UNIVERZA V LJUBLJANI
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URŠKA NABERGOJ MAKOVEC

VREDNOTENJE ZDRAVLJENJA NEONATALNE HIPERGLIKEMIJE Z INSULINOM NA INTENZIVNEM ODDELKU ZA NOVOROJENČKE V BOLNIŠNICI V DUNEDINU

EVALUATION OF INSULIN TREATMENT OF NEONATAL HYPERGLYCAEMIA AT THE NEONATAL INTENSIVE CARE UNIT AT DUNEDIN HOSPITAL

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This Master's Thesis was performed at The School of Pharmacy, University of Otago, Dunedin, New Zealand and The Faculty of Pharmacy, University of Ljubljana, Slovenia. I worked under the mentorship of prof. dr Aleš Mrhar, PharmD, PhD and co-mentorship of Associate Professor Natalie Medlicott, BPharm, PhD.

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STATMENT

I hereby declare that I have performed and written this Master's Thesis by myself under the mentorship of prof. dr Aleš Mrhar, PharmD, PhD and co-mentorship of Associate Professor Natalie Medlicott, BPharm, PhD.

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ABSTRACT

Glycaemic control in neonates can be poor due to physiological and biochemical mechanisms (e.g. insulin resistance, glucose intolerance) that inhibit efforts to maintain normal blood glucose concentrations (BGC). Neonatal hyperglycaemia is a frequent complication in premature and very low birth weight (VLBW) neonates and has become a significant risk factor for morbidity and mortality in the neonatal period. Additionally there is lack of a widely established definition, diagnosis and treatment for neonatal hyperglycaemia. Normal glucose levels can be managed by decreasing glucose intake or insulin administration. Since glucose is needed for growth, prolonged restriction can adversely affect the neonate's nutritional status and hence adversely affect growth and development. Therefore, insulin is given to maintain tight glycaemic control and preserve glucose uptake. Insulin is currently administered by continuous intravenous infusion and is dosed using a sliding scale. Although it has been determined as a safe and effective therapy, the data to support its common use is limited and potential complications such as hypoglycaemia are still a serious risk. Insulin treatment needs to be well controlled with frequent monitoring of blood glucose levels and adjustments to the insulin dose.

This research sought to investigate the current dosing regimen for insulin used at Dunedin Hospital Neonatal Intensive Care Unit (NICU). We conducted a retrospective chart review of 53 neonates, who received insulin treatment in the past 6 years and collected data relevant to the treatment (e.g. BGC, insulin infusion rates, carbohydrate (CH) intake). We chose and presented three cases of differing complexities of hyperglycaemia treatment to get a better understanding of the therapy. All our research subjects were born prematurely at an average 25.97 ± 2.04 weeks of gestation, weighing an average 793 ± 180 g. The average time taken to achieve glycaemic control was 6.04 ± 4.30 days and the most common insulin dose was 0.03 U/kg/h. At the start of insulin treatment CH intake was preserved and in the majority of infants oral feeds were introduced. All parameters involved in this research show a high range of results. This supports the complexity of this condition and its treatment. This study only depicts how hyperglycaemia is managed and investigates selected factors involved in its treatment. For any protocol and treatment modification further research is required. More statistical analysis and modelling should be done to determine which parameters have the greatest impact on shortening and simplifying insulin therapy.

RAZŠIRJENI POVZETEK

Ob rojstvu se stalni dotok glukoze preko placente prekine in novorojenček se temu ustrezno prilagodi s spremembami v metabolizmu in hormonskem ravnovesju. Raven insulina pade, poveča pa se sproščanje glukagona in kateholaminov, ki aktivirajo glikogenoglizo, glukoneogenezo, lipolizo in ketogenezo. Te spremembe zagotavljajo konstanen vir energije za novorojenčka do prvega obroka in pozneje med hranjenjem. Vsi novorojenčki pa teh prilagoditev ne zmorejo izvesti in je njihova sposobnost uravnavanja ravni glukoze v krvi okrnjena.

Neonatalna hiperglikemija lahko, posebno pri nedonošenčkih in novorojenčkih z nizko porodno težo, povzroči resne zaplete. Je motnja, ki pomembno prispeva k deležu obolevnosti in smrtnosti te populacije, zanjo pa trenutno ni natančno postavljene definicije, diagnoze ter načina zdravljenja. Večinoma je opredeljena kot koncentracija glukoze v plazmi večja od 8.3 mmol/L, ne glede na novorojenčkovo starost ali težo. Navadno se pojavi v prvih petih dneh življenja, glavna dejavnika tveganja sta nedonošenost in nizka porodna teža, saj prizadene od 45 do 80 % novorojenčkov s porodno težo pod 1000 grami. Posebna oblika neonatalne hiperglikemije je neonatalni diabetes mellitus (NDM), ki je genetskega izvora in je lahko stalni (»permanent«) ali prehodni (»transient«). Diagnostika neonatalne hiperglikemije je težavna, ker je velikokrat asimptomatska oziroma so simptomi in znaki nespecifični in bi lahko bili posledica spremljajočih bolezenskih stanj. Njen nastanek sicer še ni prav pojasnjen, predvidevajo pa, da jo povzroča skupek fizioloških in biokemijskih mehanizmov, kot so insulinska rezistenca, relativno pomanjkanje insulina, nezmožnost jeter zavirati glukoneogenezo kljub povišani ravni glukoze, nezrelost glukoznih transportnih sistemov ter nizek periferni prevzem glukoze v mišice in maščobno tkivo. Nezdravljenje povišanih vrednosti glukoze v krvi lahko povzroči možgansko krvavitev, ki je tudi glavni vzrok smrti pri tem obolenju, motnje elektrolitskega ravnotežja, dihalno stisko ter druge patologije. Na dolgi rok pa lahko vpliva na nevrološki in vedenjski razvoj otroka.

Normalne vrednosti glukoze v krvi lahko dosežemo z zmanjševanjem vnosa glukoze ali z dajanjem insulina. Z zmanjševanjem vnosa glukoze sicer lahko dosežemo primeren nivo le-te v krvi, vendar lahko hkrati tudi močno prizadenemo novorojenčkovo rast in razvoj. Zato v praksi uporabljamo drugo metodo dajanja insulina, s katero ohranimo normalen vnos glukoze in hkrati preprečimo previsoke vrednosti glukoze v krvi. Novorojenčki prejemajo insulin preko infuzije, odmerjanje pa uravnavamo glede na maso ter območje

krvnega sladkorja (t.i. sliding scale). Čeprav je bilo zdravljenje z insulinom sprejeto kot varno in učinkovito, je dokazov, ki temu pritrjujejo malo in še vedno obstaja veliko tveganj in zapletov, povezanih s takim načinom zdravljenja (npr. hipoglikemija). Zato taka terapija zahteva veliko nadzora, konstantno spremljanje vrednosti glukoze v krvi ter prilagajanje odmerka insulina.

V diplomskem delu smo želeli ovrednotiti trenutni režim odmerjanja insulina za zdravljenje neonatalne hiperglikemije na intenzivnem oddelku za novorojenčke v bolnišnici v Dunedinu. Pregledali smo zdravstveno dokumentacijo 53 novorojenčkov, ki so se na tem oddelku v zadnjih šestih letih zdravili z insulinom. Ob pregledu smo v tabelo zbrali podatke o gestacijski starosti, spolu in porodni teži novorojenčka, nato pa kronološko vnašali vrednosti glukoze v krvi, odmerke insulina ter prejemanje ogljikovih hidratov, tako paranteralno kot peroralno. Z deskriptivno analizo smo določili čas, ki je bil potreben za doseganje normalne ravni glukoze v krvi, ter dejavnike, ki na ta parameter vplivajo. Za boljše razumevanje načina zdravljenja smo, izmed 53 preiskovancev, izbrali tri primere, ki se med seboj razlikujejo po kompleksnosti ter grafično prikazali potek njihovega zdravljenja.

V študijo je bilo vključenih 31 fantov in 22 deklet. Rojeni so bili v povprečju pri 25.97 ± 2.04 tednih gestacijske starosti, njihova povprečna porodna teža pa je znašala 793 ± 180 gramov. Povprečni čas zdravljenja z insulinom je bil 6.04 ± 4.30 dni, pri čemer je bil minimalni čas zdravljenja 0.38 dni, maksimalni pa 15.55 dni. V 43.4 % je bil bolnišnični protokol upoštevan in so zdravljenje z insulinom pričeli po dveh zaporednih vrednostih glukoze preko 10.0 mmol/L. Povprečni odmerek insulina v času terapije je bil 0.05 ± 0.05 U/kg/h, infuzija pa je bila največkrat nastavljena na 0.03 U/kg/h. Vnos ogljikovih hidratov se je tekom zdravljenja ohranjal in čeprav je bila večina preiskovancev (88.7 %) hranjena tudi peroralno, je delež tako zaužitih ogljikovih hidratov nizek (7.16 %). Vsi parametri, ki smo jih spremljali v naši raziskavi (vrednost glukoze v krvi, odmerek insulina, vnos ogljikovih hidratov, peroralna prehrana), kažejo veliko razpršenost, kar dodatno potrjuje, kako zapletena je neonatalna hiperglikemija in njeno zdravljenje.

Zanimale so nas tudi morebitne povezave med spremljanimi parametri. Ugotovili smo, da na čas zdravljenja z insulinom najbolj vpliva gestacijska starost, obstajajo pa tudi povezave med časom zdravljenja in vrednostjo glukoze v krvi ob začetku zdravljenja, časom

zdravljenja in začetnim odmerkom insulina ter časom zdravljenja in celokupnim vnosom ogljikovih hidratov.

Naše raziskovalno delo je le majhen korak k izboljšanju zdravljenja neonatalne hiperglikemije. Uspeli smo prikazati kako poteka zdravljenje v praksi in ovrednotili dejavnike, ki nanj vplivajo. Rezultati našega dela kličejo po dodatnih raziskavah, statističnih analizah in modeliranju, ki bodo določili dejavnike z največjim vplivom na pozitiven razplet zdravljenja. To bo pripomoglo k oblikovanju novih smernic in čim bolj učinkovitemu zdravljenju neonatalne hiperglikemije.

LIST OF ABBREVATIONS

BGC	Blood glucose concentration (glucose concentration in plasma)
BW	Birth weight
CA	Chronological age
CH	Carbohydrate
D10	10% dextrose infusion
D5	5% dextrose infusion
DOB	Date of birth
EBM	Expressed breast milk
ELBW	Extremely low birth weight
GA	Gestational age
G	Gender
LBW	Low birth weight
NDM	Neonatal diabetes mellitus
NICU	Neonatal Intensive Care Unit
OFC	Occipitofrontal head circumference
PEPCK	Phosphoenolpyruvate carboxykinase
PNDM	Permanent neonatal diabetes mellitus
TNDM	Transient neonatal diabetes mellitus
TOB	Time of birth
TPN	Total parenteral nutrition
VLBW	Very low birth weight

1. INTRODUCTION

1.1 Foetal metabolism

During pregnancy foetal growth and development are entirely dependent on continuous transplacental nutrient transfer from the mother.

The principal energy source is glucose and levels in the foetus are in equilibrium with the maternal glucose pool. Glucose is transported across the placenta by facilitated diffusion and under physiological conditions there is no significant glucose production (1).

However, enzymes needed for gluconeogenesis are already developed by 8 weeks gestation; this shows the capability for independent glucose regulation by the foetus. Under conditions such as maternal starvation or placental insufficiency gluconeogenesis is activated and in response to higher glucose transfer from diabetic mothers, the foetus secretes higher concentrations of insulin (2). Glucose metabolism accounts for 65% of foetal metabolism, the rest is mainly accounted for by lactate, amino acids, triglycerides, fatty acids, glycerol and keto acids (1, 2).

The foetal endocrine milieu is characterized by high insulin and low glucagon plasma levels. Although insulin is present from 13 weeks gestation, it is inactive until the onset of corticosteroid actions in the late second trimester (3).

The metabolic effects of insulin do not differ from those of adults. Insulin promotes glucose uptake in the liver and muscle leading to glycogen synthesis from glucose, lactate, pyruvate and alanine. Glycogen content in the liver reaches 50 mg/g by term. It also stimulates fatty acid synthesis and glucose uptake in the adipose tissue to enhance triglyceride synthesis and fat disposition. Synthesised glycogen and fat serve as stores for metabolic changes at birth.

As well as the metabolic effects, insulin plays an important role in foetal growth. It promotes muscle protein synthesis by enhancing the entry of amino acids into the muscles as well as inhibiting protein degradation and lipolysis (4).

1.2 Neonatal metabolism

1.2.1 Changes at birth

At birth the nutrient flux from the mother is suddenly discontinued and the neonate is forced to activate its own glucose production to preserve fuel supplies for vital functions until the first exogenous nutritional intake (1).

Insulin levels fall rapidly and there is a surge in glucagon. Low insulin/glucagon ratio induces glycogenolysis and gluconeogenesis. To generate more gluconeogenic substrates (lactate, alanine, glycerol) glucagon promotes lipolysis, β-oxidation of fatty acids and proteolysis. Additionally, catecholamine and cortisol levels rise to support glucagon actions (1 - 3).

1.2.2 Metabolic fuels for the neonate

Immediately after birth blood glucose concentrations fall rapidly and until feeding is established endogenous glucose production (glycogenolysis and gluconeogenesis) is the only source of glucose for the newborn. Since this accounts for approximately only 70% of the brain's energy needs, ketone bodies and lactate serve as important fuels for the brain in this period (3).

1.2.3 Term infants

The rapid fall in blood glucose reaches its minimum concentration in the first hours of life. Afterwards glucose levels start rising and are stabilised in 12 to 24 hours, without feeding (1).

The rate of endogenous glucose production is estimated to be 4 – 6 mg/kg/min. Glycogenolysis represents one third of this production and glycogen liver stores are depleted within 12 hours.

The other two thirds are accounted for by gluconeogenesis. Low insulin and high glucagon levels activate phosphoenolpyruvate carboxykinase (PEPCK), the rate-limiting enzyme in this pathway. Its activity increases and gluconeogenesis reaches its peak twelve hours after birth. Glucose is synthesised mostly from lactate (30% of total endogenous glucose production), while alanine and glycerol contribute 10% each (1, 3).

The neonatal brain is able to utilise ketone bodies as a fuel. Hepatic ketogenesis has limited capacity during the first eight hours of life, but after twelve hours neonates show a high ketone body turnover (12 – 22 µmol/kg/min). This is seen in an adult only after several days of starvation. It seems that ketogenesis is an important part of metabolic adaptation to extrauterine life. During the first week of age glucagon remains high and insulin levels low.

