight the risk and this also applies to pre-operative fasting practice.

All the “healthy” patients booked for elective minor or intermediate surgery usually fast for a period of 8 to 12 hours pre-operatively at Dr George Mukhari Academic Hospital and there is usually no intravenous fluid or glucose being administered during this period.

Pre-operative fasting can promote or cause hunger discomfort/pain, thirst, irritability dehydration, electrolyte imbalance and hypoglycaemia.

In this study it was found that “healthy” paediatric patients of ages between 2 and 11 years booked for elective minor or intermediate surgery, the vast majority (98 %) of patients who were given non-glucose containing solution as a maintenance solution intra-operatively were capable of maintaining their normal blood glucose levels at the conclusion of the surgical procedure.

All the studied (201) patients were fasted for 6 to 12 hours pre-operatively, only 3 (1.4%) (Two patients from group A and one from group B) were found to have fasting blood glucose below the normal levels (3.8 mmol/L) pre-operatively, before the administration of intravenous fluids. This percentage is in keeping with the incidence of pre-operative hypoglycaemia reported in some studies.4-7
In group B (1% dextrose ringer’s lactate), the post-operative increase in blood glucose concentration was significantly higher when compared to pre-operative levels (4.99 ± 0.3 mmol/L pre-operatively and 6.53 ± 0.5 mmol/L post-operatively).

The increase in blood glucose concentration in this group predisposed patients to the risk of hyperglycaemia which is accompanied by many complications. In comparison to other studies done\textsuperscript{22,23,24,50}, the incidence of pre-operative hypoglycaemia post fasting was found to be lower in this study. This difference was attributed to the definition of hypoglycaemia criteria used in this study which differs from study to study.

Plain ringer’s lactate solution was demonstrated to be sufficient when use as a maintenance solution intra-operatively in healthy children of age between 2 and 11 years in terms of maintaining blood glucose levels within the normal limits as represented by 98% of these cases, demonstrated in Table 4.6.

Infusing glucose containing solutions intra-operatively, there is an increase in the risk of developing hyperglycaemia which is also asymptomatic or masked by general anaesthesia.

Many studies on this topic have been done since the early 1900’s. These studies vary in methodology used thus making it difficult to apply knowledge gained from them to the age group of patients that was not included in the study group. The current available information from these studies on hypoglycaemia as an effect of pre-operative fasting in children predict the incidence of hypoglycaemia to be between zero and 2.5%.\textsuperscript{4-7}

There are different opinions about predisposing factors or causes of hypoglycaemia in children and these opinions vary widely. This is what makes it difficult to reach consensus on preventative and management strategies.

Some hypoglycaemia predisposing factors mentioned are high risk group of patients (premature, low birth weight and critically ill) and prolonged fasting periods. Pre-operative fasting periods are not strictly adhered to in Dr George Mukhari Academic Hospital, according to the current recommended pre-operative fasting periods by APA.\textsuperscript{1}

Some authors believe that “healthy” paediatric patients younger than 6 years of age have a low incidence of hypoglycaemia even when fasted for more than 10 hours.\textsuperscript{5} Some however believe that limiting the fasting periods and use of glucose containing solutions could alleviate the risk of peri-operative hypoglycaemia in healthy children even though is found to be of a small percentage.
Other authors however could not confirm that the duration of fasting had an influence on the pre-operative blood glucose concentration.\textsuperscript{22, 23} Nilsson et al\textsuperscript{25} found that limiting the fasting period and administering glucose containing solution in the peri-operative period may not be necessary as these patients are capable of maintaining normoglycaemia.

Furthermore, studies by Hagerman\textsuperscript{45} et al and JH Vander Walt\textsuperscript{51} et al on paediatric age group also failed to demonstrate hypoglycaemia after pre-operative fasting overnight of 10 to 16 hours.

Routine use of glucose containing solutions intra-operatively in children started to gain its popularity in the 1970’s after the discovery of certain children developing hypoglycaemia peri-operatively. The rationale of this practice was basically based on preventing and managing the few patients that could otherwise be in danger if they indeed developed hypoglycaemia either pre-operatively or intra-operatively.

