CONTINUOUS GLUCOSE MONITORING SYSTEM VERSUS SELF-MONITORING BLOOD GLUCOSE IN TYPE 1 DIABETES CHILDREN (RoSEC): A RANDOMIZED CONTROLLED TRIAL

DR MUHD ALWI MUHD HELMI

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE (PAEDIATRICS)

UNIVERSITI SAINS MALAYSIA

2020

CHAPTER 1:

THE PRELIMINARIES

THE TITLE PAGE

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ACKNOWLEDGEMENT

I want to acknowledge the Malaysia Endocrine and Metabolic Society for the grant provided. I want to thank Dr. Amiro Mohd Radzi, Dr. Nurshafinaz Mohd Fezal, Mrs. Wan Saleha, and Mrs. Nik Salmiah, our research assistants. To Mrs. Nurul Azurah Mohd Roni and Mrs. Noraida Hasssan, the two librarians of University Sains Malaysia have assisted me in referencing steps using endnote and literature searching. Dr. Nor Rosidah and Dr. Siti Azrin for assistance in preparing the research proposal. Mr. Faris, our department officer who has, helps in the purchase of the CGMS device. Lastly, to Miss Zulaikha, HUSM biostatistics student in her assistance on the statistical analysis of data and preparation of the research proposal.

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LIST OF ABBREBIATION AND NOMENCLATURE

ANOVA	Analysis of variance
ANZCTR	Australia New Zealand Clinical Trial Registry
AUC	Area under the curve
B40	Bottom 40% of the population
BMI	Body Mass Index
BSL	Blood sugar level
CGMS	Continuous glucose monitoring system
CI	Confidence interval
DM	Diabetes Mellitus
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HE/wk	Hypoglycemic episodes per week
IQR	Interquartile range
M40	Middle 40% of the population
RoSEC	Research on safety and efficacy of CGMS
SD	Standard deviation
SMBG	Self-monitoring blood glucose

T1DM	Type 1 diabetes mellitus
T20	Top 20% of the population
T2DM	Type 2 diabetes mellitus
TIR	Time in range
TIT	Time in target range
USM	Universiti Sains Malaysia

ABSTRAK

Latar belakang

Uji kaji rawak secara selari di satu pusat tunggal ini dijalankan ke atas dua pulud dua pesakit Kencing Manis Jenis Satu (T1DM) dengan purata umur 14 tahun. Peserta dibahagikan kepada dua kumpulan, kawalan dan intervensi.

Objektif

Objektif ujikaji ini adalah membandingkan kawalan glicemik dan kekerapan episod hipoglicemia antara Sistem Pemantauan Gula Berterusan (CGMS) dan Pemantauan Gula Sendiri Berkala (SMBG) dalam kalangan kanak-kanak yang menghidap Kencing Manis Jenis 1 (T1DM).

Intervensi

Setiap peserta memakai alat CGMS pada permulaan ujikaji. Dos insulin kumpulan intervensi (n=11) ditentukan berdasarkan maklumat daripada alat CGMS manakala kumpulan kawalan (n=11) berdasarkan maklumat daripada data SMBG. Bacaan gula (BSL) purata dalam sebulan dan purata bilangan episod hipoglicemia dalam seminggu (HE/wk) setiap bulan diukur pada permulaan, bulan pertama, kedua dan ketiga. HbA1c diukur pada permulaan dan pada bulan ketiga kajian.

Dapatan

Ciri-ciri asal peserta dalam setiap kumpulan adalah sepadan. Segala data dianalisis menggunakan kaedaah Analisis Variasi Berulang (ANOVA). Beza purata HbA1c dalam kumpulan adalah tidak ketara, p=0.322. Terdapat perbezaan ketara dalam purata bulanan episod hipoglicemia mingguan dalam kumpulan dan di antara kumpulan, p=0.004, dan p=0.037.

Konklusi

Dalam mengoptimakan kawalan glicemik, CGMS dan SMBG adalah setara, namun CGMS lebih berkesan dalam mencegah hipoglicemia.

ABSTRACT

CONTINUOUS GLUCOSE MONITORING SYSTEM VERSUS SELF-MONITORING BLOOD GLUCOSE IN TYPE 1 DIABETES CHILDREN (RoSEC): A RANDOMIZED CONTROLLED TRIAL

Background

A single centre, randomized, parallel-group controlled trial was conducted involving twenty-two type one Diabetes Mellitus (T1DM) patients with the mean age of 13.8 years assigned to either intervention or control group.