When enteral feeding is established, blood glucose concentrations are determined by the time interval between the feeds. Feeding also affects gut development (structure, function and growth) by inducing the secretion of gut regulatory hormones (1).

1.2.4 Preterm infants

There was a long-term belief, that preterm infants have lower blood glucose levels than term neonates in the first days of life. This misunderstanding came from different feeding practices in the past, where preterm infants were routinely starved in the first days. Nowadays nutrition (parenteral or/and enteral) is introduced early and it is thus uncommon to find low blood glucose levels in preterm neonates (1).

The fall in glucose levels in the first hours, however, is greater in preterm than in term infants and there is controversial evidence surrounding a neonate's capability for glucose production. Some evidence suggests rather high levels of gluconeogenic substrates, but limited activity of important gluconeogenic enzyme glucose-6-phosphatase, probably due to immaturity of enzymatic pathways (1, 3). On the other hand, rates of gluconeogenesis similar to term neonates have also been reported (1).

In comparison with term neonates, preterm infants have lower ketone bodies and free fatty acids concentrations and show inadequate ketogenic response to low glucose levels. This is possibly because of a combined failure of lipolysis and ketogenesis. Concentrations increase after enteral feeds suggesting feeding induces ketogenic enzymes in preterm neonates (1, 3).

While in term neonates the first enteral feed already has an effect on secretion of the gut hormones, this is not the case in preterm neonates. Preterm neonates need regular feeds and afterwards there is a surge in multiple gut hormones (1).

Finally, basal insulin secretion is believed to be higher in preterm neonates (1).

1.3 Neonatal hyperglycaemia

1.3.1 Definition and diagnosis

Hyperglycaemia is a frequent complication in preterm neonates and has become a significant risk factor for morbidity and mortality in the neonatal period.
Generally, hyperglycaemia has been defined as plasma glucose concentrations greater than 8.3 mmol/l (150 mg/dL) or whole blood glucose concentrations greater than 6.9 mmol/L (125 mg/dL) regardless of gestational or postnatal age and weight. It often occurs in the first three to five days of life, although it can also be found later in early life (10 days and more) (5, 6).
However, these values vary among different institutions. A survey done in Australasia, that included 23 tertiary Neonatal Intensive Care Units, reported 6 different definitions of hyperglycaemia with most units defining hyperglycaemia as BGC above 10 mmol/L (7).

The difficulty with diagnosing this condition is often the asymptomatic state and lack of specific signs, which would distinguish hyperglycaemia from other possible disorders. Some of the more recognizable clinical signs are weight loss, glycosuria, dehydration due to osmotic diuresis, ketosis, metabolic acidosis and failure to thrive. The last three are also common for neonatal diabetes mellitus (NDM) (6).

1.3.2 Prevalence and epidemiology

The incidence of hyperglycaemia ranges from 45% in very low birth weight infants (VLBW< 1000 g) up to 80% in extremely low birth weight infants (ELBW< 750 g). Low birth weight (LBW) and prematurity are two main risk factors and are both inversely related to the incidence (6).
Other significant risk factors are intrauterine growth restriction, stress (increased catecholamines and glucocorticoides), high rates of intravenous glucose and lipid

infusions, insufficient insulin secretion and absence of enteral feeds. However, these are all related to prematurity and LBW (5).

1.3.3 Neonatal diabetes mellitus (NDM)

NDM is a rare type of neonatal hyperglycaemia, which occurs in one case per 300 000 – 500 000 live births. It typically occurs in small for gestational age neonates in the first six months of life. Clinically it presents with high blood glucose concentrations due to failure in insulin secretion, glycosuria, dehydration, failure to thrive, acidosis and ketosis (8).
The main difference between neonatal hyperglycaemia and NDM is the genetic origin of NDM. There are two types of NDM, transient (TNDM) and permanent (PNDM), which can only be distinguished with genetic analysis (9).

TNDM occurs in intrauterine-growth retarded neonates in the first week of life and goes into remission after a variable period. It is treated with insulin via intravenous infusion or subcutaneous injection. Some patients with TNDM develop permanent diabetes mellitus in puberty or early adulthood (9, 10).

PNDM occurs in first three months of an infant's life and usually requires insulin therapy for life. An alternative therapy is oral sulphonlyureas, for patients with potassium channel neomutation (subunit Kir 6.2) (9, 10).

1.4 Etiology of neonatal hyperglycaemia

Although neonatal hyperglycaemia is not completely understood, it is thought to develop from a combination of mechanisms and causes.

1.4.1 Insulin resistance

Preterm infants experience acute catabolic stress due to counter-regulatory stress responses to prevent hypoglycaemia, acidosis, hypoxia, alterations in intravascular volume and pain. Additionally many premature infants suffer from other conditions (e.g. sepsis, necrotizing enterocolitis) at the same time. These conditions increase the level of proinflamatory cytokines (TNF-α, IL-1, IL-6), catecholamines and other inflammatory markers. Insulin levels are higher in preterm neonates than term neonates, but increased levels of

inflammatory markers change insulin receptor signalling, causing central (liver) and peripheral (muscle and adipose tissue) insulin resistance. They even promote hyperglycaemia with increasing corticotrophin-releasing hormone and induce glucocorticoid synthesis (11, 12).
Another factor that can increase insulin resistance and suppress insulin secretion is the use of inotropes and corticosteroids in interventions of intensive care (13).

1.4.2 Relative insulin deficiency

Increased insulin resistance calls for adequate pancreatic response, which preterm neonates are incapable of for several reasons.
Premature birth interrupts normal physiological development of pancreatic β-cells, which are immature and therefore unable to compensate for higher insulin demands. Despite immaturity, they are sensitive to changes in BGC and insulin levels, but respond with the secretion of higher levels of proinsulin instead of mature insulin. Proinsulin is ten times less active and not able to control blood glucose concentrations (13, 14).

Immaturity effects the expression of glucose transporter GLUT-2, which results in a reduced insulin response in preterm neonates in comparison with term neonates. Another factor adding to insulin deficiency is the delay in introducing enteral feeds, which prevents stimulation with incretins (11).

1.4.3 Hepatic unresponsiveness to glucose infusion and concentrations

Preterm and LBW infants are not able to inhibit their glucose production in the liver as a response to exogenous glucose infusion or high BGC. This failure is caused by hepatic insulin resistance (11, 12).

1.4.4 Immaturity of the glucose transport system.

Glucose transporters GLUT-1, GLUT-2 and GLUT-4 are important in managing hyperglycaemia. Their expression depends on an infant's maturity.
GLUT-1 dominates in foetal and early neonatal life and decreases after birth. GLUT-2 regulates glucose release in hepatocytes and insulin secretion in β-cells. Limited expression of this transporter could be the reason for an infant's inability to suppress endogenous glucose production when exogenous glucose is administered.

GLUT-4 appears later in gestation and its role is to manage glucose uptake of skeletal, cardiac muscle and adipose tissue. Since its expression is decreased, these tissues are insensitive to circulating glucose (6, 12).

1.4.5 Limited number of insulin-dependent tissues

Additionally to low GLUT-4 expression, premature neonates have little skeletal and adipose tissue resulting in a decreased peripheral glucose uptake (11, 12).

1.5 Complications and consequences of neonatal hyperglycaemia

Initially moderate hyperglycaemia was thought to have a beneficial physiological effect on glucose dependent organs (liver, lung, spleen, endothelial cells). These organs have high metabolic demands especially in critical illnesses and therefore higher glucose availability provides energy for such requirements (11, 14).
The possible short-term benefits of increased BGC are outweighed by the harmful effects hyperglycaemia causes.

The spectrum of complications high BGC causes ranges from clinically manageable to devastating. Mortality in hyperglycaemic infants is increased; predominantly the cause of death is intracranial haemorrhage. Serious morbidity related to hyperglycaemia shows as retinopathy of prematurity and sepsis.

Pathologies behind increased BGC are:

- a rise in serum osmolarity, leading to osmotic diuresis resulting in dehydration and polyuria. If serum osmolarity exceeds 300 mOsm/L, it may cause cerebral haemorrhage.
- electrolyte imbalance presenting as hyponatremia and hypokalemia.
- increased respiratory rate requiring higher ventilation, which can cause respiratory stress disorder in these fragile neonates.
- steatosis and impaired secretion of hepatic triglycerides (5, 6).

Many studies have investigated the causes of increased mortality and morbidity in premature neonates, but data on long-term outcomes of survivors are limited.

Lugt et al. (15) performed a retrospective follow-up study where they investigated the effects of neonatal hyperglycaemia, treated with insulin, in survivors at two years of age. Their findings show hyperglycaemia has no effect on long-term growth, but has a negative influence on neurological and behavioural outcomes (15).

1.6 Management of neonatal hyperglycaemia

1.6.1 Suggested management

Textbooks and manuals of neonatal care (2, 16) suggest the following for managing neonatal hyperglycaemia:

a) Diagnose and treat any possible underlying causes or disorder (e.g. sepsis, stress, drugs, NDM).
b) Calculate glucose infusion rate. If ≥ 12 mg/kg/min reduce infusion rate.
c) If BGC ≥ 10 mmol/L or osmotic diuresis occurs lower glucose infusion rate to 4-6 mg/kg/h and start insulin treatment with continuous i.v. infusion at 0.01 - 0.2 U/kg/h (the usual starting dose is 0.05 U/kg/h).
d) Monitor BGC to prevent hypoglycaemia; if it occurs discontinue insulin infusion.
e) Commence enteral feeds if tolerated.

1.6.2 Advantages and disadvantages of insulin therapy

Treatment of neonatal hyperglycaemia was firstly limited to reducing glucose infusion rates as insulin was considered unsafe due to the risk of hypoglycaemia. From the 1980s onwards many controlled trials were conducted in order to refute this belief. The safety and efficacy of insulin therapy, given as continuous i.v. infusion, was investigated to treat neonatal hyperglycaemia (17 - 22).

Trials mostly consisted of two to three groups – one receiving insulin therapy, one receiving standard care (lowering glucose infusion rates) and a control group of healthy infants. Observations focused on changes in glucose tolerance, caloric intake and weight gain. All studies concluded hyperglycaemic newborns benefit from the use of insulin, as results show an increase in glucose tolerance, higher caloric intake and better weight gain in comparison to other groups.

Reduction of glucose was never discarded as ineffective, but the disadvantage of inadequate nutrition and consequently poor growth prevailed (17 - 22).

As well as determining out how to optimally manage neonatal hyperglycaemia, there was an international multicentre randomised controlled trial investigating the role of early insulin in VLBW infants (NIRTURE). This trial aimed to determine whether early insulin replacement therapy would reduce hyperglycaemia and effect outcomes in treated neonates.

Beardsall et al. (23) conducted a pilot study on 16 neonates divided in two groups – intervention and standard care. They tested the hypothesis that early elective insulin treatment with dextrose support would improve glycaemic control and IGF-I levels. Findings concurred the hypothesis as results showed an increase in IGF-I bioactivity and improvement in blood glucose control. Increased IGF-I could lead to enhanced brain growth and less retinopathy of prematurity in such neonates (23).

Then the NIRTURE (Neonatal Insulin Replacement Therapy in Europe) study was initiated on the same bases as the pilot study. 195 infants received early insulin therapy and 194 received standard care. The study showed that early insulin therapy reduces hyperglycaemia, but increases hypoglycaemia and mortality at 28 days of life and has therefore little clinical benefit (24).
The NIRTURE study also investigated the prevalence and determinants of hyperglycaemia in preterm neonates. They identified that the independent risk factors for hyperglycaemia were increasing prematurity, small size at birth, sepsis, lipid infusion and use of inotropes. Interestingly, there was a lack of association between dextrose infusion rate and risk of hyperglycaemia (25).

Although tight glycaemic control with insulin has been shown to be effective, it cannot erase its weaknesses. Treatment with insulin has to be well controlled as episodes of sudden decreases in BGC and hypoglycaemia remain serious risks. It demands constant BGC monitoring (every 1-2 hours) and adjustments in the insulin dose (6).

Newer studies put the safety and effectiveness of such treatment back under review. A study by Alsweiler et al. (26), published in March 2012, questions the common use of insulin in managing neonatal hyperglycaemia as few data support its use. They conducted a randomised, controlled trial on 88 infants and concluded that neonates on insulin had higher weight gain and occipitofrontal head circumference (OFC), but linear growth was slower. The latter suggested that the weight gain was due to an increase in fat rather than muscle and bone. This increase in fat raised concerns as premature infants have more intra-abdominal tissue at term-corrected age and a higher risk for insulin resistance in childhood or early adulthood (26).

1.6.3 Management of neonatal hyperglycaemia at Dunedin NICU

The Dunedin Hospital NICU Medication Manual (*Appendix I.*) defines clinically significant hyperglycaemia as a BGC of 10 mmol/L or more, for two consecutive levels, four hours apart. Clinically significant hypoglycaemia is present with a BGC < 2.6 mmol/L.

Insulin (rapid acting, neutral human monocomponent insulin) is currently administered by continuous intravenous infusion and is dosed using a sliding scale (*Table I*).

Table I. Example of a sliding scale, used at Dunedin NICU

Blood Glucose Level	**Dose**	**Infusion Rate (0.1 unit/mL)**
>20 mmol/L	0.07 units/kg/hour	0.7 mL/kg/hour
15 – 20 mmol/L	0.05 units/kg/hour	0.5 mL/kg/hour
10 – 15 mmol/L	0.03 units/kg/hour	0.3 mL/kg/hour
7 – 10 mmol/L	0.01 units/kg/hour	0.1 mL/kg/hour
<7 mmol/L	Stop infusion	Stop infusion

After insulin is commenced, the dose is titrated after each BGC measurement according to the sliding scale. BGC should be checked hourly after initiating the insulin infusion and once stabilised, can be done every three hours.

2. AIMS AND OBJECTIVES

2.1 Aim

We will investigate the time taken to achieve normal glucose levels using the current dosing regimen for insulin used at Dunedin Hospital NICU.

2.2 Specific objectives

2.2.1 Specific objective 1 - Literature review

We will conduct a review of insulin treatment for neonatal hyperglycaemia using online databases Scopus and Medline.

2.2.2 Specific objective 2 - Retrospective chart review at Dunedin Hospital NICU

Neonates, who may have received insulin at NICU over the past six years (2006 - 2012), have been identified in a related project. We will review clinical notes of these patients and identify those who were treated with insulin.

