JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
SHORT REPORT

Feasibility and safety of using an automated decision support system for insulin therapy in the treatment of steroid-induced hyperglycemia in patients with acute graft-versus-host disease: A randomized trial

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Keywords
Decision support system, Feasibility trial, Steroid-induced hyperglycemia

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J Diabetes Investig 2019; 10: 339–342

doi: 10.1111/jdi.12919

Clinical Trial Registry
European Clinical Trials Database
EudraCT 2014-004418-27

ABSTRACT

Steroid-induced hyperglycemia (SIHG) has shown to independently increase the risk for mortality in patients with acute graft-versus-host disease, and it is still unclear whether SIHG might be a modifiable risk factor. Therefore, a feasibility trial was carried out aiming to evaluate the performance of a standardized decision support system (GlucoTab [GT]) for insulin therapy in patients with SIHG. A total of 10 hyperglycemic acute graft-versus-host disease patients were included and treated either with GT or standard of care during hospitalization. Follow-up duration was 6 months. Comparing the GT versus standard of care group, 364 versus 1,020 glucose readings were available during a median of 41 days (interquartile range [IQR] 22–89) and 101 days (IQR 55–147) of hospitalization. The median overall glucose levels were 151 mg/dL (123–192) versus 162 mg/dL (IQR 138–193) for GT and standard of care, respectively ($P < 0.001$); hypoglycemia rates were comparably low. Treatment of SIHG with an algorithm-based system for subcutaneous insulin was feasible and safe.

INTRODUCTION

Acute graft-versus-host disease (aGvHD) represents a frequent and potentially life-threatening complication occurring after allogeneic hematopoietic stem cell transplantation, and is characterized by an activation of donor T cells and release of pro-inflammatory mediators leading to host tissue apoptosis and necrosis affecting the skin, gastrointestinal tract, and liver[1].

As first-line standard therapy, high-dose systemic glucocorticoids are recommended[2], causing steroid-induced hyperglycemia (SIHG) in up to 80% of treated patients[3,4].

We and others have recently identified SIHG as a potent and independent predictor for adverse outcome in patients with hematological malignancy[5] and aGvHD[4,6]. Whether hyperglycemia represents a causal contributor to inferior outcome and an intensive glucose-lowering strategy might have an impact on the unfavorable prognosis remains unclear to date and needs to be further investigated in a randomized controlled trial.

During the past decades, automated decision support systems (DSS) recommending insulin dosing for hospitalized patients have been repeatedly tested and introduced into clinical practice[7,8]. Until present, such systems were exclusively tested and approved for the treatment of in-hospital (stress) hyperglycemia or type 2 diabetes mellitus, but not for patients with SIHG.

The aim of the present study was to evaluate the feasibility and safety using an automated DSS that incorporates an algorithm for basal–bolus insulin therapy (GlucoTab) in

Received 27 June 2018; revised 2 August 2018; accepted 14 August 2018

hospitalized patients with aGvHD in a randomized controlled pilot trial as a prerequisite for a future multicenter outcome trial comparing intensive glucose control achieved by a DSS with conventional glucose control.

METHODS

Study design

We carried out a single center, randomized, controlled feasibility trial in 10 hospitalized aGvHD patients developing hyperglycemia (i.e., >2 fasting glucose values >140 mg/dL) after initiation of systemic glucocorticoid therapy.

The study was approved by the local ethics committee (27-116 ex 14/15), registered (EudraCT Number: 2014-004418-27) and carried out in accordance with the declaration of Helsinki. All patients gave written consent before any study-related procedure.

Participants were randomly assigned using a web-based randomization tool (www.randomizer.at) to either insulin therapy suggested by GlucoTab (GT group) or to routine care according to local standards of care (SOC group)[9]. Follow-up duration was 6 months. If patients were readmitted to hospital during the follow-up period, they were treated according to the initial randomization result.

Despite the feasibility design and therefore small patient population, a randomized controlled trial design was chosen in order to oppose two different therapeutic approaches for the management of in-hospital hyperglycemia in patients with aGvHD. The primary aim of the study was to investigate the feasibility and safety of GlucoTab in the treatment of SIHG. Feasibility was assessed by the median glucose and percentage of plasma glucose (PG) values in the target range during systemic corticosteroid therapy. The main safety end-point was the number of hypoglycemic events.