Objectives

The primary and secondary objectives were to compare the glycaemic control and frequency of hypoglycaemia between Continuous Glucose Monitoring System (CGMS) and Self-Monitoring Blood Glucose (SMBG).

Intervention

All respondents wore the CGMS device at the beginning of the study. Intervention group (n=11) had their insulin adjusted based on the CGMS data, while the control group (n=11) were based on SMBG. Monthly average blood sugar level (BSL) and monthly mean hypoglycemic events per week (HE/wk) were measured at baseline, first month, the second month, and third month. HbA1c levels were measured at baseline and in the third month.

Results

The baseline characteristics were similar. The data were analysed using repeated measure analysis of variance (ANOVA). The mean difference of HbA1c within the group was not statistically significant with p=0.322. There were significant differences in the monthly mean HE/wk within and between groups, p=0.004, and p=0.037.

Conclusion

In conclusion, CGMS is equivalent to SMBG in optimising glycaemic control but is more effective in detecting hypoglycaemia in children.

CHAPTER 2:

THE TEXT

2.1 INTRODUCTION

The incidence of Type 1 Diabetes Mellitus (T1DM) is increasing by 3% annually worldwide[1,2]. T1DM is the most common form of Diabetes Mellitus (DM) and accounts for 74.4% of all diabetic children and adolescents in Malaysia. T1DM is associated with various neurological and cardiovascular complications[1,3]. It has a seven times higher risk of death from coronary heart disease compared to the normal population and two times more than in Type 2 Diabetes Mellitus[4]. A good glycaemic control reduced the risk of neuropathy and a more than 50% reduction in the early stages of microvascular complications such as retinopathy and nephropathy in patients with T1DM[5]. Few factors could affect glycaemic control among children and adolescents with T1DM. These include age[6], BMI, high daily basal insulin dose[1,7], duration of diabetes[8-10], compliance to blood glucose monitoring and insulin regimen[11-13], types of insulin, and quality of life[14,15].

In Malaysia, more than 50% of T1DM patients age less than twenty years old have poor glycaemic control with HbA1c of more than 10.0%[1]. Managing adolescents with T1DM is a great challenge to clinicians and family members. Adolescents, in general, have poorer glycaemic control and more severe hypoglycaemic events compared to children and adults[16]. This poor control is because they have poorer adherence to dietary restriction, treatment plan, and glucose monitoring associated with various psychosocial factors such as fear of social rejection from peers, risk-taking behaviour, affective disorders such as anxiety and depression, and burnout[1,2,16]. This problem had drawn a lot of attention from various stakeholders to come out with better, more convenient, and

affordable forms of blood sugar monitoring and methods to administer insulin to overcome some of the known limitations in the management of T1DM.

Good metabolic control can be achieved with intensive therapy and more frequent monitoring of blood glucose[4,9,14]. Self-monitoring blood glucose (SMBG) has been the conventional means of blood glucose monitoring at home. However, SMBG only provides intermittent readings of glucose level without giving a whole 24-hour-picture of glucose variability. Alternatively, the Continuous Glucose Monitoring System (CGMS) was introduced in the early year 2000. CGMS measures subcutaneous interstitial fluid glucose every few minutes for a few days[17]. It offers the potential to optimize glycaemic control as well as to detect subclinical hypoglycaemic events. CGMS device can be integrated with an insulin pump to analyse and fine-tune the dose of insulin in either real-time or retrospective more accurately[18].

In 2001, Chase et al in a randomized clinical trial involving small number of children with type 1 DM (n=11), all on intensive insulin therapy with HbA1c value of more than 8.0% concluded that CGMS able to significantly reduced HbA1c without increasing hypoglycaemic events with the mean ± SD reduction in HbA1c of 0.36% ± 0.07% ($p<0.01$)[16] In another study involving 28 Italian type 1 DM children with poor glycemic control, Silvana et al found that after 3 month and 6 month of using CGMS, HbA1c level reduced significantly compared to baseline HbA1c with p-value of 0.05 and 0.032 respectively. The HbA1c level reduced significantly even among patient with poor compliant[17]. Similar finding was reported in a cross-over randomized controlled trial of 27 diabetic patient aged 5-19 years, patients were randomised to two groups, namely an open and blind arm. In the open arm group, the continuous data (CGMS) was used to

guide the insulin adjustment, whilst in the blind arm, CGMS data were kept to investigator. After 3 months, the study arms were crossed over. HbA1c decreased significantly in the open arm from 7.70% to 7.31% (p = 0.013)[18].