Of those neonates who received insulin treatment, the following information will be collected:

- Gender (G)
- Date and time of birth (DOB, TOB)
- Gestational age (GA)
- Birth weight (BW) and weight changes during treatment
- Blood glucose concentrations
- Starting date and duration of insulin treatment
- Starting and finishing dose of insulin
- Changes in insulin dose during treatment
- Glucose infusion concentrations and rates
- Oral feeds (type and volume)

The sample size required for this study will be 50 neonates.

2.2.3 Specific objective 3 - Descriptive data analysis

A descriptive analysis on the collected data will be conducted to determine the time needed to achieve glycaemic control with the use of current dosing regimen at NICU. Moreover we will investigate which factors influence the duration of insulin treatment and which of these variables are correlated. The aim of this analysis will be to assess the current protocol and determine further research and improvements required for this protocol.

3. METHODS

3.1 Specific objective 1 - Literature review

We conducted a literature review using Medline and Scopus. We focused on neonatal metabolism and neonatal glycaemic disorders, primarily on neonatal hyperglycaemia and its treatment.

We reviewed literature written in English using following queries:
neonatal hyperglycaemia, insulin, neonatal hyperglycaemia AND insulin, insulin AND neonate, insulin AND neonates AND hyperglycaemia, insulin AND neonate AND neonatal hyperglycaemia.

3.2 Specific objective 2 - Retrospective chart review at Dunedin Hospital NICU

We identified patients who received insulin from the preselected list. We then conducted a retrospective chart review for each neonate. Data was collected from observation charts, laboratory result charts and medication charts and entered into a Microsoft Excel 2007 spread sheet chronologically from date of birth until a few days after the insulin treatment ceased.

We allocated each neonate an identification number (e.g. subject 1, subject 2) and recorded his or her gestational age (weeks + days), gender, birth weight (grams), date and time of birth.

Afterwards we entered the following data chronologically:

- Current weight (grams)
- Blood glucose concentrations (mmol/L)
- Glucose infusion sources and rates (mL/h)
- Oral feeds sources, volume (mL) and frequency
- Insulin infusion rates (mL/h) and concentrations (U/kg/h)

An example of the spread sheet is presented in *Appendix II*.

3.3 Specific objective 3 - Descriptive data analysis

3.3.1 Presentation of insulin treatment

We chose three cases that best describe the complexity and variation of insulin treatment. One that required a minimum number of interventions (Case 1), one with a medium number of interventions (Case 2) and one with a high number of interventions (Case 3). We created scatter plots using Microsoft Excel 2007 to represent:

- blood glucose concentrations timeline
- insulin dosing timeline
- total carbohydrate intake timeline

3.3.2 Descriptive analysis

Descriptive analysis of collected data was conducted using SPSS 16.0 for Windows (SPSS Inc. 2007) and Microsoft Excel 2007 software.

In SPSS 16.0 we used the following procedures:

- Frequencies for nominal variables (gender, oral feeds yes/no, concentration changes in insulin dose yes/no).
- Frequencies for some scale variables (e.g. time BGC $\geq$ 10.0 mmol/L, number of hyperglycaemic episodes, times insulin was stopped and restarted).
- Explore for all other scale variables (e.g. GA, BW, BGC, insulin dose, CH intake).
- Correlate $\rightarrow$ Bivariate to see if there are any correlations between variables we investigated.

To present descriptive statistics for certain variables we created tables with descriptive values such as mean, median, standard deviation, minimum, maximum, range, interquartile range and mode. Tables were supported with different charts (box plots, histograms and bar charts) for easier illustration of data distribution.

When investigating bivariate correlations we created simple and matrix scatter dots and calculated Pearson correlation coefficients.

4. RESULTS AND DISCUSSION

4.1 Literature review

As there is not yet a well-established definition and treatment for neonatal hyperglycaemia, literature, such as textbooks, is not very extensive. Hence our research focused mainly on articles published in various scientific publications, especially from neonatology and paediatrics. Considering neonatal hyperglycaemia as a relatively rare disorder, focused on a narrow population, the amount of published articles addressing the topic is impressive, dating from 1960s until today.

We learned how different studies were designed and how the management of this condition has been changing from reducing carbohydrate intake to the use of insulin, weighing up the advantages and disadvantages of both approaches. The review also showed us there is a lack of studies, with a greater sample size to give more significant results and answers about how the treatment of neonatal hyperglycaemia should be optimised.

4.2 General study information

We reviewed the clinical notes of 163 patients and identified 53 neonates who were treated with insulin (N=53). Although data for carbohydrate intake for one neonate was missing, we did not exclude this neonate from the study.

Insulin treatment varied a lot among subjects accounting for the differences in how long we observed each subject and how much data we collected. Observations commenced at birth and finished a few days after insulin treatment ceased or another significant event occurred (e.g. transfers, death). The average time observation period was 15.80 ± 6.60 days (minimum 2.27, maximum 37.05 days).

4.3 Patient characteristics

Table II. Patient characteristics

Gender		**N**	**%**
	Male	31	58
	Female	22	42

	Mean	**SD**	**Range**
Gestational age (weeks)	25.97	2.04	7.57
Birth weight (g)	793	180	970

4.4 Presentation of insulin treatment

Three cases of differing complexities of hyperglycaemia treatment are presented below to get a better understanding of the insulin therapy as a whole. From Case 1 to Case 3 the severity of hyperglycaemia increases, therefore more intensive therapy and different approaches were needed. Cases vary mainly in the duration of insulin treatment, changes in insulin dosing and the number of interventions needed during the treatment period.

4.4.1 Case 1 (low number of interventions)

A preterm male infant was born at a gestational age of 27 weeks, weighing 865 g. Initial BGC were within the normal range (3.0 – 6.3 mmol/L) until day five when they started increasing. By day eight, BGC rose above 10.0 mmol/L and insulin was started at 0.03 U/kg/h (BGC = 11.8 mmol/L) and then adjusted according to the sliding scale. BGC remained high until day ten when BGC dropped below 7.0 mmol/L (BCG = 6.6 mmol/L) and the insulin infusion was stopped. The neonate received parenteral nutrition with dextrose 10% (D10) as a source for carbohydrate throughout this period. From day three the neonate was fed orally.

Table III. Patient blood glucose concentrations in mmol/L (mean ± SD).

BGC	7.6 ± 2.6
BGC before insulin	6.7 ± 2.7
BGC on insulin	9.9 ± 1.2
BGC on day 1	5.0 ± 0.0

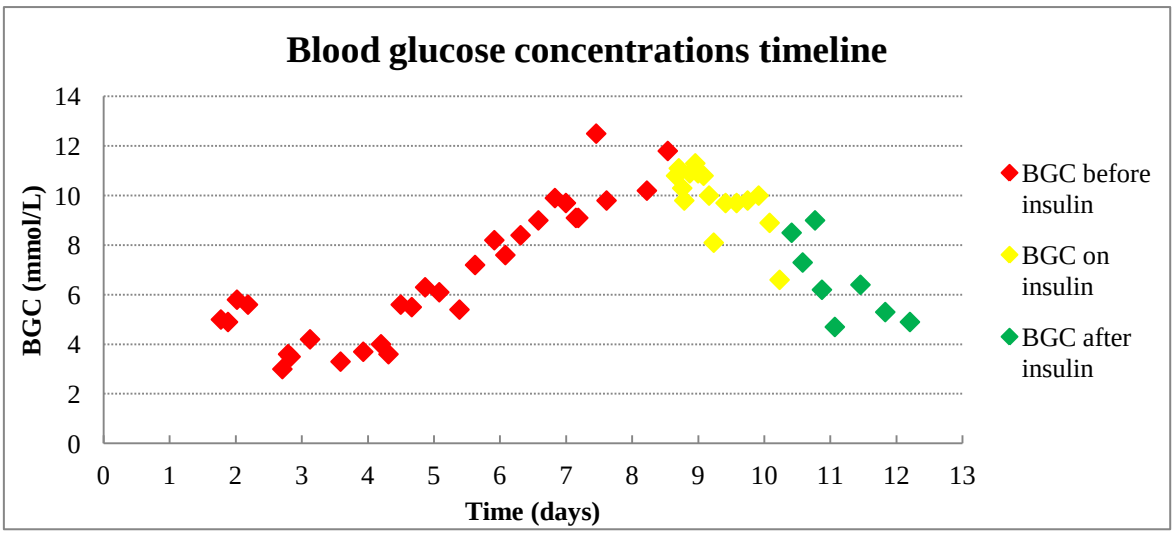

Figure 1. Scatter plot representing changes in blood glucose concentrations in Case 1.

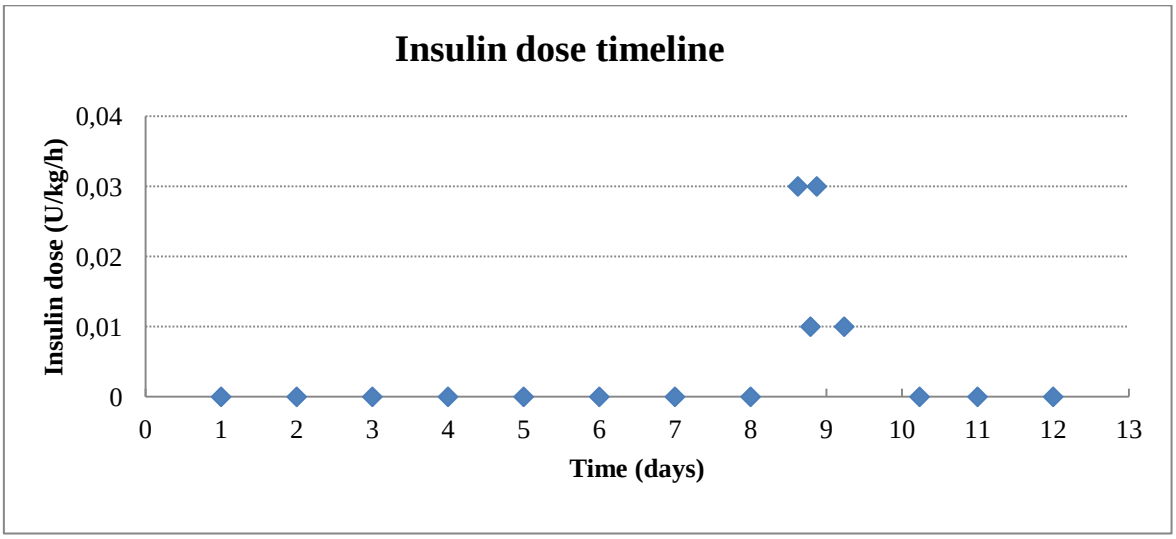

Figure 2. Scatter plot representing the dosing regimen for insulin in Case 1.

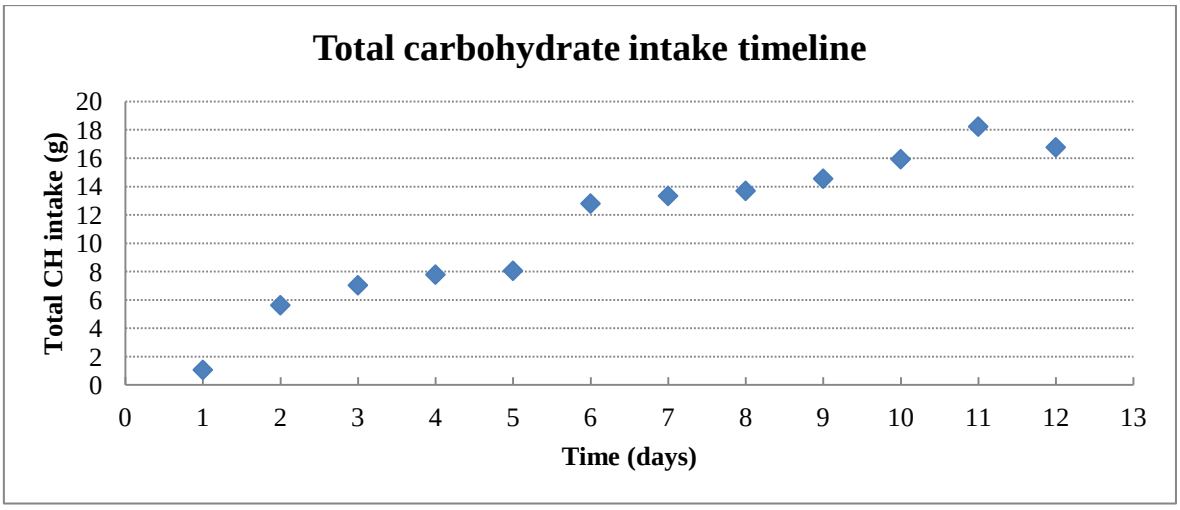

Figure 3. Scatter plot representing total carbohydrate intake (intravenous and oral) in grams for Case 1 on each day.

Case 1 represents a non-complicated insulin treatment of neonatal hyperglycaemia. When BGC increased to over 10.0 mmol/L, insulin was started in order to lower BGC and maintain the patient's carbohydrate intake. The time of the insulin infusion was short (1.61 days) and on average the infant received 0.02 U/kg/h of insulin. There were no additional complications (e.g. hypoglycaemia) and therefore no other interventions were needed. Insulin was effective in achieving glycaemic control in this case.

4.4.2 Case 2 (medium number of interventions)

A preterm male infant was born at a gestational age of 23+3 weeks, weighing 745 g. He was hypoglycaemic at birth (BGC = 2.5 mmol/L) and was started on D10 infusion immediately. BGC stabilised within a few hours in the range 4.4 – 8.6 mmol/L. On day four, three glucose measurements showed values over 10.0 mmol/L and insulin was started at 0.03 U/kg/h. BGC varied considerably and constant adjustments to the insulin dose were needed. Insulin was stopped and restarted three times. The infant received parenteral nutrition, mostly as D10, and was fed orally from day four.

Table IV. Patient blood glucose concentrations in mmol/L (mean ± SD).

