ISPAD-JDRF FELLOWSHIP AWARD PROGRESS REPORT

Title: Super Bolus: a remedy for a high glycemic index meal in children with type 1 diabetes on insulin pump therapy?

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BACKGROUD

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

The glycemic peak is a common consequence of ingesting carbohydrate-rich meals [2]. To achieve the postprandial glycemic target, carbohydrate (CHO) counting can be a crucial factor [3–6]. A single mealtime insulin dose will cover a range of CHO amounts, with the insulin dose calculated for a meal containing 60 g CHO covering 10 g variations in CHO quantity (50–70g) [7]. Interestingly, the postprandial glycemic peak rises with increasing CHO intake in a range of 20–80 g of CHOs, but meals containing over 80 g do not cause a greater glycemic peak and instead cause prolonged hyperglycemia [8, 9]. PPH is most often preceded by high glycemic index (h-GI) meals, which causes great glycemic variability, leading to a fast hyperglycemia increase followed by the rapid decline of glucose levels [10–14]. The area under the blood glucose curve (AUC) is 20% larger after the h-GI meal containing the same amount of CHOs compared to a low glycemic index (l- GI) meal [13]. It was also proved that in T1D patients, CHO-based meals caused an increase in the blood glucose level peak within 60–90 min with variations among individuals [10, 11, 15]. PPH and rapid and large glycemic fluctuations are adverse prognostic factors and are related to the development of cardiovascular complications, enhancement of oxidative stress, retinopathy, and certain types of cancers [5, 16]. Furthermore, a correlation between poor glycemic control and negative psychological outcomes, such as depressive symptoms, has been reported in teenagers (10–16 years) [17]. Although it is indicated that patients with T1D should consume l-GI products, the recommendation is rarely followed, especially in the pediatric population [18, 19]. One of the most important goals of T1D treatment is to imitate physiological insulin secretion as closely as possible, thereby maintaining blood glucose levels within the normal range. Previous studies have shown that early preprandial rapid-acting insulin analog administration up to 15–20 min before a meal resulted in lower postprandial glucose excursions compared to 30 min, taken directly at the start of eating [20, 21]. This strategy resulted in a lower rate of PPH without an increased risk of hypoglycemia. Other strategies, such as an additional dose of insulin, were also considered as a possible solution to the h-GI meal issue. Previous studies showed that a 30% increase in the insulin dose led to lower postprandial glycemia and did not cause a higher incidence of hypoglycemia episodes, but the frequency of hyperglycemia remained high [22].

Over the last few years, the idea of “Super Bolus” as a potential solution to the h-GI meal problem has been observed and practiced by some patients every day. This type of bolus is not clearly and unequivocally defined. The general establishment of a bolus is related to the removal of basal insulin and boosting of prandial insulin [23].

The proposed solution of Super Bolus is a combination of two components:

1.An increased dose of prandial insulin (50%) for the quick coverage of h-GI meals

2.Stopped basal insulin during the following 2–4 h to account for the increased levels of active insulin in circulation after intake of the bolus to prevent hypoglycemia.

There is a lack of clinical studies concerning this type of bolus, and the available literature only refers to in silico studies and clinical practice [23, 24]. A comprehensive and effective solution to this important clinical problem presented above, which is frequent especially in the pediatric population, has not yet been established. This study aimed to determine whether Super Bolus is more effective than Normal Bolus in preventing PPH and avoiding late hypoglycemia after an h-GI meal in children with T1D treated with continuous subcutaneous insulin infusion.

METHODS

Trial design: This study was designed as a randomized, double-blind, crossover study with an allocation ratio of 1:1. The trial was registered at ClinicalTrials.gov (NCT04019821) before the inclusion of the first patient. Any important changes in the protocol are introduced.

Intervention: The intervention involved the administration of insulin for an h-GI breakfast in the form of Super Bolus. The participants ate a h-GI breakfast for the two following days and received a prandial insulin bolus in the form of a Super Bolus 1 day and a Normal Bolus the next day. The h-GI breakfast consists of breakfast cereal, cornflakes with added cold milk: 50g CHO came from the cornflakes and 10 g of CHO from the 2% milk (200ml). Super Bolus is defined as the 50% increase in prandial insulin dose compared with the dose calculated based on the individual patient's insulin-carbohydrate ratio (ICR) and the simultaneous suspension of basal insulin for 2 h. The definition of Super Bolus is based on the patients' best experiences. Normal Bolus was defined as the prandial insulin dose calculated based on the individual's ICR.