In a randomized, controlled, multicentre study of 120 children and adults comparing continuous glucose monitoring (n = 62) to conventional home monitoring blood glucose level (n = 58), HbA1c level at 26 weeks post intervention, was lower in the continuous group than in the control group with a difference of -0.27%; 95% CI -0,47 to-0.07; p = 0.008. Battelino et al in the same study also found that total duration per day of hypoglycemia, glucose level less than 63 mg/dL, was significantly shorter in the continuous glucose monitoring group (ratio of means 0.49 [95% CI 0.26–0.76], P = 0.03) Time spent in hypoglycemia below 70 mg/dL and below 55 mg/dL was significantly shorter in the continuous glucose monitoring group (P = 0.01 and P = 0.05 respectively)[19].

However, some studies unable to demonstrate the effectiveness of CGMS in improving glycemic control. For example, Yates et al concluded from a randomized control trial conducted among well control type 1 DM Australian children less than 18 years (HbA1c <10%), CGMS has no added value in improving glycemic control compared to intermittent finger-prick SMBG together with frequent outpatient reviews. [0.4% (95% CI 0.7 to 0.1)] vs [0.4% (95% CI 0.8 to 0.2)][20]. Besides that, Yates et al found that each 1% reduction in HbA1c among CGMS group was associated with 7% increase in period of hypoglycemia (R^2 0.22, P 0.06) and an 18% increase in the percentage of nocturnal hypoglycaemia (R^2 0.2, P 0.08)[20]. In the latest Cochrane meta-analysis in 2012, five randomized control trials of mixed design – parallel and crossover design, that involved T1DM children randomized into either retrospective CGMS or SMBG were analysed [21]. Respondents in the intervention group wore CGMS device for three consecutive days

multiple times throughout the study period. HbA1c were taken at baseline and post intervention [8,14,18,22]. There was no significant difference in the changes of mean HbA1c between the CGMS and SMBG users in all of the studies.

This **RoSEC** (Research on Safety and Efficacy of Continuous Glucose Monitoring System) trial aims to determine whether the use of data from retrospective CGMS to fine-tune insulin dosage would result in better HbA1c and average BSL per month without increasing the frequency of hypoglycemia.

2.2 STUDY PROTOCOL

Dissertation Proposal

School of Medical Sciences, Universiti Sains Malaysia

Prepared in Partial Fulfillment of the Requirements for the Degree of
Masters of Medicine (Pediatrics)
2016/2020

CONTINUOUS SUBCUTANEOUS GLUCOSE MONITORING VERSUS SELF-MONITORING BLOOD GLUCOSE IN PAEDIATRIC PATIENTS WITH TYPE 1 DIABETES (RoSEC): A RANDOMIZED CONTROLLED TRIAL

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Dissertation Research Proposal

TITLE: CONTINUOUS SUBCUTANEOUS GLUCOSE MONITORING IMPROVED GLYCAEMIC CONTROL AND REDUCE RATE OF HYPOGLYCEMIA IN PAEDIATRIC PATIENTS WITH TYPE 1 DIABETES IN HUSM KUBANG KERIAN, KELANTAN: A RANDOMIZED CONTROLLED TRIALS

1. INTRODUCTION

1.1 Background

Type 1 Diabetes is the most common type of diabetes among children and adolescents and the incidence is increasing by 3% per year worldwide[2,23]. Of the estimated 500,000 cases of type 1 diabetic children worldwide, 29% are from the South-East Asian region and 26% from the Western Pacific region[24]. In Malaysia, it has been estimated that Type 1 Diabetes accounts for 74.4% of children and adolescents[1].