It is also important to note that there are difficulties in detecting pre- or intra-operative hypoglycaemia as the signs and symptoms are not always present or even when present are not reliable.

General anaesthesia which is used for most surgical procedures in the paediatric population, masks these signs and makes it even more difficult to detect hypoglycaemia clinically. Depending on the severity, hypoglycaemia has been found to induce or worsen brain damage by increasing the risk of hypoxic-ischaemic brain or spinal cord damage especially in the newborns.\textsuperscript{2, 3}

Prevention or empirical treatment of peri-operative hypoglycaemia and its complications became the main reason for the use of intra-operative glucose containing solutions.

The next question that had to be answered was how much glucose concentration is enough to prevent hypoglycaemia, lipolysis and ketosis yet not cause hyperglycaemia.

As little as 0.9% of glucose concentration in a solution may be sufficient to prevent ketosis and hypoglycaemia in children intra-operatively, while concentrations of 5% and above are associated with development of hyperglycaemia.\textsuperscript{19}

The current recommended available guide on the glucose concentration in intra-operative fluids is 1 to 2% maximum in order to prevent intra-operative hypoglycaemia, lipolysis and hyperglycaemia.\textsuperscript{13}
Because of the known low incidence of peri-operative hypoglycaemia, in the vast majority of healthy paediatric patients it is considered not necessary to administer glucose containing solutions in the peri-operative period nor there is a need to routinely monitor their blood glucose.\textsuperscript{2, 9, 25}

The physiological stress response to trauma, surgery and anaesthesia varies depending on the magnitude of the surgery and the type of anaesthesia used. As a result of the physiological effects due to stress response by the body there is a marked increase in gluconeogenesis by the liver, a decrease in insulin release from the pancreas and a reduction in peripheral utilization of glucose by the tissues leading to an increase in plasma glucose levels.

Authors who believe that it is not necessary to supplement glucose intra-operatively, use these physiological changes as the rationale for their practice. These physiological changes are believed to be sufficient enough to maintain normoglycaemia in healthy children under anaesthesia. They also suggest that by supplementing glucose, the risk of developing hyperglycaemia becomes very high. With this practice it is very important to keep in mind that the stress-induced peri-operative increase in blood glucose levels is not a consistent finding, therefore this would not apply to all the patients.\textsuperscript{5}

Hyperglycaemia is also linked to a series of complications: dehydration, electrolyte imbalance, impaired immunity and poor wound healing.\textsuperscript{32}

Hypoglycaemia has been defined differently in variety of studies as blood glucose levels ranging from less than 2.2 to 3.3 mmol/L.\textsuperscript{52-54} According to this study, hypoglycaemia was defined as blood glucose levels below 3.8 mmol/L using the criteria of the American diabetes association.\textsuperscript{54} Using this criteria, the total number of children who were found to be hypoglycaemia pre-operatively was three (1.4%).

Apart from just using different criteria to define hypoglycaemia, it is of great importance to also note the different age groups used and the ASA classification of the studied patients in these different studies, which could be the explanation of having different results even though some studies were conducted in the same place (Graham\textsuperscript{22} and Thomas\textsuperscript{23}).

Another factor reported in these studies as the reason for having different prevalence was the different timings of the operations; one study was conducted in the morning and the
other in the afternoon. It was suggested that overnight fasting was not as deleterious as daytime fasting with regard to blood glucose levels.

5.2 SUMMARY AND INTERPRETATION OF THE RESEARCH FINDINGS

It is clear that there are many factors that influence the blood glucose concentration peri-operatively. These factors range from peri-operative pain, anxiety, surgical and anaesthetic stress. Fasting periods need to be standardised in all institutions in order to avoid the dangers associated with prolonged fasting.

It is clearly demonstrated in this study that a large majority (more than 90%) of paediatric patients of ages between 2 and 11 years are capable of maintaining normal blood glucose levels when only given plain ringers lactate as a maintenance fluid intra-operatively and there is a low risk of developing hypoglycaemia with fasting duration of 6 to 12 hours.

