HYPOGLYCAEMIA AS A CONSEQUENCE OF PRE-OPERATIVE FASTING: MYTH OR REALITY?

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ABSTRACT

Background: The fatal risk of pulmonary aspiration of gastric contents during anaesthesia had since been recognized and consequently preoperative fasting guideline is usually prescribed to prevent this. Concern about development of hypoglycaemia during prolonged fasting has often been expressed, especially in children. **AIM**: This study is intended to determine the fasting blood glucose in preoperative patients of different age groups who were fasted for varying duration of time, and determine whether indeed hypoglycaemia occurs during inadvertently prolonged fasting which we often encounter in our practice setting. **Methodology:** A prospective cohort study of fasting blood glucose (FBG) of patients presenting for elective surgery in the principal investigator's operating rooms at the National Orthopaedic Hospital, Enugu, Nigeria was carried out. Blood glucose meter was used for estimation of glucose in capillary whole blood of the patients and the obtained data were analysed using SPSS version 16.0 statistical software. Comparison of mean values was done using the Chi-square test with statistical significance put at $P < 0.05$. **Results:** Out of one hundred and thirty three patients studied with mean age of 30.2 ± 19.60 years (range: 1-72 years), and mean duration of fasting 12.73 ± 2.01 hours, (range: 8-16 hours), the mean fasting blood glucose was found to be 91.49 ± 13.36mg/dl (range: 58 - 124mg/dl). No relationship was found between age and FBG (Pearson's correlation coefficient, r = 0.025). Likewise duration of fasting did not relate with FBG (Pearson's correlation coefficient, r = 0.088). One patient (0.8%) had hypoglycaemia, with blood glucose of 58mg/dl. **Conclusion:** Hypoglycaemia as a consequence of pre-operative fasting is rare, even in non-infants fasted for considerably long hours. Neither patient's age, gender, nor duration of fasting had any significant influence on the fasting blood glucose of the patients.

KEYWORDS: Hypoglycaemia; pre-operative fasting; whole blood; Plasma.

INTRODUCTION

Mortality from regurgitation and aspiration of gastric contents under anaesthesia, had since been documented [1] with several developments eventually leading to the prescription of pre-operative fasting guidelines [2-3]. Despite a fairly good knowledge of these fasting guidelines by medical practitioners, the preoperative fasting period is frequently extended far beyond the limits owing to the overnight fast that precedes a normal scheduled operation list, busy theatre sessions and logistic constraints, with concerns about the likely development of hypoglycaemia, especially in children in whom scanty glycogen store is often cited. These supposedly valid concerns were supported by frequent and severe hypoglycaemia reported in fasted children populations [4,5]. In what appears to be a stark contradic-

tion, several other determinations of the incidence of this hypoglycaemic phenomenon by various researchers [6-8] reported that it is quite uncommon, with correlation between duration of fasting and blood glucose often lacking.

Normal glucose homeostasis: The liver stores up glucose as glycogen in the post-absorptive state, and releases it into the circulation between meals to match the rate of glucose utilization by the tissues, through the process of glycogenolysis. During prolonged fasting, with the exhaustion of liver glycogen, gluconeogenic conversion of muscle-derived amino acids (predominantly in the liver) becomes the principal source of circulating glucose. Muscle glycogen though larger than the liver glycogen is not directly available for maintenance of blood glucose concentration due to lack of glucose-6-phosphatase in muscle. It's modest contribution to blood glucose is only through anaerobic glycolysis to lactate which eventually becomes a substrate for gluconeogenesis – a pathway known as the "Cori cycle". The modest decline in blood glucose levels during prolonged fasting rarely results in hypoglycaemia as compensatory mechanisms come into play; with cessation of insulin secretion at blood glucose levels of

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4 mmol.l^{-1} (73mg/dl) and increased secretion of counter-regulatory hormones (cortisol, adrenaline, glucagon and growth hormone), at blood glucose levels of 3.9 mmol.l^{-1} (71mg/dl).