T1DM is associated with various complications including retinopathy, nephropathy, neuropathy and cardiovascular morbidity. In fact, T1DM is 7 times more risk for developing coronary heart disease compared to normal population and 2 times more than in T2DM[3]. In Malaysia, commonly reported complication was microalbuminuria in 8.5%, nephropathy (3.6%), retinopathy in 3.2% and neuropathy in 1.0% of patient[1]. Risk factors for microangiopathic complications include poor glycemic control, duration of diabetes, family history of complications, onset of puberty, smoking,

hyperlipidemia and hypertension[2]. Diabetes Control and Complications Trial (DCCT) has demonstrated that a good glycemic control resulted in reduction of neuropathy and more than 50% reduction in the early stages of microvascular complications such as retinopathy and nephropathy in T1DM[4]. DCCT also concludes that with every 10% reduction of hba1c, 44% reduction of risk of diabetic complication will be achieved.

Adolescent in general has poorer glycemic control and more severe hypoglycemic episodes compared to children and adult[1,2]. Unfortunately, in Malaysia, more than 50% of T1DM patients < 20 years of age had poor metabolic control with HbA1c > 10.0%[1]. Self-monitoring blood glucose (SMBG) has been a known tool to provide an immediate documentation of capillary blood glucose level via a glucometer. However, SMBG only delivered intermittent readings of glucose level without giving a whole 24-hour-picture of glucose variability. Alternatively, glucose level can be monitored continuously be reviewed retrospectively or real-time with continuous glucose monitoring system. Frequent monitoring of blood glucose allows average glucose level that correlates well with HbA1c level to be monitored and more intensive therapy given safely[15].

Hypoglycemia is one of the most serious complication of type 1 DM. Hypoglycemia is defined as glucose level of less than 3.6 mmol/L (65 mg/dL). However, a glucose value of <3.9 mmol/L (70 mg/dL) is the cut-off value for intervention[25]. Frequent and severe hypoglycemia can lead to permanent neurological damage and can reduce cognitive function in children[26]. Even though tight glycemic control can prevent microvascular complications, it can lead to increased risk of symptomatic hypoglycemia[14]. Besides that, frequent hypoglycemic episodes can reduce the counter-

regulatory endocrine response and clinical neuroglycopenic symptoms and thus reduce awareness of hypoglycemia[14].

Due to this, a continuous glucose monitoring system (CGMS) was introduced more than 10 years ago which use minimally invasive device to measure continuous subcutaneous interstitial fluid glucose every 1 - 5 minutes in 24 hours[15], CGMS offers the potential to optimize glycaemic control as well as detects subclinical hypoglycemic episodes as it provides a continuous data on variability of blood glucose levels throughout the day which will guide the adjustment of insulin more accurately[14].

1.2 Justification to Conduct the Study

This **RoSEC** (Research on Safety and Efficacy of Continuous Glucose Monitoring System) trial aims to determine whether with the use of data from CGMS to fine tune insulin dosage would result in better glycaemic control without increasing the frequency of hypoglycemia. The recent systematic review, looking at the efficacy and safety of the continuous glucose monitoring system concluded that CGMS can improve glycemic control among type 1 DM adult and children, however half of the study were of poor quality (jaded score <3) with small sample size and short duration of study[27]. Besides that, to date, there is no similar study done in Malaysia or Southeast Asia region to look at the effectiveness of CGMS in improving glycemic control. Furthermore, the sample population of the previous clinical trials have much lower mean HbA1c level compared to children and adolescent with type 1 DM in HUSM based on a preliminary retrospective study on this cohort that found that mean HbA1c among this cohort is much higher (mean 11.0, s.d 2.31)[28,29]. Therefore, with this RCT, we are hoping to improve not only the

glycaemic control but also the rate of hypoglycaemia among our patients by using the data from CGMS to fine tuning the diabetic management.

1.3 Literature Review

In 2001, Chase et al in a randomized clinical trial involving small number of children with type 1 DM (n=11), all on intensive insulin therapy with HbA1c value of more than 8.0% concluded that CGMS able to significantly reduced HbA1c without increasing hypoglycaemic events with the mean ± SD reduction in HbA1c of 0.36% ± 0.07% ($p<0.01$)[16] In another study involving 28 Italian type 1 DM children with poor glycemic control, Silvana et al found that after 3 month and 6 month of using CGMS, HbA1c level reduced significantly compared to baseline HbA1c with p-value of 0.05 and 0.032 respectively. The HbA1c level reduced significantly even among patient with poor compliant[17]. Similar finding was reported in a cross-over randomized controlled trial of 27 diabetic patient aged 5-19 years, patients were randomised to two groups, namely an open and blind arm. In the open arm group, the continuous data (CGMS) was used to guide the insulin adjustment, whilst in the blind arm, CGMS data were kept to investigator. After 3 months, the study arms were crossed over. HbA1c decreased significantly in the open arm from 7.70% to 7.31% ($p = 0.013$)[18].