This is true if the patients are within the age group of this study, with a pre-operative health status of ASA I or ASA II, the fasting duration limited to 12 hours maximum and the pain management that is satisfactory in the peri-operative period (this includes, pre-, intra- and post-operative periods). In this group of patients, it is not mandatory to routinely monitor the blood glucose concentrations intra-operatively.

The addition of dextrose into intravenous fluids used as maintenance solutions intra-operatively, is only recommended in high risk patients (e.g. premature, small for gestational age, critically ill and those on glucose containing solutions pre-operatively).

Administering dextrose containing solutions may warrant monitoring as this can cause hyperglycaemia.

5.3 CONTRIBUTION OF THE STUDY

This study will share light on fluid management and Intra-operative glucose management in paediatric group.
It will also help in reinforcement of pre-operative fasting in children as recommended by available literature as well as helping in reinforcing of the importance of pain management in children.

5.4 LIMITATIONS OF THE STUDY

Findings could only be limited to the age group (2 to 11 years) in the study.

Patients in this study belonged to low risk group for peri-operative hypoglycaemia.

Because of various definitions of hypoglycaemia, normoglycaemia and hyperglycaemia, findings are limited to the definitions used in this study.
CHAPTER 6

6.1 CONCLUSION

Based on personal observation, different colleagues in the department of anaesthesiology in Dr George Mukhari academic hospital, it is obvious that there is no general standard practice on the intra-operative dextrose fluid use as maintenance fluid in the paediatric group.

Different practices vary from no glucose supplementation to adding 1%, 2%, 2.5% dextrose into the maintenance fluid used intra-operatively.

At least there is consensus and agreement reached when it comes to the maximum dextrose (2.5%) concentration that can be used intra-operatively.

Blood glucose monitoring in Dr George Mukhari academic hospital is not routinely done in “healthy” paediatric patients going to theatre for elective surgery. This makes it very difficult to almost impossible to quickly detect hypoglycaemia as signs and symptoms are not reliable.

In an attempt to come up with a “solution” that would standardize the paediatric management in my department and ensuring patients safety at all times, this study is intended to help in the drafting of departmental protocol addressing: pre-operative fasting, blood glucose monitoring and fluid plus glucose management in healthy paediatric management peri-operatively.

Patients given plain Ringer’s lactate without dextrose added showed a statistically significant increase in blood glucose concentration from baseline to normoglycaemic ranges (4.94 ± 0.6 mmol/L pre-operatively to 5.90 ± 0.8 mmol/L post-operatively). These results were found to correlate with the findings of Welborn et al (1986)^5,7

According to the results found in this study, it is NOT necessary to add glucose to plain ringer’s lactate in this age group (2 to 11 years), ASA classification (ASA I and II) and presenting for minor or intermediate elective surgical procedure which this study was based on. These paediatric patients belong to the low risk group for developing hypoglycaemia intra-operatively.

Therefore plain ringer’s lactate is sufficient to maintain the blood glucose concentration levels within normal limits when used as a maintenance solution in children.
Peri-operative blood glucose management should not be seen as an isolated entity, but focusing also on all other factors that play a role in the body’s physiological management of glucose in the peri-operative period (e.g. pain, discomfort, anxiety, anaesthetic stress, surgical stress nutritional and health status).

### 6.2 RECOMMENDATION

It must also always be kept in mind that not all patients respond the same way to the same stressor, therefore individualisation of patients is highly recommended.

It is not necessary to supplement glucose in healthy children (ASA I-II) between ages 2 and 11 years booked for minor or intermediate surgery.

There is no need to routinely monitor glucose in this patient group as it was found that more than 90% of patients’ blood glucose concentration levels were within the normal ranges \((3.8 - 7.7\text{mmol/L})\). Routine monitoring would not be cost effective and would also be labour intensive.

Advice to adhere to the pre-operative recommended fasting protocols.

Proper pain management using all methods available (pharmacological, physical and multidisciplinary approach), as pain can have an influence in increasing gluconeogenesis.

