brief report

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Add-on treatment with intermediate-acting insulin versus sliding-scale insulin for patients with type 2 diabetes or insulin resistance during cyclic glucocorticoid-containing antineoplastic chemotherapy: a randomized crossover study

The aim of this study was to compare the effectiveness and safety of intermediate-acting insulin (IMI) titrated on body weight and glucocorticoid dose with that of short-acting sliding-scale insulin (SSI) in patients on recurrent high-dose glucocorticoid-containing chemotherapy. We enrolled 26 patients with type 2 diabetes mellitus or random blood glucose level >12 mmol/l in a previous cycle of chemotherapy in a randomized crossover study. In two consecutive cycles of glucocorticoid-containing chemotherapy, participants were treated with either IMI or SSI, as add-on to routine diabetes medication. We compared time spent in target range (3.9–10 mmol/l), measured by continuous glucose monitoring (CGM), and the occurrence of hypoglycaemia. IMI resulted in a higher proportion of glucose values within target range than SSI (34.4 vs 20.9%; $p < 0.001$). There were no severe or symptomatic hypoglycaemic events. Two participants in each group had a subclinical hypoglycaemia detected only by CGM. Once-daily IMI resulted in better glycaemic control than SSI in patients with glucocorticoid-induced hyperglycaemia during chemotherapy. Safety was not compromised as the incidence of hypoglycaemia was low and not different between both regimens.
Keywords: basal insulin, continuous glucose monitoring, glycaemic control, insulin therapy, randomized trial

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Introduction

Glucocorticoid agents are frequently used as a component of cyclic antineoplastic therapy. Glucocorticoid therapy provokes hyperglycaemia in 46–100% of patients with diabetes, and in 40–70% of patients without known diabetes [1,2]. Hyperglycaemia during chemotherapy has been associated with increased chemotoxicity and anecdotally with hyperglycaemic emergencies [3,4]. Treating glucocorticoid-induced hyperglycaemia (GCIH) can be challenging, especially when glucocorticoids are prescribed in high doses for a short period, as in patients receiving cyclic glucocorticoid-containing chemotherapy [5].

Postprandial hyperglycaemia occurs ~3 h after oral administration of prednisone and dexamethasone, and postprandial hyperglycaemia continues until 24–36 h after administration [2]. The duration of action of intermediate-acting insulin (IMI) is ~12–18 h [6]. When administered in the morning, the glucose-lowering profile of IMI covers the hyperglycaemic profile caused by glucocorticoid treatment. Sliding-scale insulin (SSI) was shown to be less effective than basal insulin. Also, it is easier to transfer patients on basal insulin from an inpatient to an outpatient setting [7,8]. In a recent survey, however, we found that SSI is still most frequently prescribed for treatment of hyperglycaemia caused by glucocorticoid-containing chemotherapy [9]. IMI has been proposed as a treatment for GCIH but it has never been evaluated in the setting of recurrent short episodes of severe GCIH in a randomized study [10].

The aim of the present study was to compare the effectiveness of IMI, titrated on body weight and glucocorticoid dose and adjusted for older age and impaired renal function, with that of subcutaneous short-acting SSI in patients with GCIH during antineoplastic chemotherapy.

Materials and Methods

We enrolled patients on cyclic glucocorticoid-containing chemotherapy in a randomized crossover study. Patients were eligible if they (i) had type 2 diabetes or random blood glucose level >12 mmol/l in a previous cycle of glucocorticoid-containing chemotherapy and (ii) were scheduled to receive glucocorticoid medication (≥12.5 mg prednisone-equivalent) on 3–10 consecutive days in each cycle.

Participants were randomized according to a 1 : 1 ratio for the order of the regimens: first SSI or first IMI as add-on to their routine diabetes medication on the days they used glucocorticoid medication. During SSI, add-on insulin was titrated on current glucose values. During IMI, insulin was titrated on body weight and glucocorticoid dose (Table S1, Supporting Information). Randomization was stratified by centre and in blocks of varying sizes. Allocation concealment was achieved

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by using opaque envelopes. For all participants, the oncologist managed antineoplastic treatment and the study team managed glucose-lowering therapy.

All participants were counselled on the proper use of insulin pens and glucose meters and on signs and symptoms of and how to counteract hypoglycaemia. They were instructed to contact the study physician in case of questions regarding glucose control.

During both cycles, participants performed capillary glucose testing four times daily: before each meal and at bedtime. Participants were allowed to use their own blood glucose meter. Blood glucoses meters were calibrated before the study and replaced if required. The study was performed in an inpatient or outpatient setting, depending on the chemotherapeutic regimen in each participant. Glucose values were also measured through a blinded subcutaneous continuous glucose monitoring (CGM) device (iPro2; Medtronic, Northridge, CA, USA).