Clinical Hypoglycaemia: The symptoms and signs of hypoglycaemia result from neuroglycopenia (headache, confusion, dizziness, weakness, apathy, double vision, amnesia, irritability, impaired judgement, lethargy, sleep disturbance, seizures and coma) and increased circulating levels of counter-regulatory hormones such as adrenaline (hunger, anxiety, tremor, palpitation, tachycardia, sweating, bounding pulse) . The cut-off blood glucose concentration for defining hypoglycaemia has been mired in the controversy created by whether clinical manifestations of neuroglycopenia, or triggering of the counter-regulatory hormones or even just deviation from the normal glycaemic response to overnight fast should indeed be the benchmark. Thus 3mmol.l^{-1} (54.5mg/dl), 3.9mmol.l^{-1} (71mg/dl) and 3.3mmol.l^{-1} (60mg/dl) respectively, have conveniently been used as cut-off blood glucose concentration to define hypoglycaemia. Without a well-defined and universally accepted blood glucose concentration for defining hypoglycaemia, a practical definition should be adjusted to the clinical situation. Whipple had in 1938 based his definition of hypoglycaemia on the "triad" of; documentation of low blood glucose concentration, concurrent symptoms of hypoglycaemia and resolution of the symptoms after exogenous glucose administration. Reliance on clinical signs and symptoms for diagnosis of hypoglycemia is however not recommended as the glycaemic threshold for the appearance of counter-regulatory hormone response and the manifestation of neuroglycopenic symptoms is dynamic; shifting to higher glucose levels in patients with sustained hyperglycaemia and to lower glucose level in those with recurrent episodes of hypoglycaemia.

Consequence of prolonged fasting: Prolonged fasting invariably produces deleterious effects on the patient such as thirst, hunger, restlessness, irritability and fluid imbalance. There are concerns that recurrent hypoglycaemia may result in permanent damage to intellectual capacity although in adults there is no concrete evidence to support this notion. In contrast, children younger than 5 years(yrs) of age do show a permanent impairment in intelligent quotient after recurrent episodes of hypoglycaemia [9]. Severe and prolonged hypoglycaemia may result in permanent impairment of brain function and death.

Glucose homeostasis in neonates and infants: The basic mechanisms of glucose homeostasis are similar to those of adults, but some critical differences make the neonate more prone to hypoglycaemia. Basal glucose requirement of the neonate is considerably higher (3-5mg/kg/min) than that of the adult (2-3mg/kg/min). The foetus which hitherto received a constant supply of glucose from the placenta, must suddenly rely on oral intake, glycogenolysis and gluconeogenesis as soon as the umbilical cord is cut. Oral intake in early postnatal life is small, glycogen stores scanty and rapidly depleted, while the rate-limiting enzyme of gluconeogenic pathway (Phosphoenolpyruvate carboxykinase) only appears after birth. Both immaturity of the metabolic pathway and lack of steady supply of substrates in the neonate, preterm infant, small for gestational age and other severely compromised infants may hinder gluconeogenesis, thereby predisposing this group of patients to hypoglycaemia.

A study of blood glucose levels of patients fasted for varying duration of time in our environment is deemed necessary in order to properly situate the often cited fear of hypoglycaemia following prolonged fasting, especially in children. This study seeks to determine the actual blood glucose of fasted patients, and ascertain whether patient's age, gender or duration of the fasting really have any influence on fasting blood glucose (FBG) levels and to determine the incidence of hypoglycaemia during pro-operative fasting in our environment..

MATERIALS AND METHODS

Study design : This is a prospective, quantitative, inferential, analytical study.

Ethics approval: The research was carried out in compliance with the Helsinki Declaration of 1975 on research ethics, as revised in 2000. Ethical approval for the research was sought and obtained from the Institutional Review Board. Written informed consent was obtained in all cases.

Study locus: Glucose estimation in *capillary whole blood* was determined in fasted patients presenting for elective surgery at the National Orthopaedic Hospital, Enugu. Nigeria.

Sample size: One hundred and thirty three (N=133).

Inclusion criteria: Patients older than one year (both gender) scheduled for elective surgery in the various specialties who fasted for at least 8 hrs and who were anaesthetised by the principal investigator were considered in the study. Infants were excluded to prevent potential harm they might suffer from fasting for 8hrs, or more.

Exclusion criteria: Known diabetics, patients on glucocorticoids or thiazide diuretic therapy as well as those on intravenous infusions were excluded from the study on account of their altered glucose homeostasis.

Method: "Accu-CHEK$^{(R)}$ Active" (Roche) glucose meter was used for the estimation of capillary whole blood glucose by reflectance photometry. No premedication was administered before sample collection from the patients. After cleaning each subject's finger with methyl alcohol 70%, a small drop of blood obtained via a lancet prick was placed on a disposable test strip im-

pregnated with glucose oxidase (enzyme electrode). With this electrochemical method of glucose estimation, the total current passing through the electrode is proportional to the amount of glucose in the blood that has reacted with the enzyme, and is displayed as the glucose concentration in conventional unit of $mgdl^{-1}$ by the glucose meter. Conversion to the S.I unit of $mmol.l^{-1}$ is obtained by dividing with a factor of 18.15.

Statistical analysis: The obtained data were analyzed using SPSS version 16.0 statistical software. Comparison of mean values was done using the Chi- square test with statistical significance put at P < 0.05.

