Super Bolus – A Remedy for A High Glycemic Index Meal in Children With Type 1 Diabetes on Insulin Pump Therapy?: Study Protocol for a Randomised Controlled Trial.

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Study protocol

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Super Bolus – a remedy for a high glycemic index meal in children with type 1 diabetes on insulin pump therapy?: study protocol for a randomised controlled trial.

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KEY WORDS: Super Bolus, high glycemic index, postprandial hyperglycemia

ABSTRACT

Background:

Postprandial hyperglycemia (PPH) is common clinical problem among patients with type 1 diabetes (T1D), especially in relation to high glycemic index (h-GI) meals. The main problem are high, sharp glycemic spikes with following hypoglycemia after h-GI meal consumption. There is lack of effective and satisfactory solutions concerning insulin dose adjustment to cover the h-GI meal. The goal of this research is to find out whether a Super Bolus is an effective strategy to prevent postprandial hyperglycemia and late hypoglycemia after h-GI meal in comparison to the normal bolus.

Methods:

A total of 72 children aged 10-18 years with T1D for at least 1 year, treated with continuous subcutaneous insulin infusion for more than 3 months will be enrolled in a double-blind, randomized, cross-over clinical trial. Participants will receive the prandial insulin bolus for h-GI breakfast in the form of Super Bolus and as Normal Bolus another day. The primary outcome measure will be the glucose level 90 minutes after administration the prandial bolus. The secondary endpoints will refer to glucose level 30, 60, 120, 150, 180 minutes postprandially; the area under the blood glucose curve within 180 min postprandially; the peak glucose and time to peak glucose level; the glycemic rise, mean amplitude of glycemic excursion, time in postprandial glucose range and the number of hypoglycemia episodes.

Discussion: There is a lack of clinical studies concerning this kind of bolus. Available literature refers only to in-silico studies and case reports. The Super Bolus was defined as a prandial insulin dose increased by 50% in comparison to the dose calculated based on individualized patient's Insulin-Carbohydrate Ratio (ICR) and simultaneous suspension of the basal insulin for 2 hours. The comprehensive and effective solution to this frequent clinical difficulty of PPH after h-GI meals has not been found yet. The problem is known and important but the presented solution innovatory and easy to apply in every-day life.

Trial registration:

The trial was registered at the ClinicalTrials.gov prior to the inclusion of the first patient, 15 July 2019 on registration number: NCT04019821.

BACKGROUND

Many medical reports and our clinical practice indicate that postprandial hyperglycemia (PPH) is the everyday struggle for people with type 1 diabetes mellitus (T1D) even when the metabolic control seems to be adequate based on HbA1c level. The definition of PPH is not clear and reproducible. American Diabetes Association (ADA) did not differentiate postmeal norms, National Institute for Health and Care Excellence (NICE) established them at the level above 162mg/dl (9mmol/L), whereas International Society for Pediatric and Adolescent Diabetes (ISPAD) above 180mg/dl (10 mmol/L).¹

Glycemic peak is an often consequence after the ingestion of a carbohydrate-rich meal.² To achieve the post meal glycemic targets carbohydrates (CHO) counting seems to be a crucial factor.³⁻⁶ A single mealtime insulin dose will cover a range in carbohydrate amounts and the insulin dose calculated for meal contains 60g CHO covers the 10g variations in CHO quantity (50-70g).⁷ Interestingly, the postprandial glycemic peak raises with increasing carbohydrate intake in the range between 20-80 grams of carbohydrates, but meals contain over 80 grams do not cause a greater glycemic peak, but prolonged hyperglycemia.^{8,9} PPH is most often preceded by h-GI meals, what caused great glycemic variability and lead to fast glycemic increase followed by a rapid decline of glucose level.¹⁰⁻¹⁴ The area under the blood glucose curve (AUC) is 20% larger after the h-GI meal containing the same amount of carbohydrates as the low glycemic index (l-GI).¹³ It was also proved that in T1D patients, carbohydrate-based meals cause blood glucose peak typically within 60–90 minutes with individual variation.^{10,11,15} PPH as well as rapid and large glycemic fluctuations are adverse prognostic factors and are implicated in the development of cardio-vascular complications, enhancement of oxidative stress, retinopathy and certain type of cancers.^{5,16} Furthermore, among teenagers (10-16years) the correlation between poor glycemic control and negative psychological outcomes as depressive symptoms was reported.¹⁷ In the interest of good glycemic control patients with T1D should consume l-GI products, but this recommendation is rarely followed, especially in pediatric population.^{18,19}