BGC	9.3 ± 3.0
BGC before insulin	6.8 ± 2.2
BGC on insulin	10.4 ± 2.8
BGC on day 1	2.5 ± 0.0

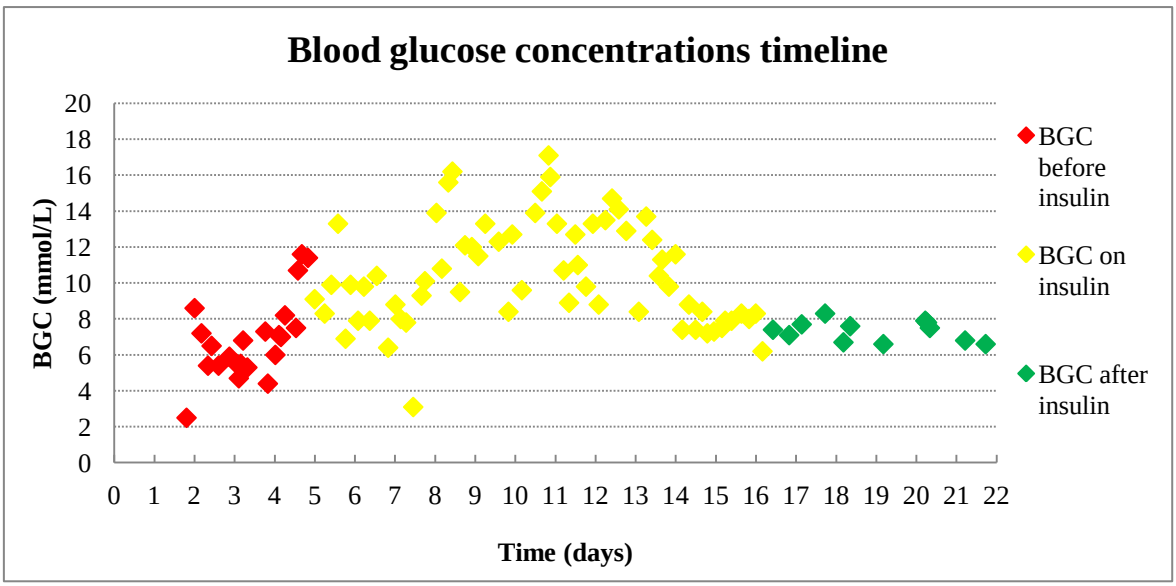

Figure 4. Scatter plot representing the changes in blood glucose concentrations in Case 2.

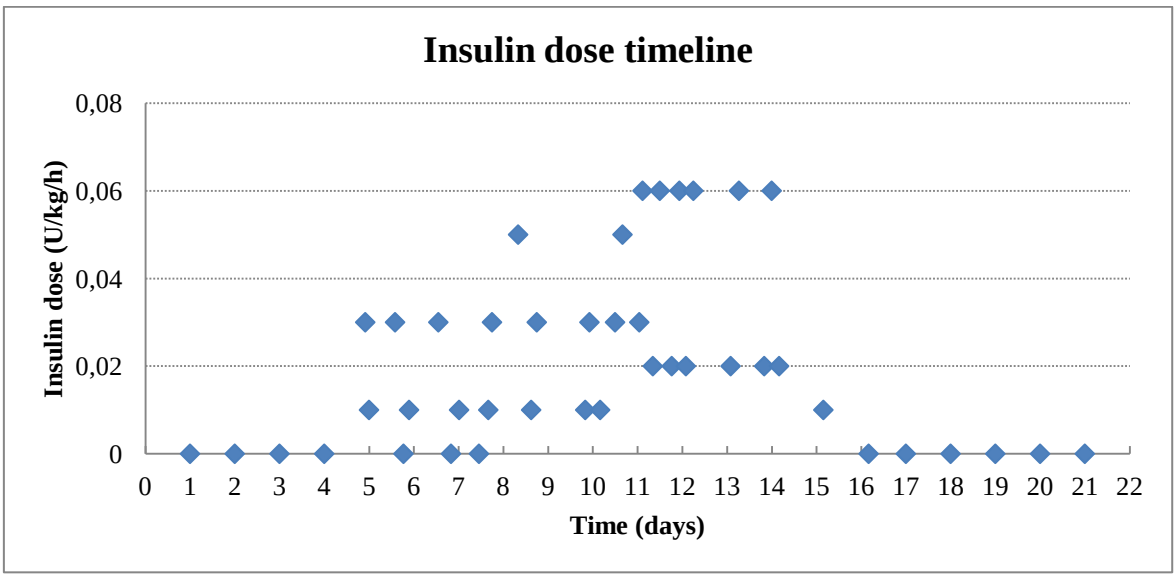

Figure 5. Scatter plot representing the dosing regimen for insulin in Case 2.

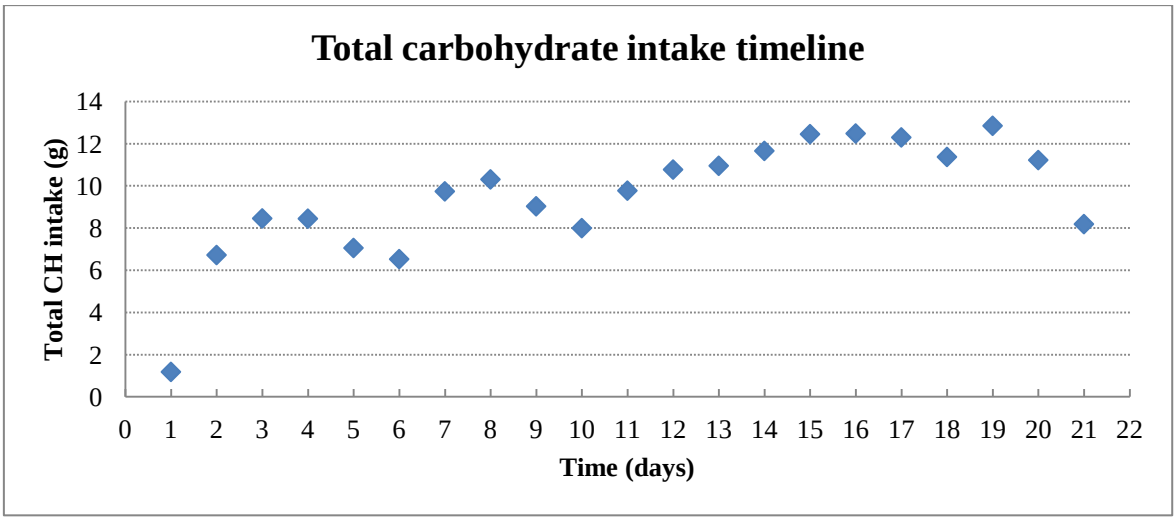

Figure 6. Scatter plot representing total carbohydrate intake (intravenous and oral) in grams for Case 2 on each day.

In comparison to Case 1 the complexity and duration of insulin treatment increased. This infant had higher BGC with the exception of the first day; therefore more intense treatment was needed to achieve glycaemic control. The total time on insulin was 10.74 days and insulin dosing was adjusted a few times during treatment. This involved increases in insulin dose as well as changes in insulin infusion concentration. On average Case 2 received 0.03 U/kg/h of insulin, with a maximum dose of 0.06 U/kg/h. According to the protocol, whenever BGC drops below 7.0 mmol/L insulin infusion is stopped. This happened three times and one BGC (3.1 mmol/L) approached hypoglycaemic levels. Although treatment took longer to lower BGC into the normal range and there were some complications, it helped preserve and even increased the CH intake during treatment.

All interventions were well managed and despite a longer period the treatment succeeded in achieving glycaemic control

4.4.3 Case 3 (high number of interventions)

A preterm male infant was born at a gestational age of 24 weeks, weighing 680 g. BGC were variable: euglycaemic at birth, then a hypoglycaemic episode, euglycaemic and then hyperglycaemic (BGC > 15.0 mmol/L) on day 6. Insulin infusion was started at 0.05 U/kg/h and was adjusted according to the sliding scale. BGC remained above 15.0 mmol/L for over four days when euglycaemia was achieved and insulin was stopped. The infant was fed parenterally and orally. Initially parenteral nutrition was D10, then dextrose 5%

(D5) and then stopped together with the insulin infusion. Thereafter the infant was fed orally.

BGC were stable for approximately four days and then BGC increased to above 30.0 mmol/L. Insulin was started immediately at 0.07 U/kg/h and the dose was increased to achieve a rapid drop in BGC. Higher BGC were observed for the second hyperglycaemic episode than the first one; insulin doses were higher and duration of treatment was twice as long. Insulin treatment was stopped and restarted eight times. Three of the treatment cessations were due to BGC lower than 4.0 mmol/L. During this time the infant was fed orally and then received D10 infusion on day 24.

Table V. Patient blood glucose concentrations in mmol/L (mean ± SD).

BGC	11.8 ± 6.1
BGC before insulin	7.9 ± 5.9
BGC on insulin	13.2 ± 6.2
BGC on day 1	7.2 ± 0.8

Table VI. Patient blood glucose concentrations in mmol/L (mean ± SD) by episodes of hyperglycaemia.

	First episode	**Second episode**
BGC before insulin	6.2 ± 4.1	11.1 ± 7.5
BGC on insulin	16.0 ± 3.7	12.4 ± 6.5

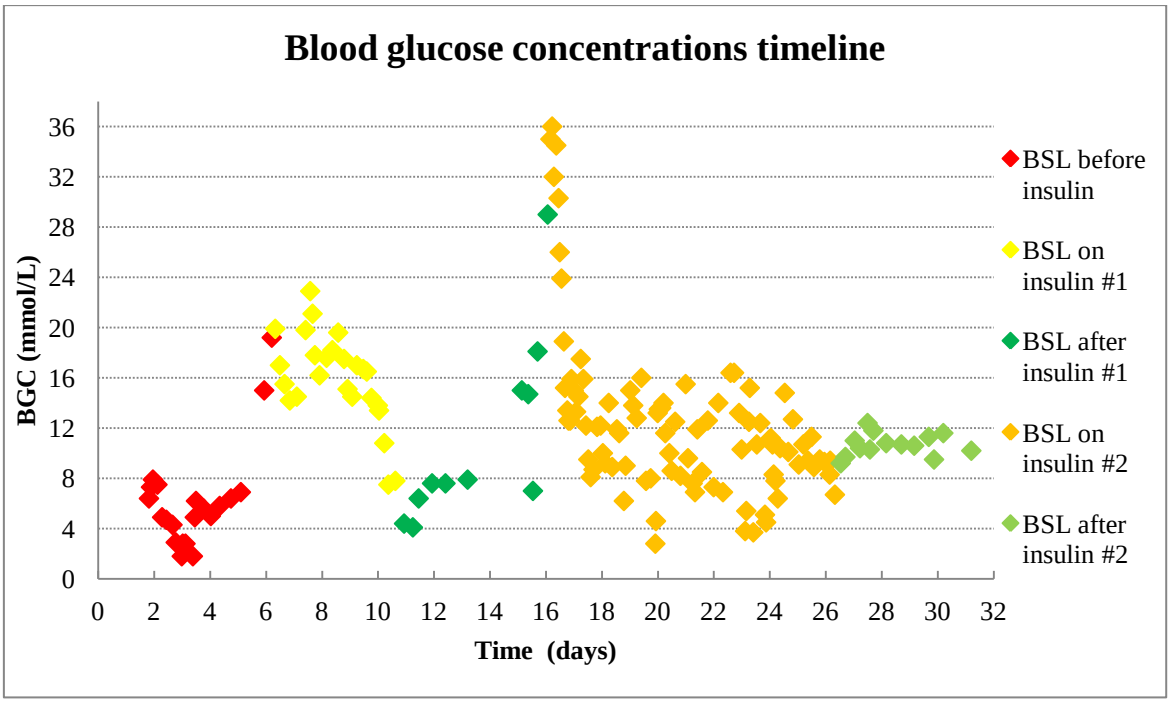

Figure 7. Scatter plot representing changes in blood glucose concentrations in Case 3.

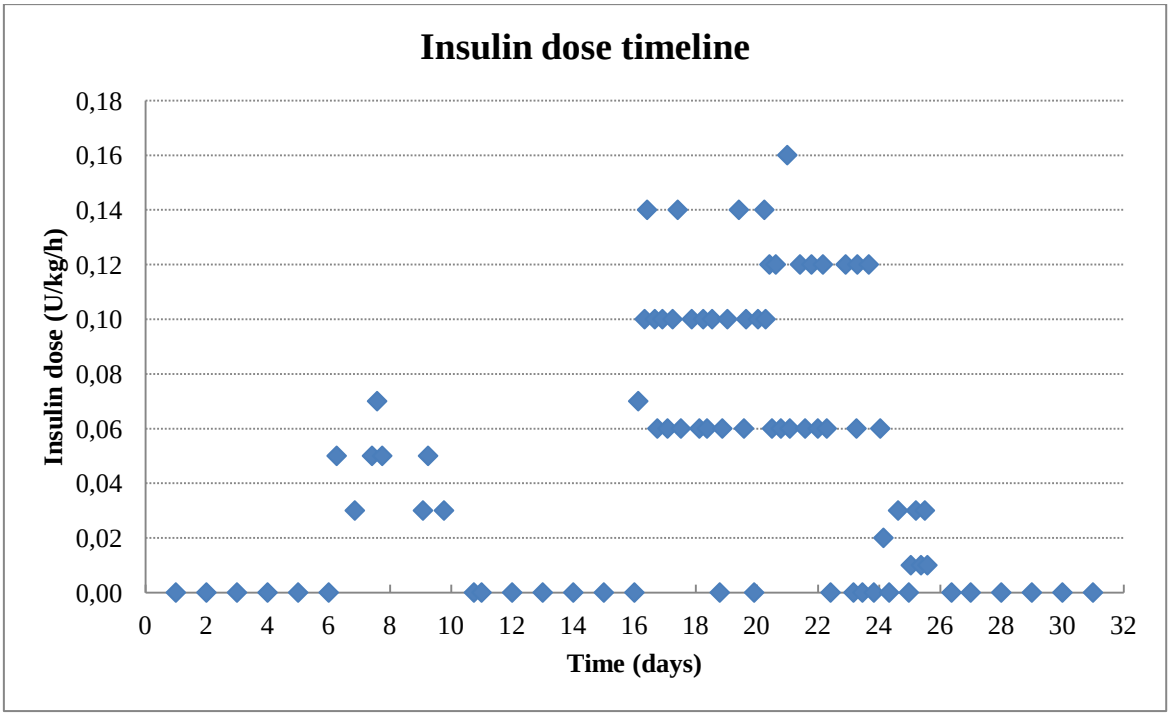

Figure 8. Scatter plot representing the dosing regimen for insulin in Case 3.

