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SYMPOSIUM

Evaluation of Implementation of a Fully Automated Algorithm (Enhanced Model Predictive Control) in an Interacting Infusion Pump System for Establishment of Tight Glycemic Control in Medical Intensive Care Unit Patients

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Abstract

Background:

The objective of this study was to investigate the performance of a newly developed decision support system for the establishment of tight glycemic control in medical intensive care unit (ICU) patients for a period of 72 hours.

Methods:

This was a single-center, open, non-controlled feasibility trial including 10 mechanically ventilated ICU patients. The CS-1 decision support system (interacting infusion pumps with integrated enhanced model predictive control algorithm and user interface) was used to adjust the infusion rate of administered insulin to normalize blood glucose. Efficacy and safety were assessed by calculating the percentage of values within the target range (80–110 mg/dl), hyperglycemic index, mean glucose, and hypoglycemic episodes (<40 mg/dl).

Results:

The percentage of values in time in target was 47.0% (±13.0). The average blood glucose concentration and hyperglycemic index were 109 mg/dl (±13) and 10 mg/dl (±9), respectively. No hypoglycemic episode (<40 mg/dl) was detected. Eleven times (1.5% of all given advice) the nurses did not follow and, thus, overruled the advice of the CS-1 system. Several technical malfunctions of the device (repetitive error messages and missing data in the data log) due to communication problems between the new hardware components are shortcomings of the present version of the device. As a consequence of these technical failures of system integration, treatment had to be stopped ahead of schedule in three patients.

continued →

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Abbreviations: (BG) blood glucose, (CLINICIP) Closed Loop Insulin Infusion for Critically Ill Patients, (EC) European Commission, (eMPC) enhanced model predictive control, (ICU) intensive care unit, (SD) standard deviation

Keywords: algorithms, critical care nursing, hyperglycemia management, insulin infusion systems

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Abstract cont.

Conclusions:

Despite technical malfunctions, the performance of this prototype CS-1 decision support system was, from a clinical point of view, already effective in maintaining tight glycemic control. Accordingly, and with technical improvement required, the CS-1 system has the capacity to serve as a reliable tool for routine establishment of glycemic control in ICU patients.

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Introduction

The presence of hyperglycemia in hospitalized patients indicates an increased risk for mortality and morbidity.[1–5] Single center trials have demonstrated that tight blood glucose (BG) improves the prognosis for intensive care unit (ICU) patients.[6–9] However, normoglycemia is not easy to establish in this environment, and multicenter trials were stopped because of the increased rate of hypoglycemia, the most common side effect of intensified insulin therapy.[10,11] Moreover, the establishment of tight glycemic control requires a shorter sampling interval for the measurement of blood glucose and increases the workload for the nursing staff.[12–14]

Development of a closed-loop control system that automatically infuses insulin on the basis of an automated algorithm, which integrates a continuous glucose signal, could help overcome these obstacles and permit strict glycemic control without increasing the workload of the ICU nursing staff. The goal of the European Commission (EC)-funded project Closed Loop Infusion for Critically Ill Patients (CLINICIP) is to develop such a low-risk monitoring and control system. A model predictive control algorithm [enhanced model predictive control (eMPC)] was adapted for the ICU patient population and has demonstrated efficacy and safety in previous investigations.[14-16] Despite considerable effort, no continuous glucose sensors with robust performance are yet available commercially for the critically ill.[17] Thus, as a first step toward a closed-loop system, a bedside decision support system (CS-1 decision support system), which integrates the eMPC algorithm in an interacting pump infusion system with a bedside touch screen user interface, was developed utilizing the B. Braun space infusion system. Based on glucose spot measurement and automatic integration of the carbohydrate content of enteral and parenteral nutrition infused via the pumps, the adaptive control algorithm (eMPC) generates insulin advice and acts as a decision support system for the ICU nursing staff.