In a randomized, controlled, multicentre study of 120 children and adults comparing continuous glucose monitoring (n = 62) to conventional home monitoring blood glucose level (n = 58), HbA1c level at 26 weeks post intervention, was lower in the continuous group than in the control group with a difference of -0.27%; 95% CI -0,47 to-0.07; p = 0.008. Battelino et al in the same study also found that total duration per day of hypoglycemia, glucose level less than 63 mg/dL, was significantly shorter in the continuous glucose monitoring group (ratio of means 0.49 [95% CI 0.26–0.76], P = 0.03)

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However, some studies unable to demonstrate the effectiveness of CGMS in improving glycemic control. For example, Yates et al concluded from a randomized control trial conducted among well control type 1 DM Australian children less than 18 years (HbA1c <10%), CGMS has no added value in improving glycemic control compared to intermittent finger-prick SMBG together with frequent outpatient reviews. [0.4% (95% CI 0.7 to 0.1)] vs [0.4% (95% CI 0.8 to 0.2)][20]. Besides that, Yates et al found that each 1% reduction in HbA1c among CGMS group was associated with 7% increase in period of hypoglycemia (R^2 0.22, P 0.06) and an 18% increase in the percentage of nocturnal hypoglycaemia (R^2 0.2, P 0.08)[20]. In the latest Cochrane meta-analysis in 2012, five randomized control trials of mixed design – parallel and crossover design, that involved T1DM children randomized into either retrospective CGMS or SMBG were analysed [21]. Respondents in the intervention group wore CGMS device for three consecutive days multiple times throughout the study period. HbA1c were taken at baseline and post intervention [8,14,18,22]. There was no significant difference in the changes of mean HbA1c between the CGMS and SMBG users in all of the studies.

1.4. Research Hypothesis

There is a significant difference in HbA1c and number of hypoglycemic episodes per week when the data of CGMS is used to fine-tune the diabetic management as compared to self-monitoring blood glucose (SMBG)

1.5. General Objective

To determine the efficacy and safety of continuous glucose monitoring system in management of Type 1 Diabetes Mellitus Children

1.6. Specific Objective

1. To compare the glycaemic control between intervention and control group in paediatric T1DM
2. To compare numbers of hypoglycemic episodes per week detected by CGMS compare to detected via SMBG
3. To compare numbers of hypoglycemic episodes per week in the intervention pre and post intervention

2. METHODOLOGY

2.1. Trial Design

A single center, randomized, double-blind, and parallel-group controlled trial with equal randomization (allocation ratio 1:1) conducted at Hospital Universiti Sains Malaysia. Subjects are randomly assigned into one of two arms, the control and intervention arm. The intervention arm is the intervention group while the control arm is the control group. Figure 1 depicts the conceptual framework of this study.

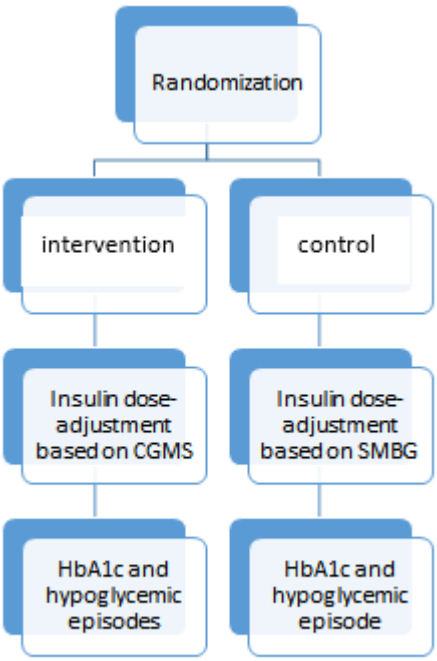


Figure 1: Conceptual Framework

2.2. Eligibility Criteria for Participants

Participants of the study are any patients diagnosed with T1DM and were followed up at HUSM Kubang Kerian, Kelantan.