We collected baseline data on diabetes and oncological history and general condition. Patient satisfaction on glucose-lowering treatment was evaluated as patient preference for subsequent cycles after study treatment. The occurrence of adverse events was evaluated at each visit.

The study was conducted in three secondary teaching hospitals: MC Slotervaart and Antoni van Leeuwenhoek Hospital, Amsterdam, and Isala, Zwolle, the Netherlands. The study protocol was approved by the institutional review board and registered at clinicaltrials.gov (NCT02155374).

The primary outcome was the difference in glycaemic control between the two cycles, defined as the proportion of time spent in glucose target range (3.9–10 mmol/l) as measured by CGM and incidence of clinical and subclinical hypoglycaemic events. Secondary outcomes were differences in mean glucose, mean daily insulin dose, chemotoxicity and patient preference. Clinical hypoglycaemia was defined as symptoms consistent with hypoglycaemia, together with a glucose value <3.9 mmol/l, and subclinical hypoglycaemia was defined as a glucose value <3.9 mmol/l (either by CGM or capillary blood glucose measurement) without symptoms.

We based the sample size on glucose control in patients on SSI and basal insulin [11,12]. We estimated the proportion of time in target range during IMI to be 16 ± 24.5% higher than during SSI. A total of 24 participants was needed to achieve 80% power. To account for potential drop-outs we planned to include 26 participants.

Results

In total, 26 patients were randomized. One patient withdrew before the start of study. Three patients discontinued study treatment (Figure S1, Supporting Information). All patients who started study treatment were included in the analysis. Table 1 shows their baseline characteristics. Dose and duration of glucocorticoid treatment were equal during both chemotherapy cycles for each participant. Four participants received chemotherapy while admitted to the hospital, all others were outpatients.

Glucose values were in the target range for 34.4% of the time when using IMI and 20.9% of the time when using SSI [difference 13.5 ± 19.1%; $p < 0.001$ (Figure 1)]. The mean ± standard deviation glucose level was 12.4 ± 2.9 mmol/l during IMI and 13.5 ± 2.8 mmol/l during SSI ($p < 0.05$). Glucose levels were lower during IMI treatment at each time point, although the difference was not statistically significant (Figure S2, Supporting Information). The IMI algorithm resulted in a median (interquartile range) total daily insulin dose of 40.3 (28.7–61.0) IU compared with 26.0 (13.5–63.0) IU during SSI ($p < 0.01$, Wilcoxon signed-rank test).

No severe or symptomatic hypoglycaemic events occurred during the study. Four participants (two in the SSI and two in the IMI group) had subclinical hypoglycaemia, detected by CGM recording only. Three out of four participants who developed hypoglycaemia used insulin at baseline. All hypoglycaemic episodes occurred towards the end of the cycles (days 3–5), and in one participant it was associated with chemotherapy-induced nausea and diminished intake. The lowest glucose value was 2.2 mmol/l during SSI and 3.2 mmol/l during IMI. The duration of the hypoglycaemic episodes was slightly longer during IMI (although the difference was not statistically significant; Figure 1). The incidence of non-hypoglycaemia adverse events was equal during both regimens. Six participants experienced a serious adverse

Table 1. Baseline characteristics.

	All randomized patients (n = 26)
Age (years)	67 (58–71)
Men, n (%)	12 (46.2)
BMI (kg/m^2)	29.1 (26.3–31.6)
Diabetes	
Type 2 diabetes	24 (92.3)
Diabetes duration (years)	9.5 (5.0–17.8)
HbA1c in patients without diabetes	
mmol/mol	51 (50–51)
%	6.8 (6.7–6.8)
HbA1c in patients with type 2 diabetes	
mmol/mol	59 (52–68)
%	7.5 (6.9–8.4)
Treatment	
Metformin, n (%)	14 (53.9)
Sulphonylurea, n (%)	1 (3.9)
Metformin + sulphonylurea, n (%)	4 (15.4)
Insulin, n (%)	13 (50.0)
Daily insulin dose, IU	4.5 (0.0–42.5)
Cancer type, n (%)	
Gastrointestinal	8 (30.8)
Hematopoietic	6 (23.1)
Lung	5 (19.2)
Breast	7 (26.9)
Cancer stage	
I (local)	1 (3.8)
II–III (local progression)	15 (57.7)
IV (distant metastasis)	8 (30.8)
Other (unknown or unclassifiable)	2 (7.6)
Glucocorticoids	
Dose (prednisone equivalent*) (mg)	50.4 (36.6–55.3)
Duration (days, per cycle)	3 (3–4)

Data are median (25th–75th interquartile range) unless otherwise stated.
*Prednisone-equivalent dose of dexamethasone is calculated as mg dexamethasone × 6.25.