One of the most important goal of T1D treatment is to imitate as closely as possible the physiological insulin secretion and thereby keep blood glucose level within the normal range. Over the last few years, the idea of Super Bolus which potentially could solve the h-GI meals' problem is observed and some patients practice them in every-day life. This kind of bolus is not clearly and unequivocally defined. The general establishment of this bolus relate to removing basal and boosting prandial insulin.²⁰ The most often Super Bolus is described as the amount of insulin calculated based on patient's own ICR increased about 50-60% with simultaneous

suspension or decrease of the basal insulin. The decrement in basal infusion should avoid late postabsorptive hypoglycemia. There is a lack of clinical studies concerning this kind of bolus. Available literature refers only to in-silico studies and clinical practice.^{20,21} The comprehensive and effective solution to the clinical problem presented above, which is important and frequent, especially in the pediatric population has not been established yet.

TRIAL OBJECTIVES AND HYPOTHESIS

The aim of this study is to determine whether Super Bolus is more effective than Normal Bolus in preventing postprandial hyperglycemia and avoiding late hypoglycemia after h-GI meal in children with T1D treated with continuous subcutaneous insulin infusion.

METHODS AND ANALYSIS

Trial design

This study is designed as a randomized, double-blind, cross-over study. The trial was registered at the ClinicalTrials.gov (NCT04019821) prior to the inclusion of the first patient. Any important changes in the protocol will be implemented there.

Study settings and participants

Participants will be recruited among the patients of the Department of Pediatric Diabetology and Pediatrics at Pediatric Teaching Clinical Hospital, Medical University of Warsaw, Poland. In case of a low recruitment rate, Diabetic Outpatient Clinic, Pediatric Teaching Clinical Hospital, Medical University of Warsaw, Poland would also be reliable source of participants. The hospital is tertiary referral center and provides medical care for more than 1000 children with T1D. The medical staff is adequately trained and competent in conducting clinical trials. The research will be conducted in accordance with the ethical standards and with the Helsinki Declaration of 1964, as revised in 2013. In case of any changes, appropriate information will be added to the protocol registry site and the bioethics committee will be informed.

Eligibility criteria

Inclusion criteria:

- age between 10 and 18 years,
- T1D as defined by ISPAD Guidelines 2018²² with duration longer than 1 year,
- insulin pump therapy for ≥ 3 months,

- written informed consent to participate in the study signed by parents (and patient older than 16 years).

Exclusion criteria:

- celiac disease,
- diabetes related complications (e.g. nephropathy),
- BMI at or above the 95th percentile and at or below 3rd percentiles for children and teenagers of the same age and sex,
- withdrawal of consent to participate in the study,
- comorbid conditions and treatment which could significantly affect glycemic values in the researchers' opinion.

Intervention

The intervention will be administration the amount of insulin for the h-GI breakfast in a form of Super Bolus. A h-GI breakfast will consist of a breakfast cereal - cornflakes with added cold milk: 50g CHO will come from cornflakes and 10g of CHO from 2% milk (200 ml). Super Bolus will be defined as a prandial insulin dose increased by 50% in comparison to the dose calculated based on individualized patient's ICR and simultaneous suspension of the basal insulin for 2 hours. The definition of Super Bolus was stated based on our patients' best experiences. Normal Bolus will be defined as a prandial insulin dose calculated based on the individual ICR.