Medicine evolution in general has brought a lot of improvements concerning patient management, to ensure safety and wellbeing of patients.

New methods that have emerged over the years as part of this evolution need to be implemented and practiced in order to benefit from these improvements.

Old methods/habits that are outdated, non-evidence based, proven not to be of benefit to patients or even caused harm to patients must be replaced by the current, evidenced based beneficial methods.
REFERENCES


45. Hagerman NS, Wittkugel. Pre-operative fasting in paediatric patients. Clinical paediatric anaesthesia, Chapter 7; p61-68.


APPENDIX A

Consent form

UNIVERSITY OF LIMPOPO (Medunsa Campus) CONSENT FORM

Statement concerning participation in a Clinical Trial/Research Project*.

A COMPARISON OF PLAIN RINGER’S LACTATE AND LOW GLUCOSE ADDED INTO PLAIN RINGER’S LACTATE SOLUTION USED AS A MAINTENANCE SOLUTION INTRA-OPEPERRATIVELY TO MAINTAIN NORMOGLYCAEMIA IN CHILDREN.

I have read the information on */heard the aims and the objectives of* the proposed study and was provided the opportunity to ask questions and given adequate time to rethink the issue. The aim and objectives of the study are sufficiently clear to me. I have not been pressured to participate in any way.

I know that photographs/electronic images/sound recordings* will be taken of me. I am aware that this material may be used in scientific publications which will be electronically available throughout the world. I consent to this provided that my name/ and hospital number* is/are* not revealed. Regarding images of the face, I understand that it may not be possible to disguise my identity, and I consent to the use of these images*.

I understand that participation in this Clinical Trial/Study/Project* is completely voluntary and that I may withdraw from it at any time and without supplying reasons. This will have no influence on the regular treatment that holds for my condition neither will it influence the care that I receive from my regular doctor.

I know that this Trial/Study/Project* has been approved by Medunsa Campus Research and Ethics (MREC), University of Limpopo (Medunsa Campus)/ Dr George Mukhari Hospital. I am fully aware that the results of this Trial/Study/Project* will be used for scientific purposes and may be published. I agree to this, provided my privacy is guaranteed.

I hereby give consent to participate in this Study.

Name of patient/volunteer .......................................................... Signature of patient or guardian ..........................................................

Place ................................ Date ................................ Witness ................................

Statement by the Researcher

I provided verbal and /or written* information regarding this Trial/Study/Project*

I agree to answer any future questions concerning the Trial/Study/Project* as best as I am able

I will adhere to the approved protocol

Name of Researcher ................................ Signature ................................ Date ................................ Place ................................

*Delete whatever is not applicable.
# APPENDIX B

Data collection sheet

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APPENDIX C

Clearance certificate

UNIVERSITY OF LIMPOPO
Medunsa Campus

MEDUNSA RESEARCH & ETHICS COMMITTEE

CLEARANCE CERTIFICATE

MEETING: 09/2014
PROJECT NUMBER: MREC/M/363/2014: PG

PROJECT:
Title: A comparison of plain Ringer’s lactate and low glucose added into plain Ringer’s lactate solution used as a maintenance solution intra-operatively to maintain normoglycaemia in children

Researcher: Dr S Kala
Supervisor: Dr MJ Mokang
Co-supervisor: Dr RO Khoob-Mpe
Hospital Superintendent: Dr Mabuse (Dr George Mukhari Academic Hospital)
Department: Anaesthesiology & Intensive Care Unit
School: Medicine
Degree: MMEd in Anaesthesiology

DECISION OF THE COMMITTEE:
MREC approved the project.

DATE: 06 November 2014

PROF GA OGANJANJO
CHAIRPERSON MREC

The Medunsa Research Ethics Committee (MREC) for Health Research is registered with the US Department of Health and Human Services as an International Organisation (OCR000419), as an Institutional Review Board (IRB00005122), and functions under a Federal Wide Assurance (FWA00009419)
Expiry date: 11 October 2016

Note:
(i) Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee.
(ii) The budget for the research will be considered separately from the protocol. PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.