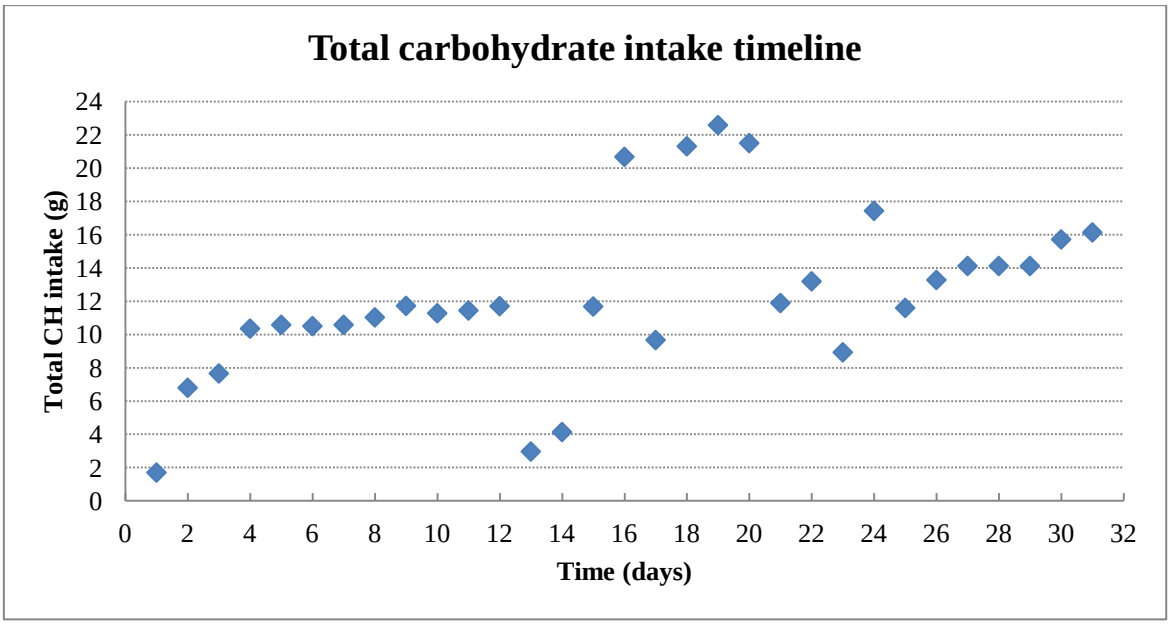

Figure 9. Scatter plot representing total carbohydrate intake (intravenous and oral) in grams for Case 3 on each day.

Case 3 experienced two hyperglycaemic episodes for which BGC rapidly raised high above the normal range. In the first episode BGC raised from hypoglycaemic levels to levels above 15.0 mmol/L within two days. Insulin was started at 0.05 U/kg/h and was continued without any other interventions for 4.49 days. In that time BGC normalised and insulin was stopped. The insulin dose during this episode ranged from 0.03 U/kg/h to 0.07 U/kg/h, with an average of 0.05 U/kg/h. There was a constant increase (*Figure 9*) in CH intake during that time, although D10 was changed to D5 on day 9. The first episode was well managed as BGC normalised within reasonable time and CH intake was preserved. With the discontinuation of insulin infusion and parenteral nutrition it looked like glycaemic control was achieved.

However, a few days later BGC increased above 30.0 mmol/L. The main goal was to achieve euglycaemia as quickly as possible so insulin was started at 0.07 U/kg/h and was constantly increased to 0.14 U/kg/h. BGC decreased to below 20.0 mmol/L, but the insulin dose remained high to lower BGC further and prevent increases in BGC. This high dose treatment resulted in three episodes where BGC dropped below 4.0 mmol/L and five episodes where BGC dropped below 7.0 mmol/L resulting in the insulin infusion being stopped and restarted. The average dose of insulin almost doubled (0.08 U/kg/h) in

comparison to the first episode and the range extended from 0.01 U/kg/h to 0.16 U/kg/h. Insulin treatment ceased after 8.68 days, although BGC remained above the normal range but was decreasing. CH intake varied a lot due to big fluctuations in BGC. The infant was fed orally the entire time and after receiving a D10 infusion on day 24, the CH intake was constant again.

This case shows the complexity of insulin treatment for neonatal hyperglycaemia. Since BGC reached such high values it was impossible for the hyperglycaemia to correct itself and the priority was to lower BGC as quickly and as much as possible to prevent any long-term damage to the infant (e.g. brain damage).

4.5 Descriptive data analysis

4.5.1 Gestational age, birth weight and gender

As already mentioned in the introduction (*1.3.2*), prematurity and low birth weight are the two main risk factors for neonatal hyperglycaemia.

On average neonates from our study were born at 25.97 ± 2.04 weeks gestation (23.00 – 30.57 weeks) and weighed an average 793 ±180 g (490 – 1460 g).

Only eight neonates were born weighing more than 1000 g, 21 would be considered as VLBW (BW < 1000g) and 24 weighed less than 750 g at birth (ELBW).

Table VII. Descriptive statistics for gestational age (weeks) and birth weight (g).

	Gestational age	**Birth weight**
Mean	25.97	793
SD	2.04	180
Median	25.28	765
Minimum	23.00	490
Maximum	30.57	1460
Range	7.57	970
Interquartile range	2.86	205

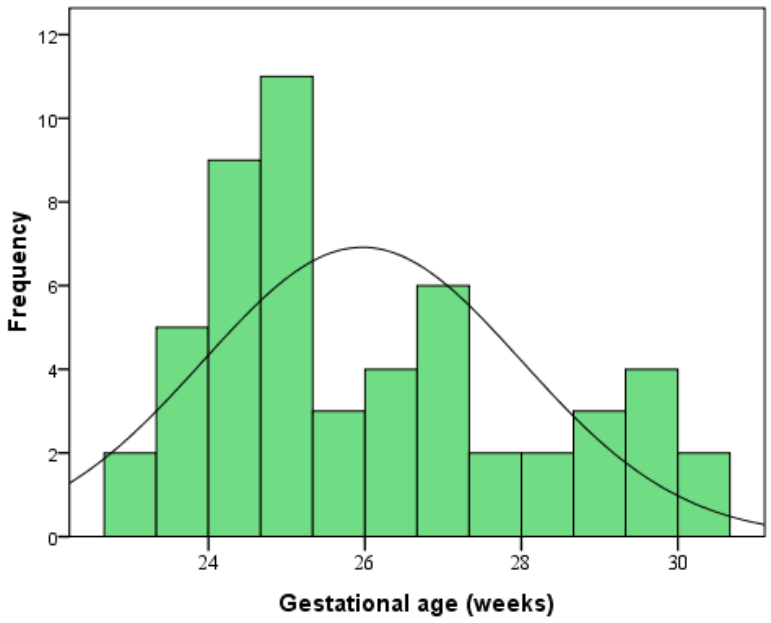

Figure 10. Histogram representing distribution in gestational age. The overlying line shows a normal distribution curve.

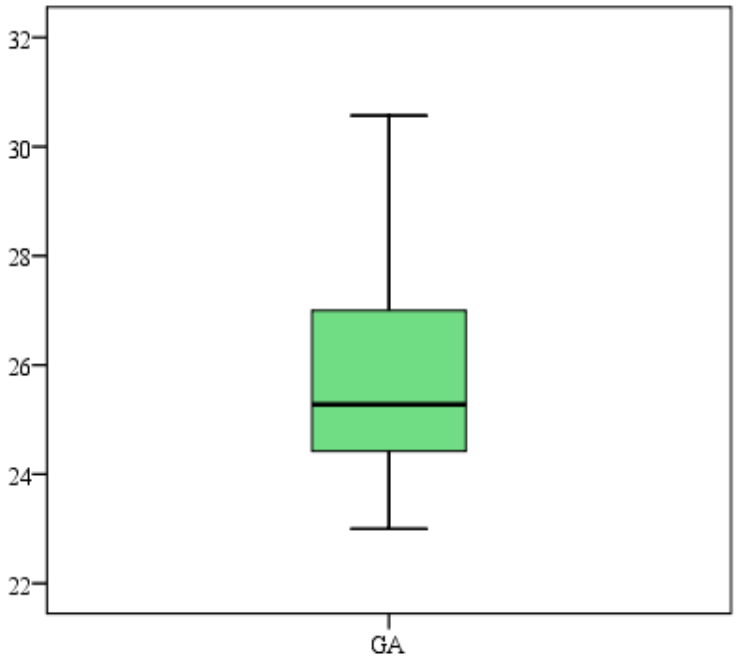

Figure 11. Box plot representing distribution in gestational age (weeks) – the box shows interquartile range and whiskers represent the range.

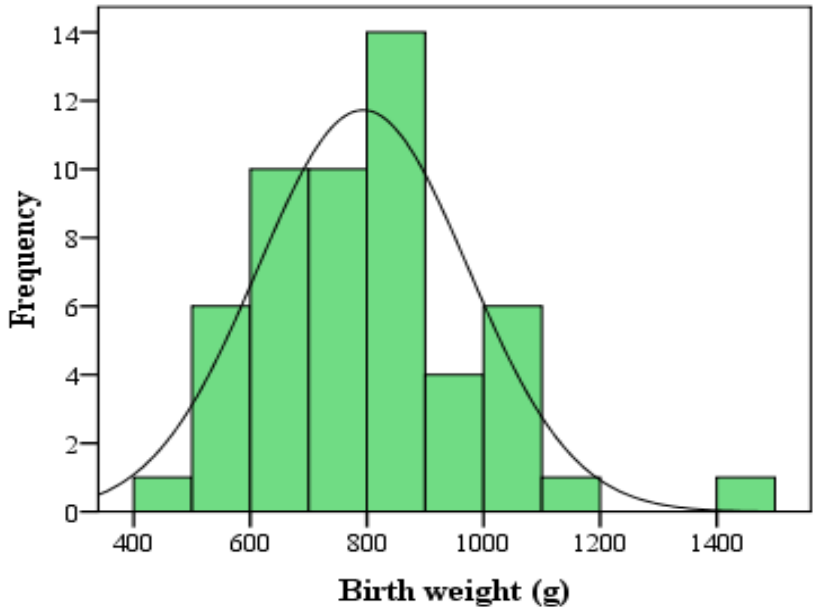

Figure 12. Histogram representing distribution in birth weight (g). The overlying line shows a normal distribution curve.

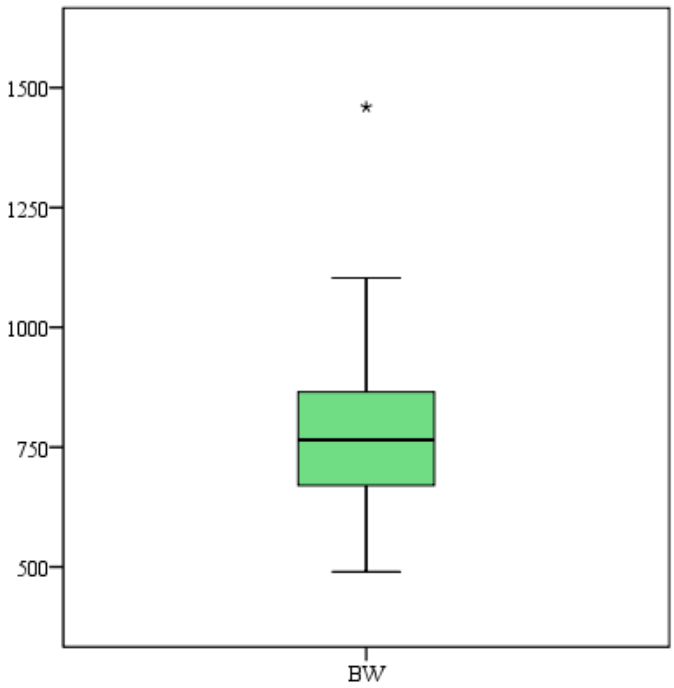

Figure 13. Box plot representing distribution in birth weight (g) – the box shows interquartile range and whiskers represent the range. The asterisk above the whiskers represents an extreme outlier.

On average females were born at a later GA than males and they cover a larger range with both the youngest and the oldest being female. Median values were the same for both groups.

Table VIII. Descriptive statistics for gestational age (weeks) factored by gender.

	Male	**Female**
Mean	25.85	26.13
SD	1.89	2.26
Median	25.28	25.28
Minimum	23.42	23.00
Maximum	29.57	30.57
Range	6.15	7.57
Interquartile range	2.86	3.26

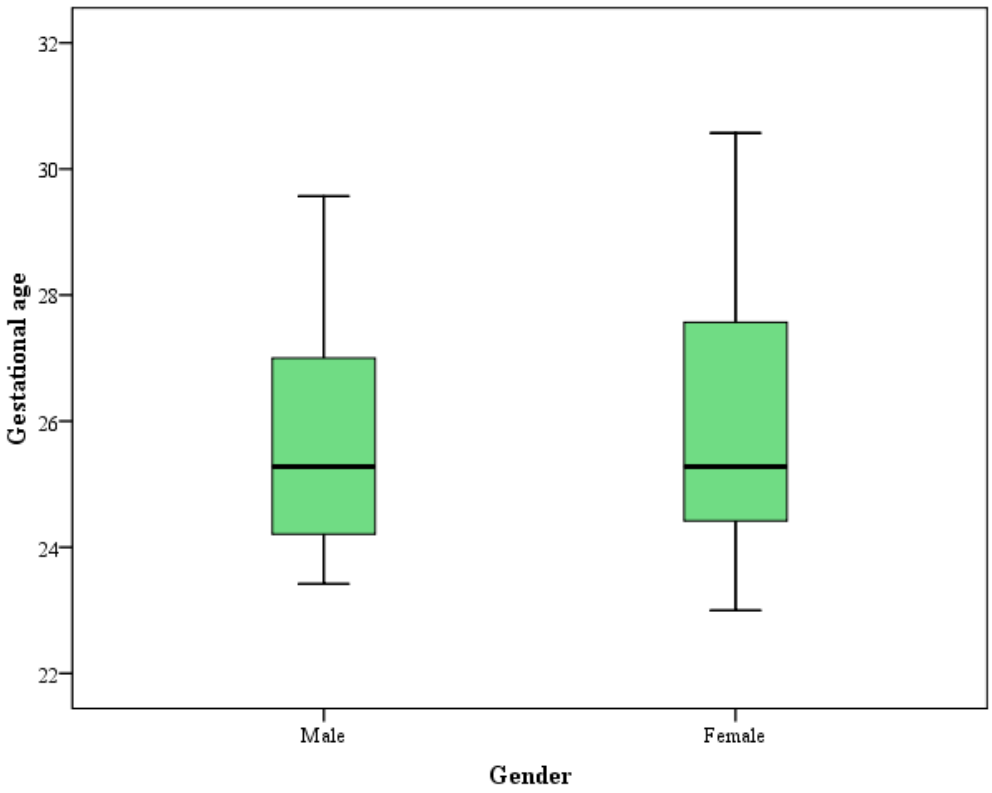

Figure 14. Box plot representing distribution in gestational age (weeks) factored by gender.