Study procedure

The study procedures are described in Table 1. Patients who will meet the study eligibility criteria, will be asked to enter the trial during hospitalization. Patients and their parents will receive oral and written information concerning the study. Verbal consent will be obtained from all participants. If the caregivers agree on participation, written informed consent will be obtained from the legal caregivers and participants older than 16 years gathered by the recruiting physician who is familiar with the study protocol. Prior to the study participants will be hospitalized and qualified into run-in period. It will last around 1 week. During that time the doses of insulin will be adjusted. The nine-point glucose profile will be handled by nurses and based on glucose values ICRs and basal insulin rate will be optimized by diabetologist to meet

target fasting and postprandial glycemia. After achieving glucose targets and adjusting meals' ICRs participants will start the allocation process.

The participants will be randomly divided into two groups: SuBo-NoBo (Super Bolus-Normal Bolus) or NoBo-SuBo (Normal Bolus-Super Bolus). The study will last for 3 consecutive days. On the first day the new infusion set with the reservoir and insulin will be inserted to minimize the chance of any leakages and occlusions to happen. Steel needle sets as long as soft cannulas will be used, depending on subject's choice. There will be no restrictions on set's insertion site, except infected and lipodystrophy areas. The Continuous Glucose Monitoring System (CGM) which will be used consists of the Enlite™ sensor with the MiniLink™ Transmitter and MiniMed® Paradigm VEO™ insulin pump (Medtronic MiniMed, Northridge, California). The proper calibration of the device will be performed. To ease glycemic excursions during the study, participants could perform the last correction insulin bolus and any modifications concerning basal insulin 3 hours before the meal bolus. To avoid asymptomatic nocturnal hypoglycemic episodes the glycemic control during the nights preceding the test meals will be intensified to perform additional blood glucose meter tests (at 12 p.m., 3 a.m., 5 a.m.).

On the second and third day, the test meal will be given as breakfast in the morning. The fasting self-monitoring of blood glucose (SMBG) will be performed by Contour® Plus Link meter with one-step calibration of CGM. If the fasting glucose value will be above 130 mg/dl (>7.2 mmol/L), the study day will be postponed until the next day. The level was established according to ISPAD 2018 Guidelines concerning premeal targets.¹ Premeal insulin will be given 15 minutes before h-GI breakfast consumption as a Super Bolus (group SuBo-NoBo) or Normal Bolus (group NoBo-SuBo) on the second day and the Normal Bolus (group SuBo-NoBo) and Super Bolus (group NoBo-SuBo) on the third day. A 15-minute time interval preceding the breakfast was established in previous studies as optimal based on rapid-acting insulin analogs onset of action.²³ The participants will be used the type of rapid-acting insulin analogs (aspart, lispro, glargine), as applied so far. H-GI breakfast was composed by the clinical dietician and will consist of cornflakes (50g carbohydrates) and 2% milk (10g carbohydrates), aggregated 60g carbohydrates. The test meal: Nestle Cornflakes glycemic index (GI) 81, glycemic load (GL) 40,5 and 2% UHT milk GI 27, GL 2,7.

The calculation of the insulin doses will be performed based on individual ICR counted per 10g carbohydrates. Normal Bolus will be calculated as $6 \times \text{ICR}$ and Super Bolus as $150\% \times 6 \times \text{ICR}$ with suspension of basal insulin for 2 hours after delivered prandial bolus. The CRF contains the protocol for both groups, the personal data and calculations concerning insulin doses will be filled in for both groups the first day. The closed envelope with patient's allocation

will be attached to CRF. The next two days depends on the allocation group, the proper type of bolus will be administered by nurses who will not be involved in the study. To ensure that the study protocols will not mix up and provide blinding at the same time the nurse who will administer the premeal bolus will check the allocation in the envelope and give the appropriate type of bolus. The study duration per one day is planned for 3 hours, during this time no additional meals, snacks or correction boluses will be allowed. Observation time 3 hours was stated as an approximation of the total lasting hypoglycemic effect after a subcutaneous insulin bolus dose. Capillary blood glucose level will be measured by Contour[®] Plus Link Meter: 0, 30, 60, 90, 120, 150, 180 min after insulin administration with simultaneously continuously working glucose monitoring system. There is a great possibility that after h-GI meal rapid glycemic fluctuations will be observed. That is why we decided to check the blood glucose level both CGM and glucometer to obtain the highest accuracy of glycemic level at the specified time point. Caregivers and patients will be instructed to report symptoms of hypoglycemia with an additional glycemia measurement if symptoms occur. Hypoglycemia will be defined as the glucose level below or equal 70 mg/dl (≤ 3.9 mmol/L) stated as clinical hypoglycemia alert, according to ISPAD Guidelines 2018.⁸ If the hypoglycemia occurs, the patient will receive 0.3g/kg of glucose/saccharose. After 15 minutes, the glucose level will be controlled again. If the hypoglycemia persists, the patient will receive the next dose of glucose/saccharose, until glucose levels over 70 mg/dl will be achieved. The presence of hypoglycemia does not suspend the study process, the SMBG will be continued as it was basically established. Records from CGM will be registered using the Medtronic Care Link Pro Software and discussed with patients for educational purposes. Participants could discontinue the trial at any point of time without giving the reason. Researchers will make every effort to supervise, educate and regularly control patients to provide the proper study process.