2.2.1 Inclusion criteria for the study;

a) Age more than 7 years old

b) Diagnosed with T1DM for at least 12 months (to exclude Partial Remission Period)

c) On intensive Regimen which are three or more daily insulin injections

d) Baseline HbA1c > 7.0% or frequent hypoglycemic episodes of >10% of monitoring per week.

2.2.2 Exclusion criteria for the study;

a) Other type of Diabetes namely Type 2 Diabetes, Maturity-onset diabetes in youth
(MODY) and Neonatal Diabetes.

b) Patient on conventional insulin regimen which are one to two times a day injection of self-mixed or premixed insulin

c) Syndromic or dysmorphic patients

2.2.3 Withdrawal criteria

As the completion of the observation needs 3 monthly interval of HbA1c monitoring, any patients who do not turn up for blood taking after 3 months post CGMS and poor SMBG records will be withdrawn from the study.

2.3. Study Area

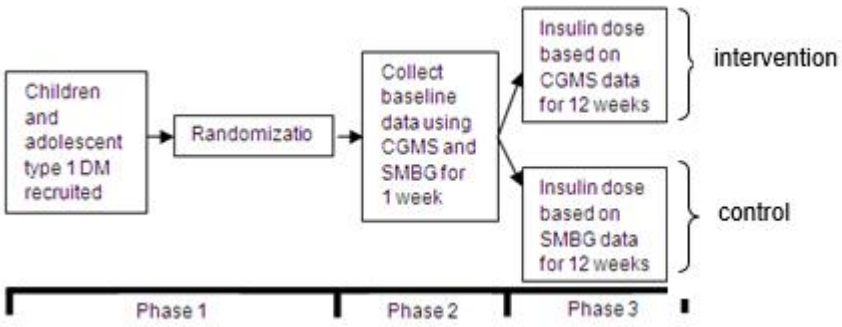
The study was conducted in Paediatric Diabetic Clinic Hospital USM, Kubang Kerian, Kelantan. The hospital is a teaching hospital for University Sains Malaysia and where the Health Campus located. Kubang Kerian is one of the major towns of Kelantan, a state in Malaysia where majority of its population are Malays from different socio-economic background. The paediatric endocrine clinic is the referral centre for paediatric endocrine

services in East Coast Malaysia. Therefore, patients that were followed-up here came from wide geographical area with the distance of travelling reaching 190km.

2.4. Intervention

In the intervention arm, patients will wear CGMS for 1 week at the beginning of the study on top of their usual 4 times per day pre-prandial self-glucose monitoring. After 1 week, the device will be removed and the data will be downloaded and analyzed. Endocrinologist will adjust the dose of insulin to be injected by patient for the next 3 month based on the data. Throughout the whole 12 weeks period, patients will continue their usual pre-prandial capillary blood glucose monitoring 4 times per day. HbA1c will be measured at baseline and at end of week12 while frequency of hypoglycemic episodes based on patient SMBG at week 1 and at week 12 will be obtained.

In the control arm, patients will also wear CGMS for 1 week at the beginning of the study on top of their usual 4 times per day pre-prandial self-glucose monitoring. After 1 week, the device will be removed and the data will be downloaded but kept stored without being analyzed. Endocrinologist will adjust the dose of insulin to be injected by patient for the next 3 month solely based on the recording of their pre-prandial capillary blood glucose monitoring. Throughout the whole 12 weeks period, patients will continue their usual pre-prandial capillary blood glucose monitoring 4 times per day. HbA1c will be measured at baseline and at end of week12. On top of that, mean SMBG per month at 1,2 and 3 month post insulin adjustment will be calculated based on patient daily SMBG. Average weekly hypoglycemic episode at month 1, 2 and 3 post insulin adjustment will also be calculated from SMBG monitoring. Detailed description of the intervention is described in figure 2.