On average males weighed more than females at birth. The male population has a bigger range and one extreme outlier (an asterisk in *Figure 15*) among them, while the minimum birth weight was that of a female subject.

Table IX. Descriptive statistics for birth weight (g) factored by gender.

	Male	**Female**
Mean	810	770
SD	192	165
Median	800	745
Minimum	510	490
Maximum	1460	1103
Range	950	613
Interquartile range	195	234

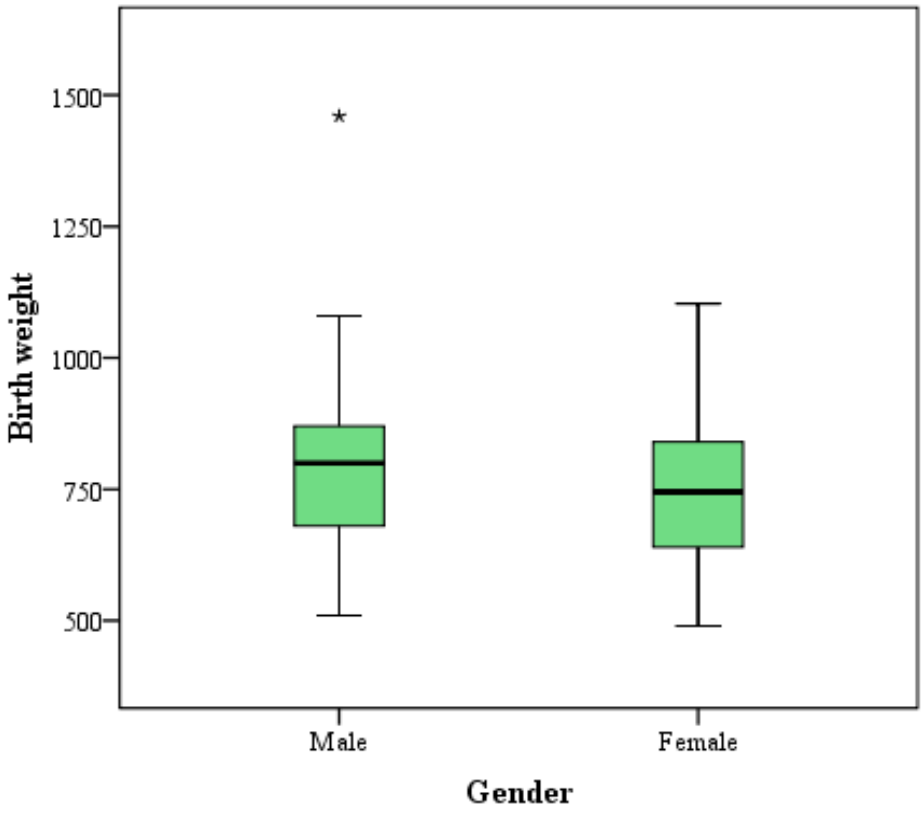

Figure 15. Box plot representing distribution in birth weight (g) factored by gender. Asterisk represents an extreme outlier.

4.5.2 Blood glucose concentrations

As previously mentioned (*4.1*) there were big differences in how much data we collected for each subject. This can be seen with the BGC data. In total we collected 3943 BGC measurements from the charts, ranging from 18 to 163 per subject, with an average of 74 measurements per subject.

According to the Dunedin NICU Medication Manual, clinically significant hyperglycaemia is defined as two consecutive BGC of 10.0 mmol/L or more, four hours apart. This occurred in 23 cases (43.4%) and insulin treatment was started. Two subjects (3.8%) received insulin with only one measurement ≥ 10.0 mmol/L, and one subject (1.9%) had 11 BGC ≥ 10.0 mmol/L before insulin treatment was started (*Figure 16*).

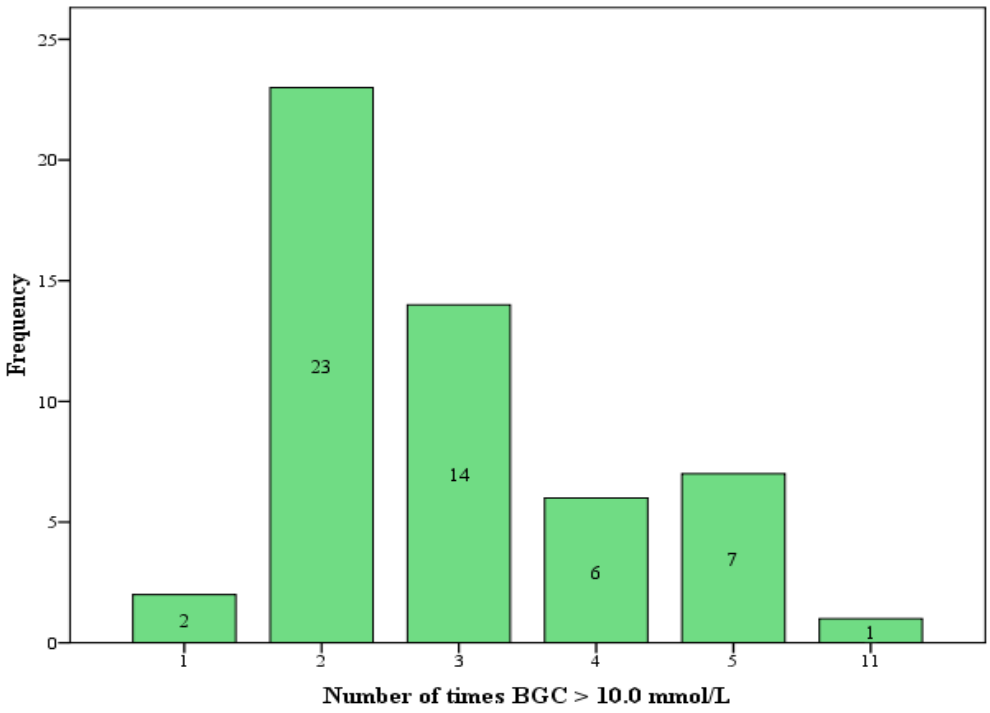

Figure 16. Bar chart representing the number of times BGC > 10.0 mmol/L before insulin was started.

As shown in *Table X*, the total mean and median BGC are not very high and would not be considered clinically significant to start insulin treatment, however the mean BGC when insulin was started is 12.7 mmol/L and therefore insulin was used according to the NICU Medication Manual. Low medium values (mean, median) could probably be attributed to a

large number of BGC measurements included in its calculation and the difference in severity of hyperglycaemia.

As expected BGC were lower at birth (day 1) and the minimum BGC overall (0.8 mmol/L) falls into this category. The maximum BGC overall (36.2 mmol/L) falls into the time period "on insulin" and the minimum value while on insulin was 1.8 mmol/L, which tells us there were episodes of hypoglycaemia. As per the sliding scale, BGC < 7.0 mmol is a sign to cease insulin treatment and the mean and median show us this was mainly when insulin treatment was ceased permanently.

Table X. Descriptive data for BGC (mmol/L) in different treatment periods.

	Total	**Day 1**	**On insulin**	**At start of insulin treatment**	**At finish of insulin treatment**
Mean	8.9	4.9	10.5	12.7	7.1
SD	3.6	2.3	3.5	2.6	2.9
Median	8.6	4.6	9.9	12.0	6.6
Minimum	0.8	0.8	1.8	5.9	1.8
Maximum	36.3	13.5	36.3	19.8	23.7

We grouped and compared median, minimum and maximum BGC values to see their distribution (*Figure 17*). Median and minimum values have similar range, while the range of maximum values is higher. All three groups have outliers, but only maximum values have two extremely outlying values (asterisk in *Figure 17*)

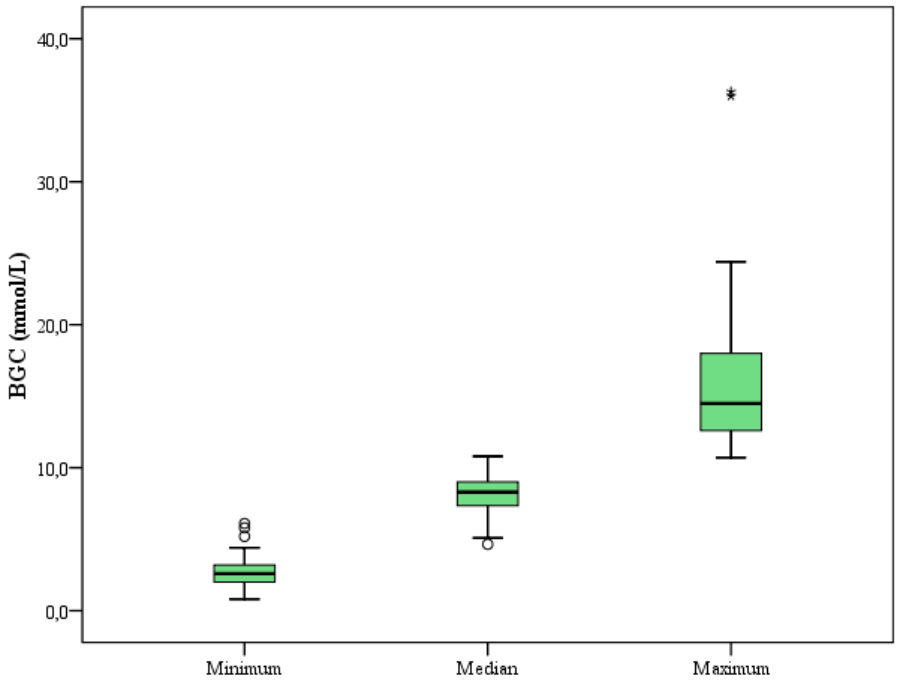

Figure 17. Box plots representing the distribution of minimum, median and maximum BGC values. Mild outliers are shown with the circle (o), extreme outliers are shown as asterisks (*).

4.5.3 Insulin treatment

Of the 53 subjects, the majority (83%) experienced only one episode of hyperglycaemia. However there were 9 cases (17%), where hyperglycaemia reoccurred and one of such cases is presented in *chapter 4.4.3*. When analysing data for these subjects we combined data for both episodes and analysed it as one episode.

The main goal of this research was to evaluate the time taken for neonates to achieve glycaemic control. The time for hyperglycaemia to develop varies from 0.34 days to 13.98 days after birth, with an average of 4.32 days. Values for duration of insulin treatment are slightly higher and we could set a hypothesis that the time needed for hyperglycaemia to develop is similar to the time needed to treat this condition.

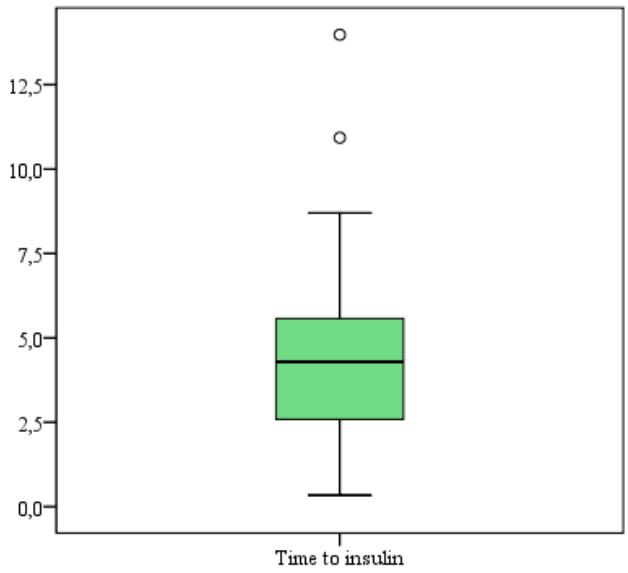

Figure 18. Box plot representing the distribution of time to insulin treatment (days) - the box shows interquartile range and whiskers represent the range. The two circles (o) show two mild outliers.

If we consider the mean value (6.04 days) alone, the time for successful treatment is not long. But the range (SD = 4.30 days, range = 15.17) indicates that each case is different and there are large differences in how long is required for neonates to successfully regulate their blood glucose levels (*Table XI*).

Table XI. Descriptive data for time parameters of insulin treatment (days).

	Time to start of insulin	**Duration of insulin treatment**
Mean	4.32	6.04
SD	2.60	4.30
Median	4.29	5.01
Minimum	0.34	0.38
Maximum	13.98	15.55
Range	13.64	15.17
Interquartile range	3.20	7.85

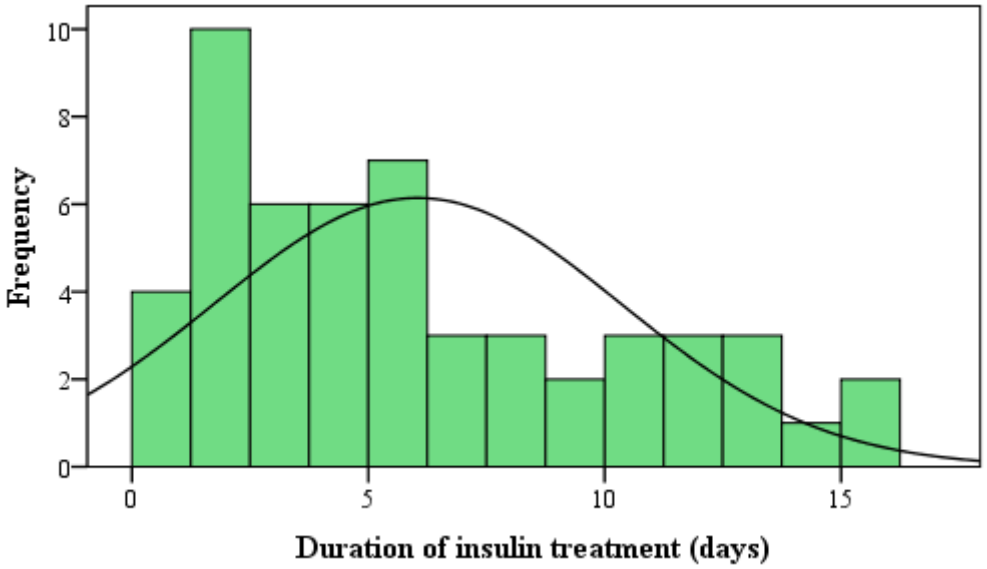

Figure 19. Histogram representing the distribution of time on insulin (days). The overlying line shows a normal distribution curve.