End points:
The following is the primary endpoint:
a) Capillary blood glucose level 90 min after the administration of the prandial bolus as meals with h-GI typically cause blood glucose level peak within 60–90 min in T1D patients

The following are the secondary endpoints:
a) Capillary blood glucose levels (CBGL) at 30, 60, 90, 120, 150 and 180 min after administration of the prandial bolus
b) The number of hypoglycemia episodes based on self-monitoring of blood glucose

The following data are based on the CGM:
a) Glycemic rise (GR)—the difference between the baseline and the maximum glucose value
b) Peak glucose level (PG)—the maximum value of glycemia during 3 h of post-mealtime
c) Time to PG
d) Area under the blood glucose curve (AUC)
e) Mean amplitude of glycemic excursion (MAGE)—the standard deviation of blood glucose (SDBG) obtained from all blood glucose

concentrations within 3 h of post-meal time
f) Time in the postprandial glucose range between 70 and 180 mg/dl (4.0–10.0 mmol/l)

The detailed study protocol was published in Trials:
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CURRENT STATUS

The study recruitment process was finished and the data was collected.
The statistician is just finishing the calculations.
The characteristics of study group is presented in Table 1.

Characteristic	
Number of participants	72
Sex, n (%)	
Female	37 (51.39)
Male	35 (48.61)
Age [years][1]	14.97 (12.96-16.30)
Duration of disease [years][1]	5.91 (2.79-9.44)
BMI[1]	20.77 (18.63-22.91)
TDD/kg[2]	0.82±0.25
Base/kg[2]	0.34 ± 0.12
HbA1c[2]	8.35 (7.45-9.30)
Breakfast's ICR[2]	1.61±0.56
Insulin type, n (%)	
Novo Rapid	29 (40.28)
Humalog	13 (18.06)
Apidra	10 (13.89)
Liprolog	19 (26.39)
Lispro	1 (1.39)
Infusion set type, n (%)	
Teflon cannula	39 (54.93)
Metal cannula	32 (45.07)
Infusion set site, n (%)	
Abdomen	19 (26.76)
Arm	18 (25.35)
Thigh	23 (32.39)
Buttock	11 (15.49)

Table 1. Characteristic of study group. Data presented as median (Q1;Q3)[1] or mean±SD[2] unless otherwise indicated. BMI- Body Mass Index, TDD/kg- daily insulin dose calculated per kg of body mass, Base/kg- basal insulin dose calculated per kg of body mass, ICR- insulin-carbohydrate ratio (defined as a dose of insulin necessary to cover 10g of carbohydrates).

We found a significant difference for the primary outcome- capillary blood glucose level 90 min after the administration of the prandial bolus. Patients who received Super Bolus had lover glucose level 154±37,4 mg/dl (95%CI, 145;162) vs 177±49,2 mg/dl (95%CI, 165;188), p<0.001. The measured glucose values during the study period are shown in Figure 1. Figure 2 presents the incremental blood glucose profiles after Super Bolus and Normal Bolus administration.