End points

Primary endpoint:

- capillary blood glucose level 90 minutes after administration of the prandial bolus, because as it was mentioned above in T1D patients meals with h-GI cause blood glucose level peak typically within 60–90 minutes.^{10,11,15}

Secondary endpoints:

- capillary blood glucose level 30,60,120,150,180 min after administration of the prandial bolus,
- the number of hypoglycemia episodes based on SMBG.

Based on data from CGM:

- glycemic rise (GR) - a difference between baseline and the maximum glucose value,
- peak glucose level (PG) - the maximum value of glycemia during 3 hours of postmeal time,
- time to PG,
- area under blood glucose curve (AUC),
- mean amplitude of glycemic excursion (MAGE),
- time in postprandial glucose range between 70 to 180 mg/dl (4.0-10.0 mmol/L).

MAGE will be defined as a standard deviation of blood glucose (SDBG) obtained from all blood glucose concentrations within 3 hours of postmeal time.

Participant timeline

The study's time scheme for enrollment, interventions and assessment is presented in Table 1.

Sample size

The sample size was estimated based on calculations by StatsDirect statistical software (V.3.1.4, StatsDirect, Chesire, UK). To show a difference of 30mg/dl (1,7mmol/L) and assuming SD of 41 mg/dl in 90th minute of the study (the primary endpoint) with $\alpha=0.05$ and 80% power, assuming a 20% withdrawal rate, a total of 72 participants will be required. We assumed that glycemia differences between the study groups mentioned above are significant for the metabolic control.

Randomization

The participants will be randomly assigned into two groups either SuBo-NoBo or NoBo-SuBo. The randomization list will be generated by a statistician using the statistical program Stats Direct (V.3.1.4, StatsDirect, Chesire, UK). Blocked randomization (blocks of four) will be used to ensure a good balance of participant characteristics in each group. The randomization list will be kept by a staff member not involved in the trial.

Blinding

All participants and investigators will be blinded throughout the study procedure. The investigator will be given randomly generated treatment allocations within sealed opaque envelopes. Once a patient has consented to enter a trial an envelope will be opened and the allocated treatment regimen will be applied. A nurse not involved in the trial will program the bolus of prandial insulin in compliance with the patient's allocation found in the sealed envelope and calculated dose of insulin. The screen of the insulin pump will be covered by the piece of black tape to avoid patient's interference. After completing the trial by all randomized subjects, sealed envelopes containing the allocation group of each person will be handled to the principal investigator.

Data collection and management

A case report form (CRF) prepared based on The International Conference on Harmonization Guidelines for Good Clinical Practice will be completed on paper form for each participant. Data will be transferred to the electronic, password-protected database. All study data papers will be stored in a locker within the study site available only for staff involved in the research. Data concern insulin requirements, HbA1c values and anthropometric parameters will be gathered from non-compliant participants and those who will cancel the agreement. Only the involved researchers will have access to dataset and participant's personal information. The data will not be shared with any company and founding institutions, they will also not influence the reliable results presentation.

Compliance

Compliance with the study protocol will be evaluate by analyzing information from the CRFs, insulin pump and CGM recorded data. If participants will not follow the study protocol, e.g. receive inappropriate dose of insulin or a wrong type of bolus, give an extra insulin dose, eat snack or basal insulin suspension will not be set if appropriate, they will be considered as a non-compliant.