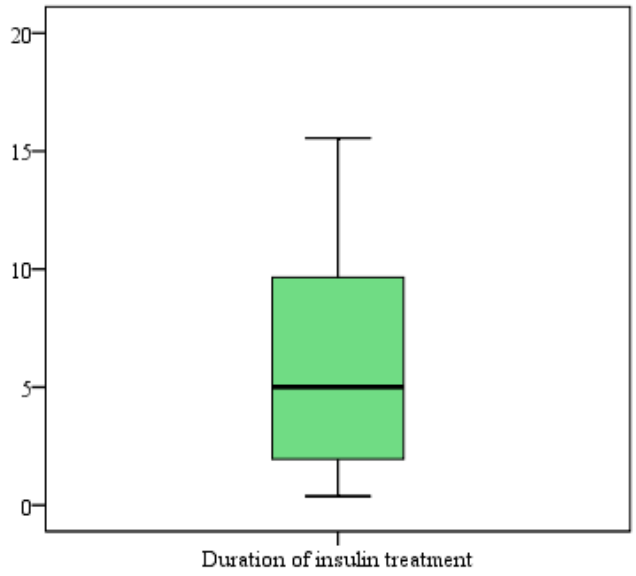

Figure 20. Box plot representing the distribution of the time on insulin (days) - the box shows interquartile range and whiskers represent the range.

There were times when the insulin infusion had to be stopped and restarted for various reasons. The number of times this happened varied from 1 to 10 (*Figure 21*); however, clinical reasons for this were not investigated in this study. The duration of insulin treatment is a sum of all these small episodes. The average time for such an episode was 1.85 days (0.02 – 11.47 days).

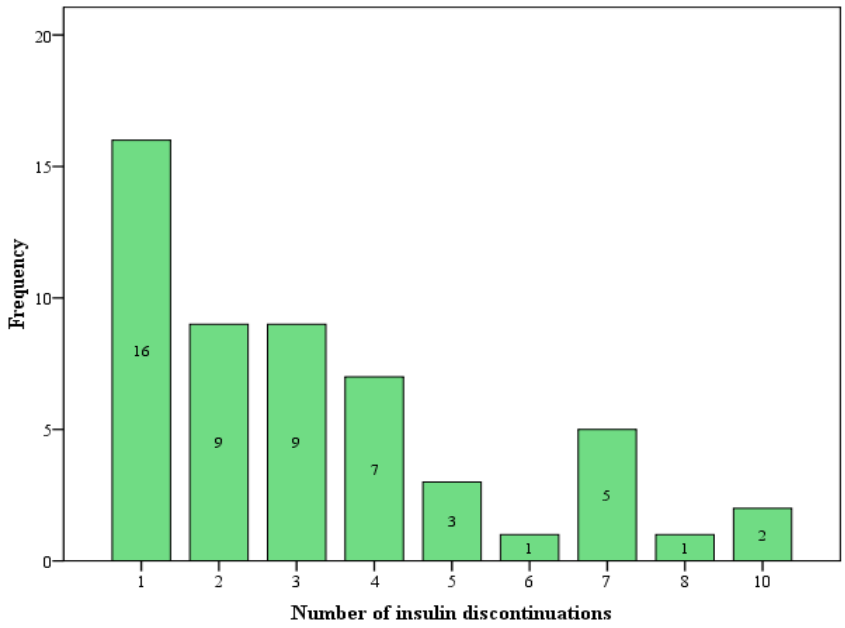

Figure 21. Bar chart representing number of times insulin was stopped.

Table XII. Descriptive statistics for dosing parameters of insulin treatment (U/kg/h). The column "Insulin dose" refers to insulin dose during treatment.

	Insulin dose	**Insulin dose at start**	**Insulin dose at finish**
Mean	0.05	0.03	0.02
SD	0.05	0.01	0.05
Median	0.03	0.03	0.01
Minimum	0.01	0.01	0.01
Maximum	0.43	0.05	0.40
Mode	0.03	0.03	0.01
Range	0.42	0.04	0.39
Interquartile range	/	0.00	0.02

We grouped and compared median, minimum and maximum values of insulin doses to see their distribution (*Figure 22).* The range and number of outliers expands from minimum, through median to maximum values.

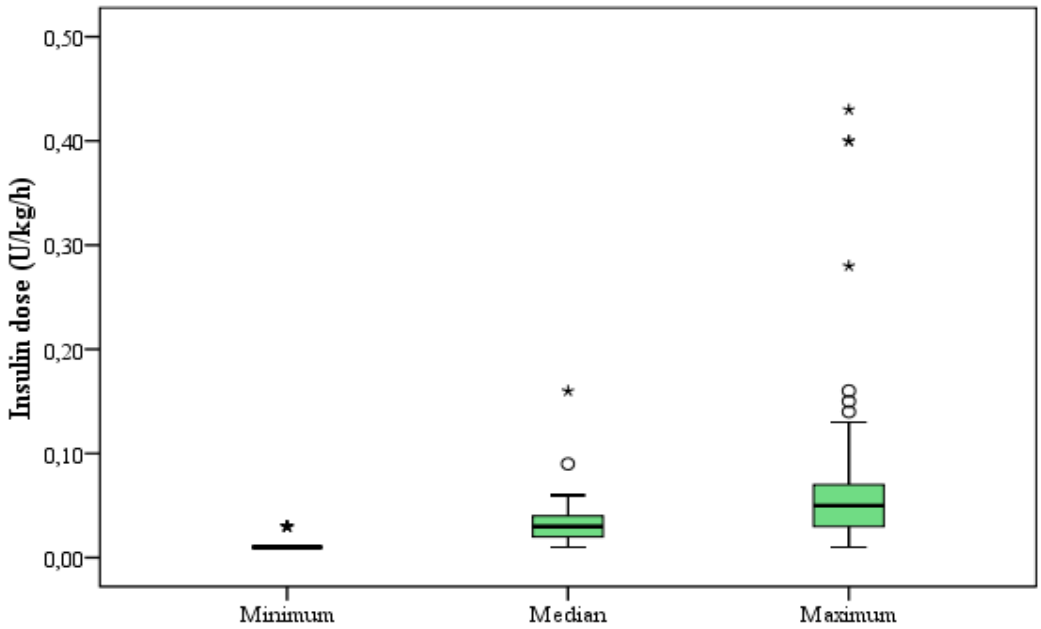

Figure 22. Box plots representing the distribution of minimum, median and maximum values of insulin infusion dose (U/kg/h). Mild outliers are identified with circle symbol (o), asterisks (*) represent extreme outliers.

Treatment mainly started with a dose of 0.03 U/kg/h and finished with a dose of 0.01 U/kg/h and the most common insulin dose was 0.03 U/kg/h. The variability of insulin dose is high with a SD of 0.05 U/kg/h and range of 0.42 U/kg/h. The variability when treatment is finished is also high with a standard deviation of 0.05 U/kg/h and range of 0.39 U/kg/h. However, the mode (0.01 U/kg/h) tells us that this is the dose most neonates finished on and this is logical considering that treatment finishes when the therapy goal (BGC < 7.0 mmol/L) is achieved.

However, insulin dose at the start of treatment, has a low variability and we could conclude that 0.03 U/kg/h is the most common starting dose. This is not surprising, as most treatments start when BGC ≥ 10.0 mmol/L and 0.03 U/kg/h is the dose given at this time.

Insulin treatment demands constant dose adjustments and sometimes changes in the sliding scale. These adjustments can be made by either changing the rate of infusion (mL/h) or the concentration (U/mL). In our research concentration changes occurred in 20.8% of cases.

4.5.4 Carbohydrate intake

All neonates included in the study (N=53) received carbohydrates during insulin treatment. Most CH (given as dextrose) was part of total parenteral nutrition (TPN) or oral feds with different milk formulas (e.g. expressed breast milk (EBM), S26, HMF). Only six neonates (11.3%) were not fed orally during insulin treatment.

On average infants received 76.3 g of CH during insulin treatment. The range was very high, ranging from 2.36 g to 209 g. This is probably due to different durations of insulin treatment as infants that were on insulin longer also received CH for longer and therefore their cumulative intake was larger. During insulin treatment 88.7% of infants were orally fed, but the average percentage that oral feeds contribute to CH intake was quite low (7.16%). The cause of this is the gradual introduction of oral feds in premature neonates, where volumes and frequency of feeds depend on how well an infant tolerates them. Since hyperglycaemia usually occurs in the first few weeks of an infant's life, low volumes and long periods between feeds prevent a high total oral intake of CH during insulin treatment for this condition. There are some exceptions to this rule, which can be seen in the outliers (e.g. 162.12 g or 77.42% of total CH intake).

Table XIII. Descriptive statistics for CH intake (g) during insulin treatment (N=52).

	Total CH	**Total CH i.v.**	**Total CH oral**	**% of CH oral**
Mean	76.28	68.14	8.14	7.16
SD	56.67	49.69	23.14	12.23
Median	60.74	55.22	2.37	3.23
Minimum	2.36	2.36	0.00	0.00
Maximum	209.39	193.27	162.12	77.42
Range	207.03	190.91	162.12	77.42
Interquartile range	75.20	66.41	7.31	8.32

The distribution of CH intake i.v. is similar to the total CH intake, while total oral CH intake shows a much lower range and has few outliers, mild and extreme (*Figure 23*). These results are not surprising as oral CH intake only covers for 7.16% of total CH intake.

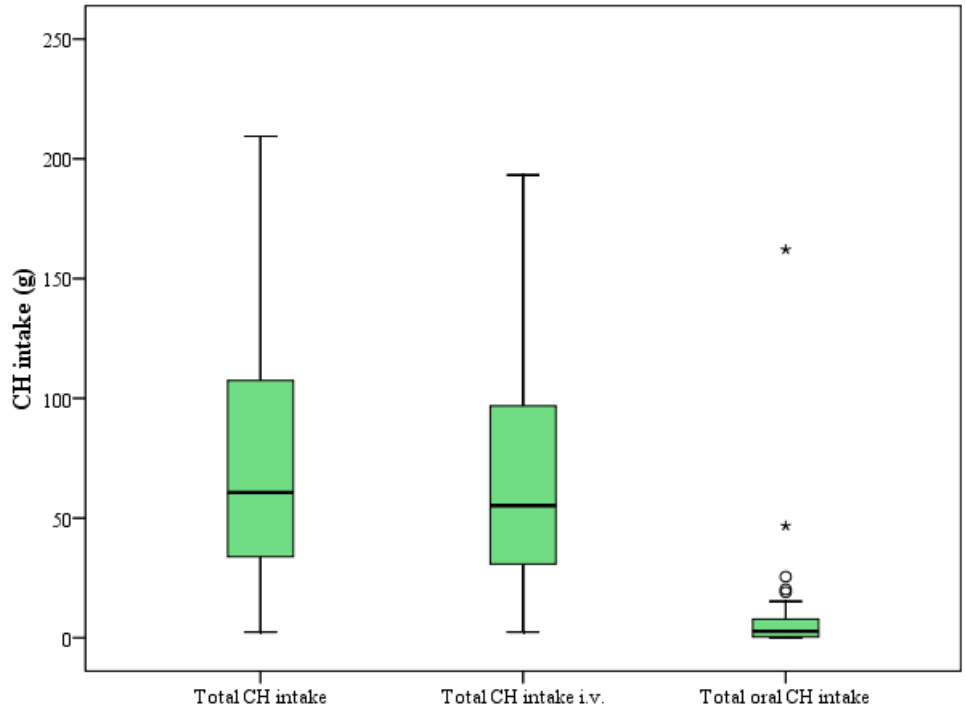

Figure 23. Box plots representing distribution of CH intake (grams). Mild outliers are shown as circles (o), extreme outliers are shown as asterisks.

Table XIV. Descriptive statistics for CH intake i.v. at start and finish of insulin therapy given as g/kg/h (N=52).

	Start of insulin treatment	**Finish of insulin treatment**
Mean	0.65	0.62
SD	0.63	0.78
Median	0.61	0.57
Minimum	0.10	0.00
Maximum	4.93	6.09
Range	4.83	6.09
Interquartile range	0.20	0.20

Managing CH intake is an important part of managing hyperglycaemia. The difference between means and medians at the start and finish of therapy is small, which means that CH intake in our subjects was preserved while being treated with insulin. Due to the percentage of oral feeds contributing to CH intake being low, we only analysed intravenous intake. The distribution of CH intake rates is quite similar at the start and finish of the treatment and both groups have two extreme outliers (*Figure 24*).

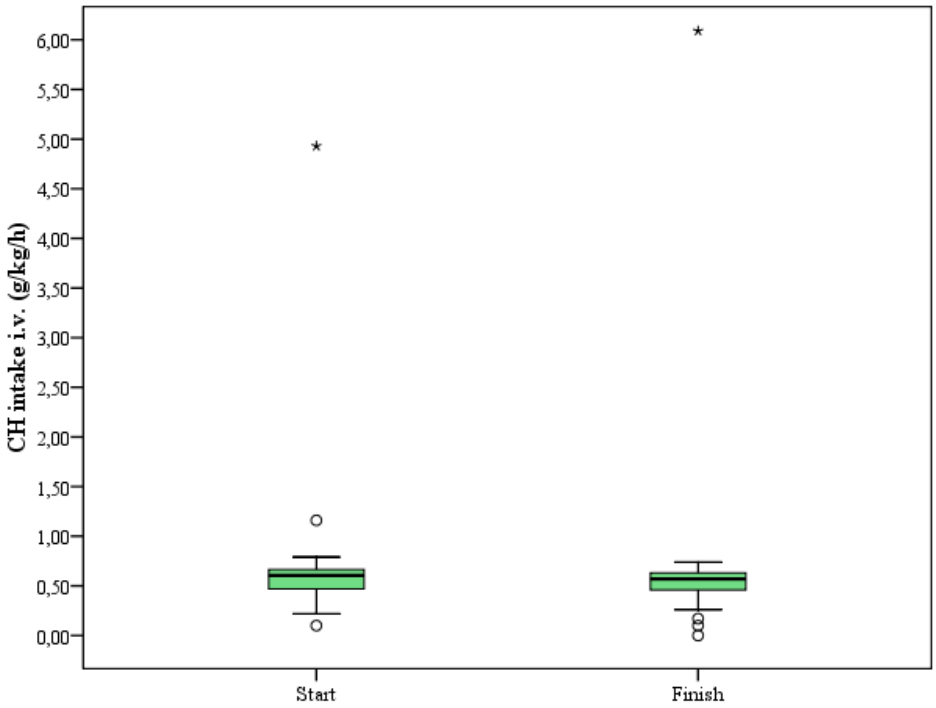

Figure 24. Box plot showing distribution of start and finish CH rates in g/kg/h). Mild outliers are shown as circles (o), extreme outliers are shown as asterisks.