Study Visit
Phase 0 (Enrolment)
Visit 0: Informed consent, baseline HbA1c measurement, clinical history review applicable inclusion and exclusion criteria, obtain consent
Randomization into intervention and control arm

Phase 1 (Baseline evaluation)
Visit 1: Sometime after visit 0 patients will come for CGM device placement
Patient will use CGM for 1 week to obtain baseline data and to evaluate compliance with using CGM.
Patient in control arm will be wearing the CGM for 1 week but will be blinded.
Visit 2: CGM will be removed after 1 week
The data will be downloaded and analyzed for patient in intervention arm while downloaded and stored in control arm.
Insulin dose for the next 12 weeks will be decided by endocrinologist based on CGMS data in intervention arm while based on SMBG data in the control arm

Phase 2 (Follow-up)
Visit 3: All patients will continue the insulin dose decided during visit 2 while continue pre-prandial SMBG 4 times per day.
Compliance to insulin and SMBG and general condition of patient including episodes of hypoglycemia will be reviewed.
Patient will receive regular phone call to ensure compliance to insulin dose and SMBG and to ask general condition of patient.
Visit 4: Patient will be reviewed in clinic after 3 months. Mean glucose level and average number of hypoglycemia episode per week on month 1,2 and 3 post insulin adjustment will be calculated.
HbA1c will be measured at the end of week 12
Data collection period ended.

Figure 2: RoSEC Study Design

2.5. Outcomes

The primary outcome of the study is HbA1c level. HbA1c will be measured 2 times, at the beginning of the study period (baseline) and at the end of week 12. The mean HbA1c value pre and post-intervention at 3 months within the group will be compared. This is to determine the effectiveness of both CGMS and SMBG. Comparison of mean HbA1c

between the arms post-intervention will determine the significance of CGMS compared to SMBG in improving glycemic control of patients.

Secondary outcomes are the mean frequency of hypoglycemic episodes per week and mean glucose level per month at month 1, 2 and 3 post insulin adjustment. Hypoglycemia is defined as glucose level of less 3.9 mmol/L detected and recorded by patient using SMBG. These will be used to determine the efficacy and safety of CGMS.

2.6. Sample Size

Changes in glycemic control (HbA1c) within group pre and post intervention is the primary outcome of RoSEC. Sample size was estimated using sample size formula[30]:

$$\mathbf{n = 2 + C\ (s/d)^2}$$

where n is the sample size, s is the population standard deviation and d is the difference of mean to be detected. C is a constant based on α and 1- β,

1- β / α	0.05	0.01
0.8	7.85	11.68
0.9	10.51	14.88

In a previous study, within group mean difference of HbA1c has standard deviation 1.1[31] If the mean difference to be detected based on expert views is 1. We will need to study 20 subjects to be able to reject the null hypothesis that the mean within groups pre and post intervention are equal, with the power of study 0.80. The Type 1 error probability associated with the test of this null hypothesis is 0.05. Taking into accounts no drop rate, total sample size required is 22.

2.7. Research Tools

Continuous glucose monitoring device used is Medtronic iPro2 Professional CGM device with enlite sensor. The device safety and efficacy has been established and was approved by FDA. Glucose value are not displayed to patient and has to be downloaded into the CGMs software and retrospectively evaluated during device removal. Intermittent capillary prick glucose monitoring was standardized using accu-chek performa glucometer with accu-chek performa test strips. Results appear in 5 seconds. It is convenient and easy to use with high accuracy. The device will be used by patient to monitor pre-prandial glucose level and to calibrate the CGMS device daily. HbA1c is measured using ion exchange high performance liquid chromatography technique at HUSM endocrine lab. The machine is calibrated every 2 weekly. The machine runs in batches every 2 to 3 days where the results will be available from the online lab results application accessible only to clinicians. CGMS will be downloaded using online software Medtronic CareLinkiPro Software that requires username and password to sign in. the data will be stored online and can be access through any computer with internet network.

3. RANDOMISATION

3.1. Sequence Generation

No sampling was done in this study. All type 1 diabetes mellitus children and adolescent more than 7 years old that were diagnosed with T1DM attending follow up under HUSM that fulfilled the inclusion and exclusion criteria are included in the study. Stratified randomization method is used to ensure similar number of patient on insulin pump and on self-injection in both groups. The random allocation sequence will be generated using website https://www.randomizer.org/. Two allocation sequences will be generated by the website. Each sequence will either be the control or intervention group. Random allocation of respondents in this study is presented in figure 3.