Monitoring

The study procedure will be performed according to the protocol. We do not intend to change the study protocol after recruiting the first patient. If some circumstances, which influence the research conditions occur, the changes will be noted at ClinicalTrials.gov (the protocol registry

site) and the Bioethics committee will be notified. An independent Data and Safety Monitoring Board (DSMB) will be established before the beginning of the study. The DSMB will review data after recruitment from 25%, 50% and 75% of participants to evaluate the study progress and adverse events.

Statistical analysis

Descriptive statistics will be calculated to characterize and present study population and baseline findings. Data normality distribution will be verified based on Shapiro-Wilk test. For continuous variables normally distributed comparison will be performed by Student's *t*-test. Continuous variables not normally distributed will be compared with Mann–Whitney *U* test. The paired *t*-test or Wilcoxon signed rank test will be used for paired comparisons of clustered data, as appropriate. Groups comparison for nominal variables will be conducted with Fisher exact test or χ^2 test, as appropriate. All tests will be two-tailed, and differences will be considered as significant at the level of *p* value ≤ 0.05 . The number of missing data will be presented for each variable. Outcomes will be presented as differences in medians for continuous data with non-normal distribution and as differences in means for data with normal distribution, both with 95% confidence interval, respectively. Nominal variables will be presented as *n* (% of group).

Data from CBGM and CGM will be analyzed separately. To evaluate capillary blood glucose level 30, 60, 90, 120, 150, 180 min after administration of the prandial bolus and the number of hypoglycemia episodes data from CBGM will be used. Data from CGM will be adopted to calculate GR, PG, time to PG, MAGE, time in postprandial glucose range between 70 to 180 mg/dl (4.0–10.0 mmol/L).

AUC will be calculated geometrically by applying the trapezoid rule. Incremental area under the blood glucose response curve (iAUC) will be defined as the sum of all sensor excursions from the baseline value for the 3-hour post meal period. Positive AUC (pAUC) will be calculated based on intersection points of the estimated curve with baseline and integration of the area above baseline.

Per-protocol analysis as a primary approach will be performed among those who finish the study according to the protocol. Additionally, data of non-compliant participants and those who will cancel the agreement will be used to perform intention-to-treat analysis as a sensitivity analysis.

Harms

During postprandial period the most likely and harmful adverse effect is the presence of hypoglycemia. Intensive glycemic control using both CGM and self-monitoring of blood glucose preserve from severe hypoglycemic events and provide the highest accuracy of glycemic measurements. Although, so many finger pricks to monitor blood glucose could be inconvenient, it is necessary to assure the safety of study procedure. Moreover, CGM related minor local adverse events such as: infection, redness, bleeding, hypersensitivity, itching, irritation or pain at the sensor site can occur. CGM will be applied by the qualified personnel to reduce the risk of complications. Data concerning all harms will be gathered and reported as indicated in the Consolidated Standards of Reporting Trials (CONSORT) extension on harms document.²⁴ Adverse events will be also noted in the individual patient's CRFs.

All serious adverse events will be immediately reported to the project leader who will be responsible for notifying the ethics committee and all participating investigators.

Discussion

It is still challenging to adjust the type and dose of insulin and the kind of insulin bolus for h-GI meals. According to Dzygało et al. neither of insulin analogs: glulisine and aspart provide a stabilized glycemic profile after a h-GI meal.²⁵ The new formulation of insulin- faster aspart with the faster onset of appearance and the greater early exposure in comparison to aspart in children and adolescents comes to use in clinical practice. A statistically significant reduction in 2-hour postprandial glycemia after standardized meal was reported.^{26,27} However, due to regulatory approval and availability the common use in clinical practice is limited. Lujif et al. demonstrated that administration prandial rapid-acting insulin analogs 15 min before a meal compared to 30 min and directly at the start of eating resulted in lower rate of PPH without increased risk of hypoglycemia.²³ That is why we decided to deliver insulin bolus 15 min before meal. O' Connel et al. tested two types of prandial bolus to h-GI meal: normal bolus (given over 3 minutes before meal) vs dual (50:50% over 2 h) and found no differences between them.¹⁰ Regardless of bolus type high glycemic excursions were still observed, with mean glycemic rise +95.4mg/dl from baseline.¹⁰ An additional dose of insulin was also considered as the possible solution for the h-GI meals issue. Groele et al. compared the dose of prandial insulin calculated by individual Insulin-Carbohydrate Ratio (ICR) with the dose increased about 30% for a h-GI meal and concluded that the frequency of postprandial hyperglycemia and hypoglycemia were similar in both groups, but the additional dose of insulin significantly reduced the glucose excursion in terms of mean postprandial glycemia (47.4±39.8 mg/dL vs