4.5.5 Bivariate correlations

For a better understanding of neonatal hyperglycaemia and its treatment, it is important to see which factors influence one another (*Figure 25*).

As expected gestational age and birth weight are such factors. The foetus grows as gestation increases and therefore the neonate will weigh more at birth. The Pearson correlation is 0.589 and it is significant at the 0.01 level (2-tailed).

The Pearson coefficient between GA and duration of insulin treatment is -0.373 and this is significant at the 0.01 level (2-tailed). Therefore with increasing GA the duration of insulin treatment shortens. This is most likely due to the maturity of the infant, who is more capable of regulating BGC than infants born at younger gestations.

Birth weight and duration may seem correlated on the scatter dot, but the Pearson correlation (-0.233) is not significant.

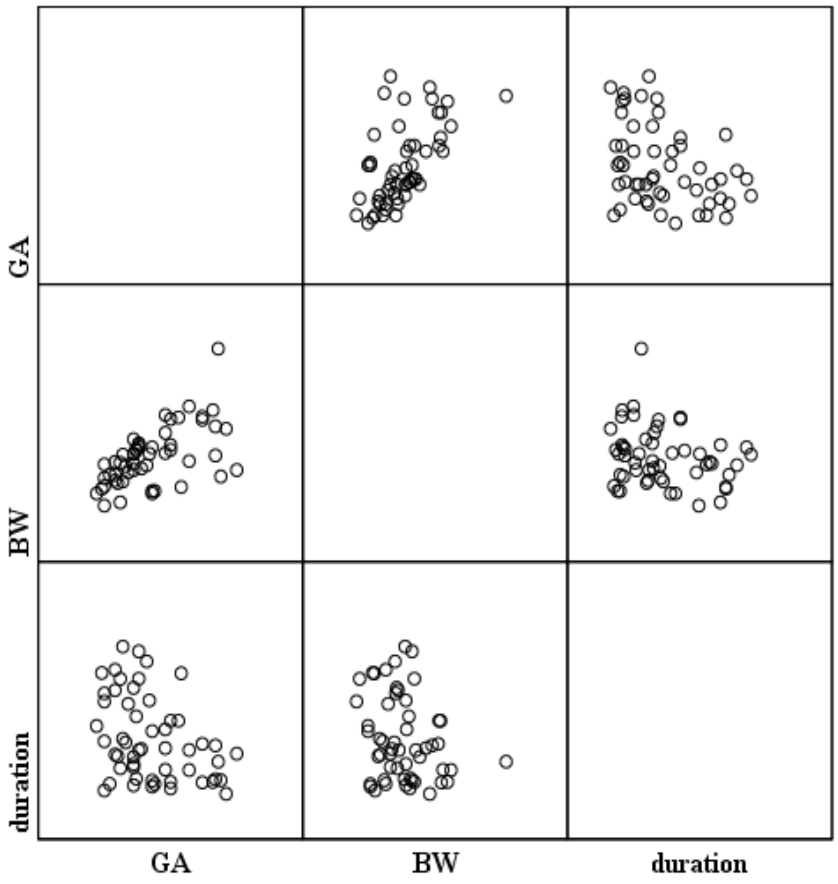

Figure 25. Matrix scatter dot showing correlations between GA, BW and duration of insulin treatment (duration).

Other significant correlations with duration of insulin treatment are shown in *Table XV* as Pearson coefficients. All correlations are significant at the 0.01 level (2-tailed).

Table XV. Pearson correlations for duration of insulin treatment with various other variables.

	Duration of insulin treatment (days)
Start dose of insulin (U/kg/h)	0.526
BGC at the start of insulin (mmol/L)	0.507
Total CH intake (g)	0.906
Total CH intake i.v. (g)	0.852
Total CH oral intake (g)	0.392

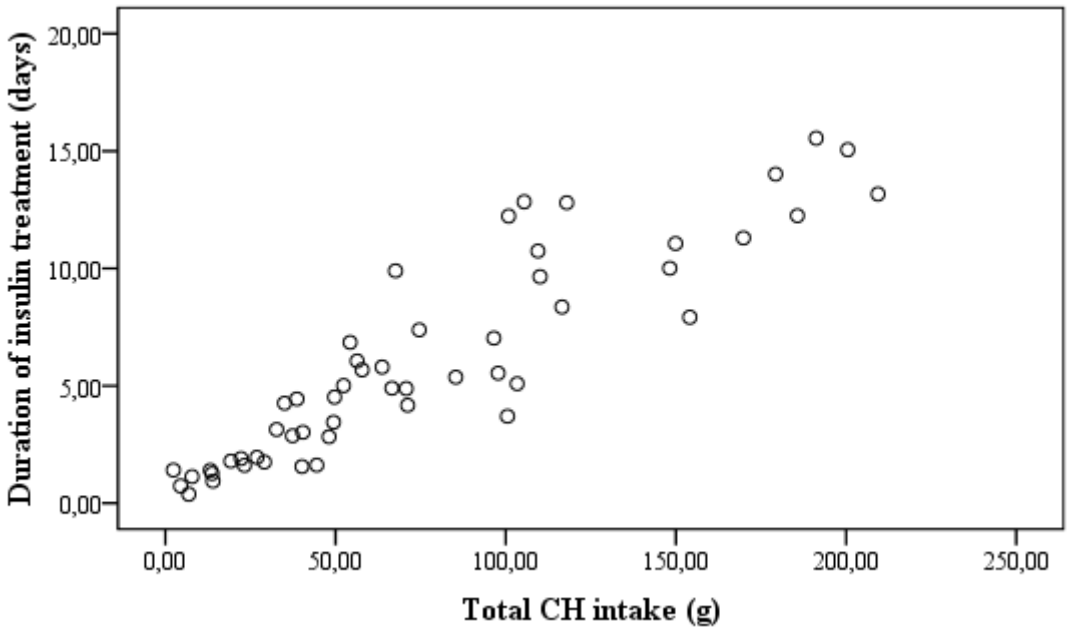

Figure 26. Scatter dot showing the correlation between total CH intake (g) and duration of insulin treatment (days).

There was a strong correlation between total CH intake and total CH i.v. intake and duration (*Figure 26*). The Pearson coefficient is close to 1 and the scatter plot shows that duration of insulin treatment is prolonged with a higher CH intake.

These correlations show a trend of possible influences among different variables and suggest areas for further research.

5. CONCLUSIONS

We investigated the treatment of neonatal hyperglycaemia at Dunedin NICU and concluded the following:

- 53 neonates with neonatal hyperglycaemia, who received insulin treatment at Dunedin NICU from January 2006 until July 2012, were identified.
- All infants were born prematurely at an average of 25.97 ± 2.04 weeks of gestation, weighing an average of 793 ±180 grams.
- The average time taken to achieve glycaemic control was 6.04 ± 4.30 days, but the results are highly dispersed, ranging from 0.38 to 15.55 days.
- The most common insulin dose was 0.03 U/kg/h.
- At the start of insulin treatment CH intake was preserved or did not decrease significantly as it probably would without the therapy. This means the growth and development of the neonates were not greatly affected.
- Oral feeds were introduced in the majority of infants. However, their percentage of the total CH intake is small.
- All of the parameters involved in this study (BGC, insulin dose, CH intake, oral feeds), show a high range of results. This shows the unpredictability and complexity of this condition and its treatment.
- Although these results show that the dosing protocol was not always followed, hyperglycaemia was successfully treated in 83% of cases. The remaining neonates experienced another episode, which was eventually successfully treated. It seems that the insulin dosing protocol and staff at Dunedin NICU are successful in managing neonatal hyperglycaemia.
- There is a strong correlation between GA and duration of insulin therapy. Correlations between variables show that the duration of treatment may also be influenced by starting BGC, starting insulin dose and CH intake. This shows there is a need for further research.
- This thesis and its results only depict how hyperglycaemia is managed and which factors are involved in the treatment. For any protocol improvements and treatment changes further research is necessary. More statistical analysis and modelling needs to be done to determine which parameters have the greatest impact on shortening and simplifying insulin therapy.

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7. APPENDICES

7.1 Appendix I – Dunedin Hospital NICU Medication Manual for insulin administration

INSULIN - ACTRAPID®

Neutral human monocomponent insulin – rapid acting

Clinically significant **hyperglycaemia** is present with blood glucose level of 10 mmol/L or more, for two consecutive levels, four hours apart. Clinically significant **hypoglycaemia** is present with a blood glucose level of < 2.6 mmol/L.

ROUTE	DOSE	PREPARATION
Continuous IV infusion (Preferred route)	*Hyperglycaemia:* 0.01 – 0.1 units/kg/hour as per sliding scale (see below) *Hyperkalemia:* See Glucose protocol	100 units/mL Dilute to 0.1units/mL with NS (see administration guidelines)
Intermittent SC doses (Discuss with consultant)	0.1 – 0.2 units/kg q12h	As above

ADMINISTRATION GUIDELINES

Step 1	Take 0.5 mL (= 50 units) of Actrapid® insulin 100 units/mL and add to 49.5 mL of 0.9% sodium chloride solution to give a **1 unit/mL** solution.
Step 2	Take 5 mL of the **1 unit/mL** solution (= 5 units) and add to 45 mL of 0.9% sodium chloride solution to give a **0.1 unit/mL** solution (infusion solution).
Step 3	Flush the lines with 20 mL of **0.1 unit/mL** solution.
Step 4	Prime the lines with the **0.1 unit/mL** solution.

As insulin binds to the NEO96E Pall Filter causing significant delays in insulin delivery to the patient, insulin should be administered BELOW this filter, ie. NOT filtered.

SLIDING SCALE

Start the insulin infusion at 0.5 mL/kg/hour (=0.05 units/kg/hour) and adjust using the sliding scale below based on subsequent blood glucose results.

Blood Glucose Level	Dose	Infusion Rate (0.1 unit/mL)
>20 mmol/L	0.07 units/kg/hour	0.7 mL/kg/hour
15 – 20 mmol/L	0.05 units/kg/hour	0.5 mL/kg/hour
10 – 15 mmol/L	0.03 units/kg/hour	0.3 mL/kg/hour
7 – 10 mmol/L	0.01 units/kg/hour	0.1 mL/kg/hour
<7 mmol/L	Stop infusion	Stop infusion

MONITORING

- Titrate dose to sliding scale after each blood glucose level.
- Blood glucose levels should be checked hourly after initiating the insulin infusion and once stabilised, can be done q3h. If the tests are carried out gently on the correct part of the foot and the appropriate lancet used, this should not cause any permanent damage to the baby's foot.

INJECTION COMPATIBILITY

- pH: 7 – 7.8
- IV Fluid:

NS	G	G10%	R	LR	W	TPN
✓	✓	✓	×	×	✓	✓

- Flush solution: NS
- Terminal injection site:

  Compatible: Ampicillin, Dobutamine, Gentamicin, Heparin, Indomethacin, Magnesium, Meropenem, Midazolam, Morphine, Potassium, Ranitidine Sodium bicarbonate, Vancomycin.

  Incompatible: Lipid (no data), Aminophylline, Dopamine, Phenobarbitone, Phenytoin.

STORAGE/STABILITY

- Refrigerate at all times.
- Once opened, the 100 units/mL vials have a 30 day expiry in the fridge, however, an arbitrary expiry of 7 days has been given due to the fact that insulin is a protein and may denature if left out in 'hot room' temperatures for long periods.
- The final solution of 0.1 units/mL has a 24-hour expiry from the time of preparation.

RATIONALE

Very low birth weight (VLBW) infants are at risk of developing hyperglycaemia, as they may have reduced glucose tolerance. The hyperglycaemia may cause increased fluid and electrolyte losses and/or hyperosmolality, but more importantly it is associated with increased morbidity – particularly with intraventricular haemorrhage – and mortality.

One way of dealing with a glucose intolerance is to decrease the glucose intake, until a level of tolerance is reached; however this may be considered unsatisfactory as it deprives the infant of the energy for necessary growth. Poor growth and prolonged energy deprivation are associated with poor neurodevelopment outcome. In order to maintain an adequate caloric intake, it is necessary to continue giving at least 85 cal/kg/day and to control blood sugar levels by other methods. The most appropriate method is to administer a controlled insulin infusion. The main risk of insulin infusion is unrecognised severe hypoglycaemia. There is a potential for this to cause permanent brain damage. For this reason, extreme care should be taken in the preparation, administration and monitoring of an insulin infusion.

COMMENTS

- The infusion should be piggy-backed (ie, Y-site) into the baby's usual IV line using a 3-way tap, placed as close to the patient as possible. This is done to minimise delays in changes to therapy as the dead space has been minimised.
- Adverse effects: May rapidly induce hypoglycaemia. Insulin resistance may develop, necessitating higher dose requirements.

7.2 Appendix II – Data collection spread sheet

ID	GA	G	BW	DOB	TOB	CA	Date	Time	Current weight	BGC	Glucose infusion	Oral feeds	Insulin infusion
17	25+2	F	670g	12/05/08	19:05								
						1	12/05/08	19:05	670 g	2.6			
							12/05/08	21:00	670 g		2.8 ml/h D10		
							12/05/08	23:30	670 g	5.3			
						2	13/05/08	4:00	670 g	8.7			
							13/05/08	7:00	670 g	10.5			
							13/05/08	1:00	670 g	10.8			
							13/05/08	17:45	670 g	11.3	3.0 ml/h D10		0.20 ml/h (0.03 U/kg/h)
							13/05/08	21:15	670 g	10.3			
						3	14/05/08	01:00	630 g	9.5		0.5 ml EBM	0.07 ml/h (0.01 U/kg/h)
							14/05/08	7:00	630 g	8.6			
							14/05/08	12:00	630 g	12.6		0.5 ml EBM	0.20 ml/h
							14/05/08	17:00	630 g	11.4	3.0 ml/h D10		

Data entered in this spread sheet is fictive to preserve anonymity of involved subjects. It serves only to depict how data was collected.