GlucoTab®

GlucoTab (Decide, clinical software GmbH, Graz, Austria) is a DSS integrated in a mobile, handheld tablet computer suggesting subcutaneous basal–bolus insulin therapy provided by the incorporated standardized insulin dosing algorithm. This device has previously been tested and implemented in routine care (CE certified in 2013) in hospitalized non-critically ill patients with hyperglycemia with or without diabetes mellitus, and has been shown to be an effective tool for the establishment of safe and tight glycemic control. However, GlucoTab has not been used for the management of SIHG thus far[7,10]. GlucoTab therapy requires four capillary glucose measurements per day (pre-meal, bedtime), and provides both bolus and basal insulin dosing suggestions. Once a patient is registered to be treated with the DSS, it recommends a first total daily insulin dose based on age, renal function and body mass index. During the course of treatment, the incorporated algorithm adapts its insulin suggestions to retrospective glycemic trends. The current version of the algorithm proposes basal and bolus insulin in a proportion of 50:50%, with the largest bolus of short-acting insulin in the morning. Dose suggestions can be overruled at any time by medical staff if deemed necessary or reasonable. In the present study, insulins aspart (NovoNordisk, Bagsvaerd, Denmark) and glargine (Sanofi-Aventis, Frankfurt am Main, Germany) were used. Further information characterizing the functionality of the algorithm and its efficacy and usability shown in previous studies are described elsewhere in detail[7,10].

For SOC, antihyperglycemic therapy was carried out at the discretion of the treating physician. According to the protocol, four daily glucose measurements were also requested in the SOC group throughout the trial.

Statistical analysis

For collection of baseline and aGvHD characteristics, we used descriptive statistics. Continuous data following a normal distribution are given as means with standard deviation, and variables with a skewed distribution are presented as medians with interquartile range (IQR). Categorical data are presented as percentages. Comparative analysis and significance testing were carried out using the Mann–Whitney *U*-test and χ^2-test. Statistical analyses were carried out with SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). As the present study was a feasibility trial, no formal sample size calculation was carried out.

RESULTS

Patient characteristics

We included 10 patients (7 women) with aGvHD in the present randomized controlled feasibility trial. The mean age was 55 ± 13 versus 60 ± 4 years for GT and SOC, respectively. Table 1 shows further patient characteristics.

Primary outcome parameters

During in-hospital glucocorticoid therapy, a total of 364 (GT group) and 1,020 (SOC group) PG values were available. The median overall PG was significantly lower in the GT group (151 [IQR 123–192] vs 162 [IQR 138–193] mg/dL), as well as median fasting PG (131 [IQR 113–164] vs 152 [IQR 134–18] mg/dL and bedtime PG (159 [IQR 133–202] vs 188 [IQR 160–211] mg/dL; $P < 0.001$, respectively). PG values at lunchtime and in the evening showed no statistically significant difference. A total of 67.2% (GT) versus 60.2% (SOC) of all values were in the recommended target range (70–180 mg/dL; $P < 0.001$). Hypoglycemia (PG <70 mg/dL) appeared rarely in both groups with no statistical difference ($P = 0.120$). None of the hypoglycemic events was symptomatically noticed, required third party help or resulted in an adverse clinical outcome. Detailed information on primary outcome parameters is shown in Table 2.

Secondary outcome parameters

The mean total daily insulin dose was significantly higher in the GT (38 ± 29 IU) versus SOC group (11 ± 12 IU), and the

Table 1 | Patient characteristics

	GT (n = 5)	SOC (n = 5)	P-value
Sex (female)	3/5	4/5	
Age (years)	55.2 ± 13.4	60.2 ± 3.66	0.421
BMI (kg/m^2)	22.8 ± 4.6	24.5 ± 5.5	0.516
Underlying disease			
AML	5	3	
ALL	0	1	
aGvHD onset after SCT (days)	27 ± 19.9	26.6 ± 5.3	0.794
GvHD (affected organs)			
Skin	5	4	
Gastrointestinal tract	5	5	
Liver	0	1	
Overall grading (Glucksberg)			
2	2	1	
3	0	1	
4	3	3	
Donor type			
Relative	1 (Haploidentical)	2 (1 Haploidentical)	
Unrelated	4	3	
Comorbidity index (HCT-CI)			
HCT-CI ≤1	0	3	
HCT-CI >1	5	2	
HLA match			
Full match (12/12)	4	3	
Mismatch	1	2	

Age, body mass index (BMI) and acute graft-versus-host disease (aGvHD) onset are shown as the mean. ALL, acute lymphatic leukemia; AML, acute myeloid leukemia; GT, GlucoTab; HCT-CI, Hematopoietic Cell Transplantation-Comorbidity Index; HLA, human leukocyte antigen; SCT, stem cell transplantation; SOC, standard of care.

mean prednisolone dose was higher in the SOC group (P < 0.001). Table 3 shows further secondary outcome parameters.