RESULTS

Only one (1) out of the one hundred and thirty three (133) patients representing 0.8%, had hypoglycemia; as defined by blood glucose of less than $60mgdl^{-1}$ ($3.3mmol.l^{-1}$). This 3yr old child who fasted for 10 hrs had blood glucose of 58mg/dl ($3.2mmol.l^{-1}$). The mean FBG of the groups were given as mean ± standard deviation. The mean FBG of the study population was 91.49 ± 13.36mg/dl (range: 58 - 124mg/dl). The mean age of the study population was 30.2 ±19.60 yrs, (range: 1 – 72 yrs). The mean duration of fasting was 12.73 ± 2.01 hours (hrs), (range: 8 – 16 hrs). Pearson's correlation coefficient (r) was used to ascertain association. There

Table 1. Minimum and maximum values and Mean of Age [yrs], duration of fasting [hrs] and FBG [mg/dl] of the study population. (N=133)

	Min- Max	Mean± SD
Age [yrs]	1-72	30.2±19.61
Duration of fasting [hrs]	8-16	12.73±2.01
Fasting blood [mg/dl]	58-124	91.49±13.36

Table 2. Comparison of mean FBG by gender

Gender	N	Mean	Mean diff	Chi-square	P	Df
Female	73	91.88±12.1	0.86	0.657	0.42	1
Male	60	91.02±17.8				

Table 3. Mean FBG [mg/dl] in various ranges of duration of fasting [hrs].

Duration of fasting [hrs]	Frequency	Mean
8-10	21 (15.8)	89.24±15.17
11-13	62 (46.6)	93.81 ±12.93
14-16	50 (37.6)	89.56 ±12.88

Table 4. Mean FBG levels [mg/dl] in the different age groups.

Age [years]	Frequency	Mean
1-10	30 (22.6)	94.87±14.13
11-20	14 (10.5)	94.71±13.13
21-30	26 (19.5)	86.96±11.73
31-40	20 (15)	87.00±13.26
41-50	19 (14.3)	91.74±12.47
51-60	16 (12)	92.44±13.43
61 above	8 (6)	96.63±15.04

Table 5. Correlations of FBG with Age and Duration of Fasting (N=133)

Age [yrs]	Pearson Correlation	1	.312(**)	-.025
	Sig. (2-tailed)		.000	.779
Duration of fasting [hrs]	Pearson Correlation	.312(**)	1	-.088
	Sig. (2-tailed)	.000		.311
Fasting blood [mg/dl]	Pearson Correlation	-0.025	-.088	1
	Sig. (2-tailed)	.779	.311	

** Correlation is significant at the 0.01 level (2-tailed).

was no correlation between age and FBG (r = 0.025). There was also no correlation between duration of fasting and FBG (r = 0.088). There is a mean difference of 0.86mg/dl in the FBG levels between the male and females in the study population; this observed difference is not statistically significant on comparison using the Pearson chi-square test [P = 0.418] and thus is a chance occurrence.

DISCUSSION

In this study *whole blood* glucose was analysed and hypoglycaemia was defined as FBG < 60mg/dl. Critical to any interpretation of FBG level is the sample type used for the analysis; *whole blood* or *plasma*, as the latter is normally 10-15% higher. Studies on prevalence of hypoglycaemia have similarly been plagued by the different definitions applied by the various authors; as 2.2 mmol.l^{-1} (40mg/dl) [10] 2.8 mmol.l^{-1} (50.82mg/dl) [11] and 3.3 mmol.l^{-1}(60mg/dl) [12] were adopted as cut-off values by different authors. Gupta and colleagues, [13] had studied fasting *plasma* glucose in fifty six (56) children aged 0.17 years – 13 years and following a fasting duration of 6 – 19 hrs. They found neither correlation between duration of fasting and fasting plasma glucose, nor between age and fasting plasma glucose. They used 60mg.dl^{-1} (3.3mmol.l^{-1}) as their cut-off for hypoglycaemia, and reported a 3.6% incidence.

Graham, [14] similarly evaluated fasting *plasma* glucose in thirty one (31) children aged < 5 years, following a fasting duration of 6-17hrs. The mean fasting plasma glucose of his study population was 4.7mmol.l^{-1} (85.3mg/dl). The plasma samples were collected post-induction and analysed by glucose oxidase method. Graham had used 2.8mmol.l^{-1} (50.82mg/dl) as cut-off for hypoglycaemia and reported 0% incidence of hypoglycaemia. He found no correlation between fasting duration and fasting plasma glucose. (Spearman's rank correlation coefficient = 0.07, p< 0.5).

In another series of one hundred and twenty eight (128) children aged 0.5 – 9 years, Jensen and co-workers, [15] reported only one case of hypoglycaemia (0.8% incidence). Their samples were analyzed by O-toluidine method and their hypoglycaemia cut-off was 2.2mmol.l^{-1} (40mg/dl). Spearman's rank correlation coefficient showed no correlation between duration of fasting and blood glucose levels. The O-toluidine method of blood glucose estimation is a chemical method which is sensitive to aldohexoses such as glucose, galactose and mannose; hence is not very specific for glucose.