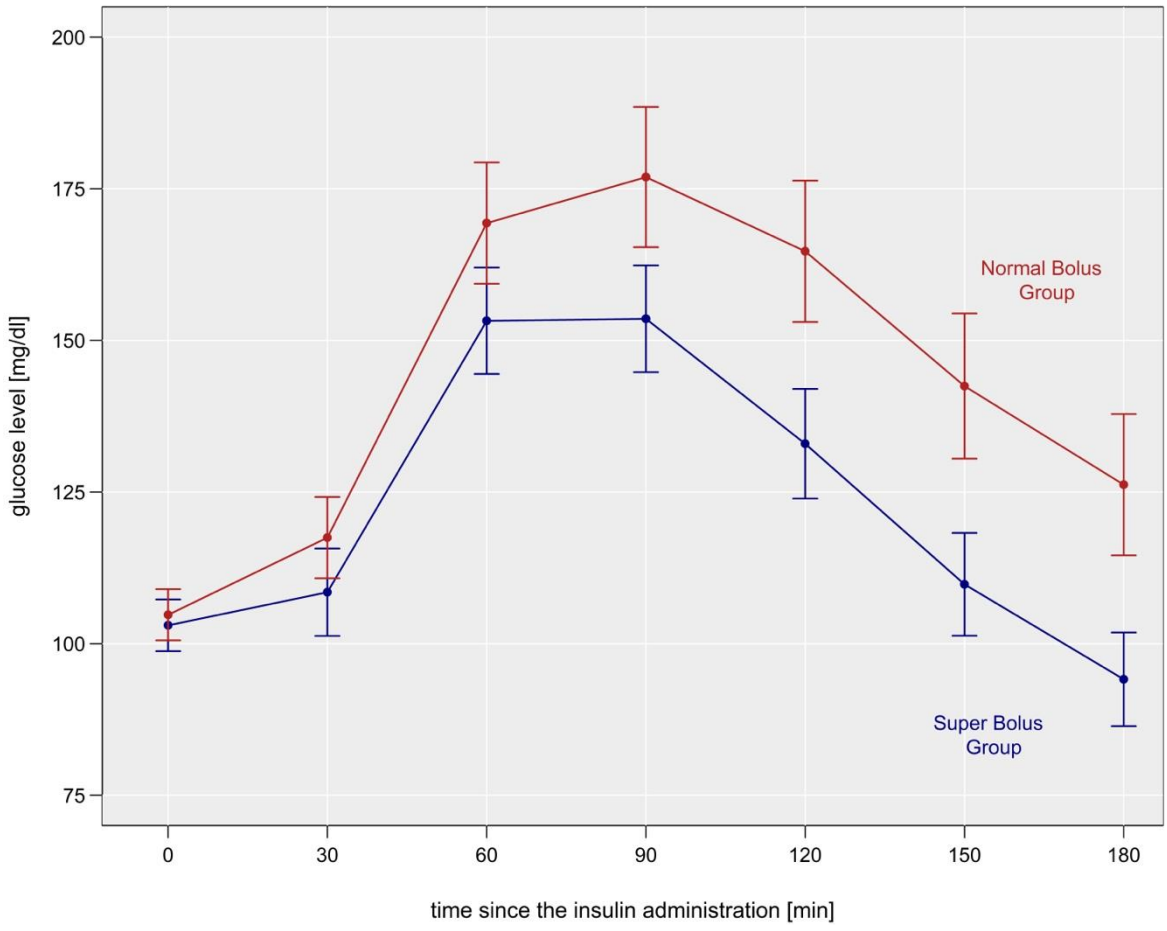

Figure 1. Glucose values measured during the study period. .