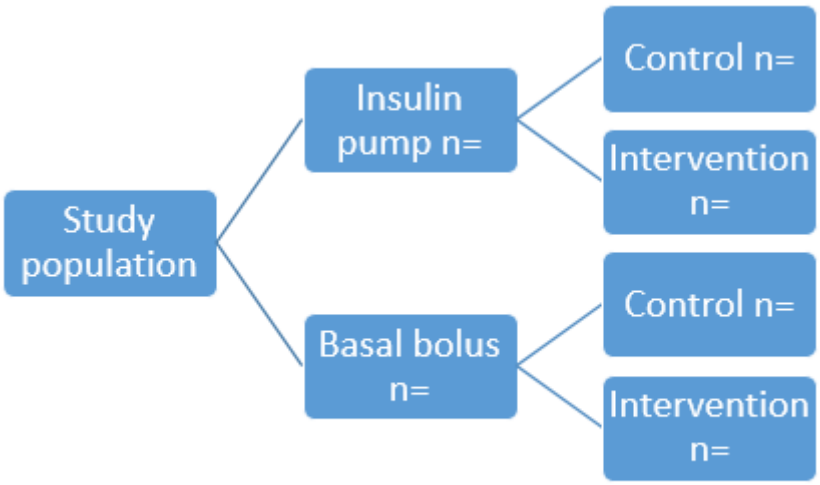


Figure 3: Random Allocation of Subjects

3.2 Allocation Concealment Mechanism and Implementation

The allocation procedure will be done by a dedicated research assistant not involved in the data collection and analysis. Interventionist (endocrinologist) and data collector will not involve in the allocation procedure. Patients will have to choose sealed opaque

envelope containing random numbers that is part of the allocation sequence during pre-study clinic visit. The chosen envelope will be kept in a dedicated drawer. The research assistant will open the envelope, identify the number chosen and the group allocation on different setting and time in the absent of patient and endocrinologist. The allocation will be made known only to the clinicians involved in the study. Patients will not be informed the number and the group allocation.

3.3 Blinding

Some parties involved in this research will be kept blinded throughout the study period. Patients will be kept blinded on the arm they are in, the CGMS data and the HbA1c. Research Assistants who helps in downloading the CGMS data will be made blind on the identity of the patient and the arm they are in. Patient will be anonymous and only be identified by the allocation number. Clinic nurses will not be told the participation of subjects into the trial and the CGMS and SMBG data will be kept blind from them. Other clinicians besides the interventionist and data collectors will be blinded form the CGMS data and outcomes. The lab technician who runs the HbA1c test will be kept blind on patients' participation into the study. All patients in both arms will be blinded and undergo the same procedure and investigation. Therefore, all patients will be given the same instruction and briefing at the beginning of the study. Patient will be identified with a research number throughout the study.

3.4 Statistical Methods

Data will be entered and analysed using SPSS version 24. The demographic and numerical data were presented by mean (SD) and median (IQR) according to data distribution. The categorical data were expressed as number and percentage. Repeated

measure ANCOVA will be used to determine the significance of the mean HbA1c difference between groups, within groups and between-within groups. From literatures, factors affecting glycemic control include age, BMI, daily basal insulin dose, duration of diabetes, type of insulin delivery, type of insulin. The number of hypoglycemia is presented in discrete numerical data and the mean difference between pre and post intervention in the intervention group will be analyzed using paired t-test if the outcome variable is normally distributed or using Wilcoxon Signed-Ranks test using median difference if the data is non-parametric. The mean difference between number of hypoglycemia per week detected by CGMS and SMBG will be compared using paired t-test using Wilcoxon Signed-Ranks test using median difference if the data is non-parametric.

4. RESULTS

4.1. Data Collection Method

Data will be collected from online pathology laboratory results, from the CGMS analysis software and patient's own blood glucose monitoring record and will be documented in a data collection form. Then, all data will be entered into SPSS software anonymously. Only research researchers can access the data to ensure privacy and confidentiality. Data will be presented as grouped data and will not identify individual subject.

4.2. Baseline Data

Table 1: Baseline Demographic and Clinical Characteristic for Each Group

Characteristic	**Intervention (n=11)**	**Control (n=11)**	**p-value**
Age (years)			
Male			
Female			
Malay			
Chinese			
Others			
Height (cm)			
Underweight			
Normal			
Obese			
Weight (kg)			
BMI (kg/m²)			
BP			
Tanner Staging			
Pre-pubertal			
Post-pubertal			
Duration of DM (months)			
Insulin Treatment:			
No of Injection/day			
Types of insulin			
Analog			