Another factor that has been cited as contributing to disparate values reported by several researchers is the influence of overnight as against daytime fasting. Redfern et al.[16] compared the fasting glucose of venous blood of twenty six (26) overnight fasted and twenty eight (28) daytime fasted children, and found the latter to have a significantly lower mean glucose level, even with a shorter mean fasting duration. There was no hypoglycaemia in either group (0% incidence). Their hypoglycaemia cut-off point was however very low; 2.2 mmol.l^{-1} (40mg/dl). In their series were patients with FBG of 3mmol.l^{-1} (54.5mg/dl) yet were not regarded as hypoglycaemic. The glucogenic effect of cortisol which is high in the morning is thought to be responsible for this phenomenon.

The high incidence of fasting hypoglycaemia (29%) reported by Thomas [4] has been generally doubted, as a similar study by Graham [14] in the same institution reported 0% incidence. Thomas had reported a mean FBG of 2.9mmol.l^{-1} (52.6mg/dl) in a series of sixty two (62) patients aged 2-14 yrs who were fasted for between 4-10 hrs. The high incidence of hypoglycaemia was actually found by Graham [14] in 5 of 18 fasted children in a subgroup consisting of children less than 47 months of age. None of the other children in his study older than 47 months had fasting hypoglycaemia, suggesting a relationship between very young age and development of fasting hypoglycaemia.

Earlier study by ffoulkes-Crabbe and Johnson [5] on 28 Nigerian children aged 2 months to 15 yrs, the mean FBG following a fast of 8.15–19 hrs was 62mg.dl^{-1} (3.42mmol.l^{-1}), (range: 27 – 85mg/dl).The subjects in the very young subgroup; 2 months – 2yrs had a significantly lower mean FBG: 54.2mgdl^{-1} (2.99 mmol.l^{-1}), (range: 27 – 62mg.dl^{-1}) than the older groups of 4 – 9yrs and 10 – 15yrs which have similar mean FBG. The two (2) children in their study (7%) who had hypoglycaemia with FBG values of 25mg.dl^{-1} (1.38 mmol.l^{-1}) and 42mg.dl^{-1} (2.31 mmol.l^{-1}) were located in the subgroup of 2months – 2yrs. Their hypoglycaemic cut-off was 45mg.dl^{-1} (2.48mmol.l^{-1}) and the *venous blood* sample of the subjects were analysed by Asatoor and King's modification of the Folin- Wu's reduction method of blood glucose estimation. They also found no correlation between the duration of fasting and FBG of the subjects. Participation of some very young infants in their study may partly account for the comparatively low mean FBG of the series.

Unlike this study, most studies on FBG had utilized *venous blood* samples which were analysed after indeterminate periods following collection in fluoride oxalate, heparin or EDTA – containing bottles in the belief that these agents prevent degradation of glucose in the sample. Shi et al [17] have noted further degradation of glucose in fluoride oxalate - containing whole blood thus advocating rapid separation of the blood pending glucose determination. There is also evidence that even the separated samples with various anticoagulants are not spared glucose deterioration over time. A recent study by Nwangwu and colleagues [18] comparing separated samples containing different anticoagulants (fluoride oxalate, EDTA and heparin) showed that at 30mins glucose is stable in fluoride oxalate; at 60mins there is increased glucose in all three samples; at

120mins there is decreased glucose in all three samples, with decrease of 16.4 % and 10.6 % in fluoride oxalate- containing samples of non-diabetic and diabetic subjects respectively.

It might interest us to know that in the health facility where the present study was carried out, the clinical chemistry laboratory estimates fasting glucose by three (3) different methods; (a) glucose oxidase method using glucose meter on *venous whole blood* collected in fluoride oxalate bottle, (b) glucose oxidase method using reagent solutions on separated *venous plasma*, or (c) copper reduction method using the non-specific reducing property of glucose on *venous whole blood*. In the glucose oxidase method using reagent solution, their glucose value is read using either colorimeter or spectrophotometer. The attendant implications of these variations are all too obvious and reflect the wider practice across frontiers.

CONCLUSION

From our study, we infer that actual hypoglycaemia during preoperative fasting is rare after infancy; even in patients inadvertently fasted beyond standard fasting guidelines.

It is highly probable that variability in definition of hypoglycaemia, sample type (whole blood *versus* plasma, capillary blood *versus* venous blood), method of analysis and recruitment of very young and underweight infants in some studies may account for the disparity in reported incidence of hypoglycaemia posted by authors of previous works.

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