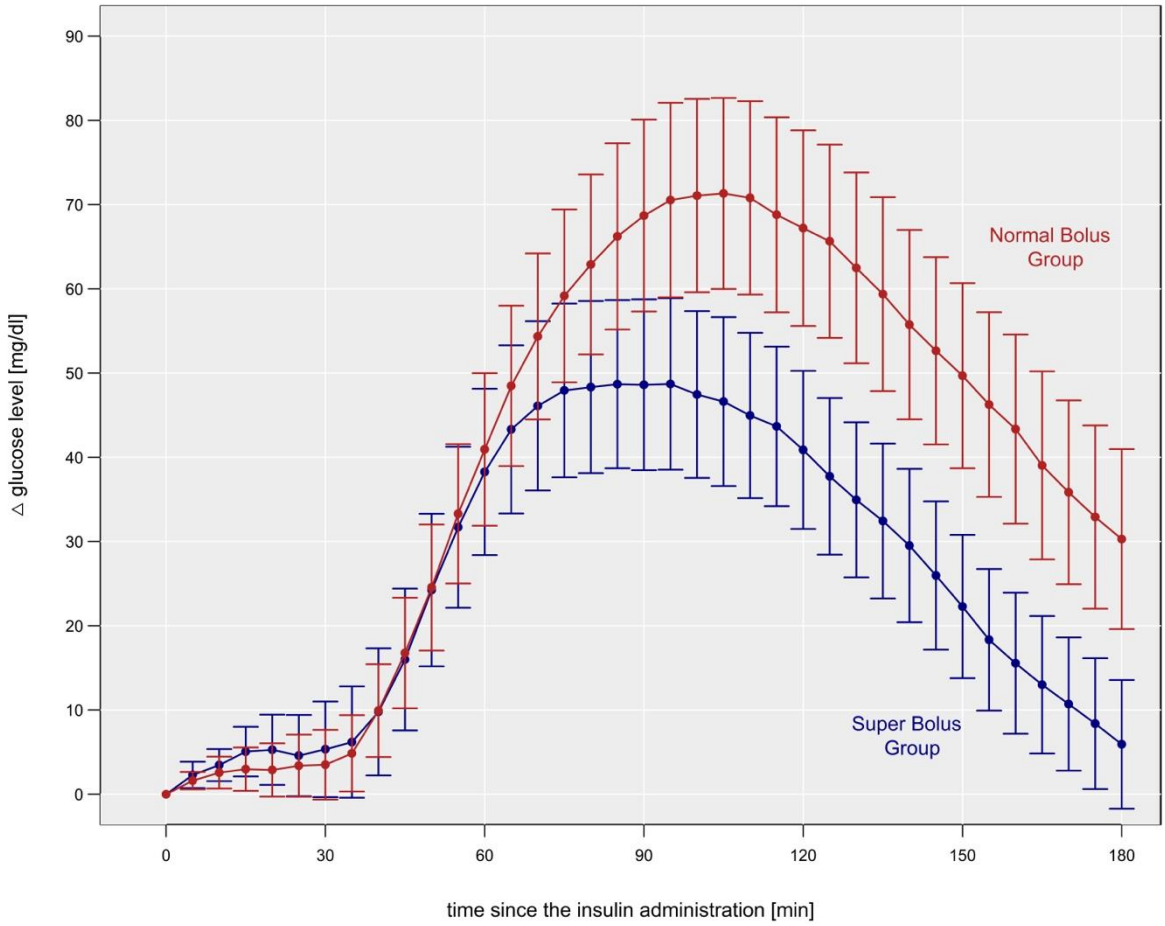

Figure 2. Incremental blood glucose profile during study period.

The study outcomes are shown in Table 2. Time in range 70-180mg/dl was longer in Super Bolus group 165 min (130-180) vs 130 min (100-180), p= .003.
More hypoglycemia episodes were noted in Super Bolus group 22 vs 15, p= .001.
Almost 80% of them were threshold value for initiating treatment for hypoglycemia (70-54mg/dl). No episodes of serious hypoglycemia as neurogenic symptoms or cognitive dysfunction were noted. The hypoglycemia occurred near the end of observation period – Super Bolus Group 145 min (35-160), Normal Bolus 155 min (30-165), p= .889.

Characteristic	Super Bolus (n=36)	Normal Bolus (n=36)	p
CBGL 0 min [mg/dl]	105.00 (89.00-119.00)	103.50 (91.00-123.50)	0.707
CBGL 30 min [mg/dl]	108.49±30.68	117.49±28.56	0.027
CBGL 60 min [mg/dl]	153.24 ±37.31	169.35±42.54	0.002
CBGL 90 min [mg/dl]	153.57±37.45	176.93±49.21	<0.001
CBGL 120 min [mg/dl]	132.96±38.45	164.69±49.64	<0.001
CBGL 150 min [mg/dl]	110.50 (82.50-128.50)	136.50 (98.00-182.50)	<0.001
CBGL 180 min [mg/dl]	92.00 (68.00-121.00)	115.00 (98.00-156.00)	<0.001
Hypoglycemia episode, n (%)	35 (48.6)	13 (18.1)	<0.001
PG [mg/dl]	158.00 (134.0-193.00)	188.00 (146.00-219.00)	<0.001
GR [mg/dl] [2]	58.00 (40.00-93.00)	90 (40.00-93.00)	<0.001
Time to PG [min.]	95.00 (70.00-120.00)	105.00 (85.00-125.00)	0.067
MAGE [mg/dl]	22,89	30,44	0.001
Time in range between 70-180 mg/dl [min.] [2]	165.00 (130.00-180.00)	130.00 (100.00-180.00)	0.003
Total AUC	22626.54±5877.49	25437.49±6880.06	<0.001

Table 2. Study results between treatment groups
CBGL- Capillary Blood Glucose Level, PG- Peak Glucose level, GR- Glycemic Rise, MAGE- Mean Amplitude of Glycemic Excursion, AUC- Area under the blood glucose curve

CONCLUSIONS:

-Super Bolus is an effective and safe strategy to avoid postprandial hyperglycemia
-Super Bolus leads to longer time in range 70-180 mg/dl after the high GI meal consumption
-Hypoglycemia episodes occurred more often after Super Bolus in comparison to Normal Bolus
-Most hypoglycemia episodes were at the alert level and occurred near the end of observation period
-It could be reasonable to suspend the basal insulin for longer than 2 hours (f.ex. 3 hours)
-Further studies are needed to find the best combination of increased dose of meal bolus and basal insulin reduction

NEXT STEPS:

We anticipate a publication from this work and the manuscript will be submitted by August 2023.We plan to submit abstract to ISPAD 49th annual conference in 2023 and the Polish Diabetes Society annual conference in 2023.
The significant contribution of ISPAD-JDRF to this research will be included in all presentations and will be noted in any publications.

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