DISCUSSION

Patients with aGvHD require high doses of steroids as first-line immunosuppressant therapy and consecutively frequently develop SIHG[1]. Recent data showed that patients with aGvHD who develop SIHG face a substantially increased risk for non-relapse mortality, and this risk correlates with the extent of hyperglycemia[4,6].

Although glucose seems to be a prognostic marker, it remains unclear whether lowering hyperglycemia influences survival of these patients, which would need to be tested in an adequately powered outcome trial.

As a first step towards such a trial, we investigated the feasibility of carrying out a randomized controlled trial using a standardized DSS for basal–bolus insulin therapy in hospitalized patients with SIHG, which could serve as a tool for standardized, intensive glucose management in a future multicenter trial.

The present trial showed that median glucose levels were significantly lower in SIHG patients treated with a standardized DSS compared with usual care, without increasing the number of hypoglycemic events. In particular, median morning and bedtime glucose readings were lower in the DSS group, suggesting that the morning short-acting insulin dose will need to be increased further in the DSS algorithm optimized for steroid-induced hyperglycemia.

It is well known that patients who use short-acting or intermediate steroids are exposed to the development of a transient rise of hyperglycemia that persists for some hours. For this reason, future versions of the algorithm will have to be aware of

Table 2 | Median glucose during different time-points, and percentage and amount of values during different glycemic ranges

Group	GT (n = 5)			SOC (n = 5)			P-value
	PG (mg/dL)	IQR (95% CI)	n	PG (mg/dL)	IQR (95% CI)	n	
Median glucose during different time-points							
Median PG morning	131	113–164	94	152	134–182	286	<0.001
Median PG lunch	148	120–185	92	157	134–182	279	0.421
Median PG evening	179	178–223	96	191	157–230	265	0.201
Median PG bedtime	159	132–202	82	188	160–211	190	<0.001
Median PG total	151	123–192	364	162	138–193	1020	<0.001
		%	n	%	n		P-value
Percentage and amount of values during different glycemic ranges							
Hypoglycemia (<70 mg/dL)		0.8	3	0.2	2		0.120
Target PG (70–180 mg/dL)		67.2	248	60.2	614		0.017
Hyperglycemia (>180 mg/dL)		32.0	113	39.6	404		0.010
Total		100	364	100	1020		

GT, GlucoTab; IQR, interquartile range; PG, plasma glucose; SOC, standard of care.

Table 3 | Secondary outcome parameters

Group	GT (n = 5)	SD/IQR	SOC (n = 5)	SD/IQR	P-value
Mean total daily insulin dose (IU)	38	±29	11	±12	<0.001
Mean prednisolone dose (mg)	85	±53	98	±59	<0.001
Mean initial prednisolone dose (mg)	113	±59	140	±53	0.458
Median time of survival (days)	105	39–161	136	86–165	0.458
Median time of hospitalization (days)	41	22–89	101	55–147	0.095
Median percentage of hospitalization	80	34–95	86	62–97	0.690
Cause of death (*n*)	4		4		
Infection (*n*)	2		2		
Relapse (*n*)	1		1		
aGvHD (*n*)	1		1		

Normally distributed parameters are given as the mean (standard deviation [SD]), non-normally distributed parameters are presented as the median (interquartile range [IQR]). aGvHD, acute graft-versus-host disease; GT, GlucoTab; IQR, interquartile range; SD, standard deviation; SOC, standard of care.

the time-point of steroid application, and also the type of steroid and its hyperglycemic potency must be taken into account in order to further improve the algorithm. These adjustments are indispensable before the system can be used in a trial investigating the effect of tight glycemic control on patient survival in aGvHD.

Apart from the hereby shown ability of GlucoTab to improve glycemia in patients with SIHG, we have to underline that we tested the device in a hospital unit that employs non-diabetologists. This emphasizes the potential benefit of GlucoTab to facilitate and standardize glycemic management for non-specified staff.

To our knowledge, this was the first trial testing a DSS for insulin therapy in patients with SIHG. The present results suggest that GlucoTab might be a suitable tool for the treatment of SIHG in patients suffering from aGvHD and other SIHG patients. Whether or not DSS-induced improved glycemia translates into a beneficial outcome in patients with aGvHD needs to be investigated in a larger outcome trial.

ACKNOWLEDGMENTS

We express our thanks to Bernhard Höll and the Decide Clinical Software GmbH for GlucoTab-related support. We also thank Beate Boulgaropoulus for giving advice in terms of writing of this manuscript.

DISCLOSURE

The authors declare no conflict of interest.

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