76.2±58.2 mg/dL).²⁸ We knew that 30% additional dose of insulin did not cause the higher incidence of hypoglycemia episodes and lead to lower postprandial glycemia, but the incidence of hyperglycemia episodes remains still unsatisfactory. To achieve reduction in frequency of postprandial hyperglycemia, decrement in glycemic rise and hypoglycemia episodes at the same time we decided to conduct this study based on Super Bolus idea. Available literature refers only to in-silico studies and clinical practice.^{20,21} The Super Bolus we defined as a boost of prandial insulin (increased by 50% in comparison to the dose calculated based on individualized patient's Insulin-Carbohydrate Ratio (ICR)) and simultaneous suspension of the basal insulin for 2 hours. During that time the insulin is still acting and 2 hours seem to be not too long for rebound effect. Moreover, our patients notified best experience concerning stated combination.

The comprehensive and effective solution to this huge and frequent clinical difficulty of PPH after h-GI meals has not been found yet. The problem is known and important but the presented solution innovatory and easy to apply in every-day life.

Strengths and limitations of this study:

- *This study is designed in a simple way with the most restricted methodology (randomized controlled trial, RCT).*
- *The findings of this RCT, will contribute to the formulation of further recommendation on the use of the Super Bolus to avoid postprandial hyperglycemia after high glycemic index meal (h-GI) in children with type 1 diabetes.*
- *The limitation of the study is the fact that the influence of the Super Bolus will be researched according to the only one type of h-GI meal, but there could exist some differences between variety of h-GI food.*

Trial status

Recruitment started in January 2020 and is planned to end in July 2021, with all patients randomized. The current protocol version is 2.0, dated 30 August 2020.

List of abbreviations:

PPH: postprandial hyperglycemia

T1D: type 1 diabetes

h-GI: high glycemic index

AUC: area under the blood glucose curve

MAGE: mean amplitude of glycemic excursion
ICR: Insulin-Carbohydrate Ratio
CHO: carbohydrates
SuBo: Super Bolus
NoBo: Normal Bolus
CGM: Continuous Glucose Monitoring System
SMBG: self-monitoring of blood glucose
GI: glycemic index
GL: glycemic load
GR: glycemic rise
PG: peak glucose level
SDBG: standard deviation of blood glucose
CRF: case report form
DSMB: Data and Safety Monitoring Board
iAUC: incremental area under the blood glucose curve
pAUC: positive AUC
CONSORT: the Consolidated Standards of Reporting Trials

Declarations:

Ethics approval and consent to participate:

The trial was approved by the Ethics Committee of the Medical University of Warsaw KB/25/2019. Verbal and written information regarding informed consent will be presented to the caregivers and/or patients. Any modifications of the protocol that may affect the conduct of the study will be presented to the committee.

Consent for publication: Not applicable.

Availability of data and materials: The full protocol will be available freely due to open access publication. The findings of this RCT will be submitted to a peer-reviewed journal. Abstracts will be submitted to relevant national and international conferences. The standards from the guidelines of the Consolidated Standards of Reporting Trials will be followed for this RCT. All investigators will have access to the final trial dataset.

Competing interests: The authors declare that they have no competing interests.

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The funders will have no role in the conception, protocol development, design, or conduct of the study, or in the analysis or interpretation of the data.

Authors' contributions: EK developed the first draft of the manuscript. KD contributed to the development of the study protocol. AS conceptualized the study and approved the final draft of the manuscript.

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