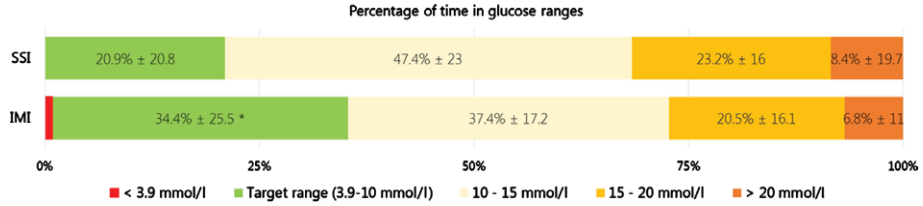

Figure 1. Difference in glycaemic control in patients with glucocorticoid-containing chemotherapy, treated with an intermediate-acting insulin (IMI) regimen and a sliding-scale insulin (SSI) regimen. The bars indicate the proportion of time spent in each glucose range and its standard deviation (s.d.). The mean ± s.d. time spent in the glucose range <3.9 mmol/l during SSI was 0.1 ± 0.3% and during IMI it was 0.8 ± 2.1% ($p = 0.21$). *$p < 0.001$.

event, all unrelated to study treatment (Table S2, Supporting Information).

Patient satisfaction was measured as patient preference for IMI or SSI in subsequent chemotherapy cycles. A total of 29% of participants preferred SSI, whereas 71% preferred IMI. Treatment preference was not associated with insulin use at baseline.

Discussion

In the present randomized controlled study we compared add-on treatment with IMI once daily with an SSI regimen. We found that IMI resulted in better glycaemic control without compromising safety. Furthermore, most patients preferred treatment with IMI over SSI. These results confirmed that, despite insulin treatment, glucocorticoids may cause severe hyperglycaemia in patients who previously had adequate glycaemic control. This is the first randomized study to compare two insulin regimens with regard to hyperglycaemia as a result of recurrent high-dose glucocorticoids.

The IMI regimen resulted in higher insulin doses and better glycaemic control compared with the SSI regimen. In routine clinical practice, body weight and previous level of insulin resistance are usually not taken into account when determining dosing of SSI, and the dose is often insufficiently adjusted [7]. In our protocol we adjusted SSI doses according to measured glucose values, but glycaemic control was still inferior compared with IMI. Patients continued the regimen of their preference in the chemotherapy cycles after study completion on the add-on insulin dose to which they were titrated during the study. The titrated dose was generally higher than the starting dose and this suggests that the glycaemic control achieved during the study follow-up underestimates the potential improvement for the complete course of chemotherapy.

We observed a low rate of non-severe and subclinical hypoglycaemia only detected by CGM, which was similar to previous studies on insulin treatment for in-hospital hyperglycaemia [11,12]. One hypoglycaemic episode occurred after diminished intake resulting from chemotherapy-induced nausea. As chemotherapy-induced nausea is a side effect of chemotherapeutic agents that may increase the risk of hypoglycaemia, caution is warranted with IMI in these cases. Despite the higher insulin doses during the IMI strategy, the incidence of hypoglycaemia was not higher during this regimen compared with SSI.

Apart from causing symptomatic hyperglycaemia or even hyperglycaemic emergencies, prolonging hospitalization and increasing disease burden in patients undergoing glucocorticoid-containing chemotherapy, hyperglycaemia may actually diminish the anti-tumour effect [13,14]. *Ex vivo* studies have shown detrimental effects of hyperglycaemia on pro-apoptotic signalling in response to anti-cancer drugs, and through inducing tumour proliferation. Various chemotherapies result in a lower proportion of cell death in a hyperglycaemic environment compared with a euglycaemic environment [15].

Because there are no good clinical data on the effects of lowering glycaemia on cancer outcome, it is difficult to define glycaemic targets in patients undergoing antineoplastic therapy. We chose a target range of 3.9–10 mmol/l because a similar range is chosen in studies on in-hospital hyperglycaemia, and because it resembles the euglycaemic condition in preclinical studies.

In conclusion, patients on glucocorticoid-containing chemotherapy frequently develop severe hyperglycaemia. Treatment of hyperglycaemia in these patients with an easy-to-use once daily IMI regimen resulted in more time in glucose target range compared with an SSI regimen, without compromising safety.

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Conflicts of Interest

None of the authors have a conflict of interest to declare.

M. G. designed the study protocol, performed the analyses and wrote the manuscript. V. G., T. V. and J. H. reviewed

the study protocol and manuscript. J. M. reviewed the study protocol, contributed to data collection and reviewed the manuscript. T. S. contributed to data collection and reviewed the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:
Figure S1. Patient flow.
Figure S2. Glucose profile.
Table S1. Study treatment.
Table S2. Adverse events.

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