The objective of this study was to test the efficacy, safety, and usability of the CS-1 decision support system in patients at a medical ICU for a period of 72 hours. Arterial blood glucose measurements were performed to assess the primary efficacy variable (percentage of time within the predefined glucose target range 80–110 mg/dl).

Methods

Study Design

The study was conducted as a single-center, open, noncontrolled clinical investigation in 10 patients at the Medical University of Graz. The protocol was approved by the institutional ethical review board local ethics committee of the Medical University of Graz. Informed consent was obtained from the closest family member, as patients were unable to give consent. The trial was conducted according to the Declaration of Helsinki and International Organization for Standardization (ISO 14155).

Study Population

Ten adult medical ICU patients who were mechanically ventilated and assumed to require at least 3 days of intensive care were checked for inclusion (>110 mg/dl or already on insulin therapy) and exclusion criteria. The study population baseline characteristics are shown in **Table 1**.

Table 1.
Baseline Characteristics of Patients[a]

Variable	CM10-CS-1
N	10
Male sex (No.)	7
Age (years)	63.4 ± 12.9
Body mass index	26.2 ± 4.6
Diagnostic category (No.)	
Cardiovascular	5
Sepsis	2
Respiratory	1
Neurologic	1
Other	1
History of diabetes [No. (%)]	2 (20)
APACHE II score[b]	28.0 ± 6.0
Blood glucose at study start (mg/dl)	137 ± 43

[a] Data presented as mean ± SD unless otherwise indicated.
[b] Acute Physiology and Chronic Health Evaluation: score was evaluated at study start. Glasgow Coma Score was scored 3 in sedated and mechanically ventilated patients.

The CS-1 Decision Support System

As illustrated in **Figure 1a**, the CS-1 decision support system (B. Braun Melsungen AG, Germany) is composed of three standard infusion pumps: two for the administration of enteral and parenteral nutrition (Infusomat® Space and/or Perfusor® Space) and one for insulin administration (Perfusor® Space). At the bottom of the CS-1 decision support system, a slide-in rack with a central user interface (SpaceControl: touch screen display) and a central hardware (SpaceCom) that includes the model predictive control version 1.04.05 algorithm have been implemented. This algorithm has demonstrated safety and efficacy in a previous laptop-based study in medical ICU patients.[16] The central hardware with the user interface (touch screen display) is connected to the infusion pumps and permanently reads the actual status and rate of the three infusion pumps. Individual enteral and parenteral nutrition products with the corresponding carbohydrate content (g/ml) are stored in the drug database of each pump. Before infusion start of enteral or parenteral nutrition the nurse has to select the type of nutrition from a pickup list on the display of the pump. Based on the type and on the infusion rate used for the selected nutrition product, the amount of administered carbohydrates is calculated and communicated with the central hardware and the eMPC, respectively. As indicated in **Figure 1a**, the glucose reading as measured has to be entered manually via the touch screen display. Based on this input and available information of administered insulin and nutrition via the pumps, the eMPC gives advice on the insulin infusion rate and a count-down timer for the next glucose measurement. In addition to other information (glucose and insulin profile and the current rate of enteral and parenteral administration), this is displayed on the user interface (**Figure 1b**). The count-down timer signals the time until the next glucose measurement in the range from 20 minutes up to 240 minutes. In addition, standard optical and acoustical alarm signals are used to alert the staff for upcoming measurements [prealarm 10 minutes before advised time point (–10), alarm at point of time (0), and in 10-minute intervals (+10, +20, +30 minutes) subsequently]. The suggested insulin infusion is displayed on the screen, but has to be entered manually and therefore confirmed by the operating nurse. To avoid the onset of hypo- or hyperglycemia by means of unattended nutrition changes, insulin infusion is automatically calculated and displayed in case the nutrition rate is changed or stopped at all.[18] All working steps as indicated in **Figure 1a** were performed by trained ICU nursing staff of the Department of Internal Medicine (Medical University of Graz). Each nurse participated in a 1-hour training session to familiarize with the CS-1 decision support system before enrollment of the first patient.

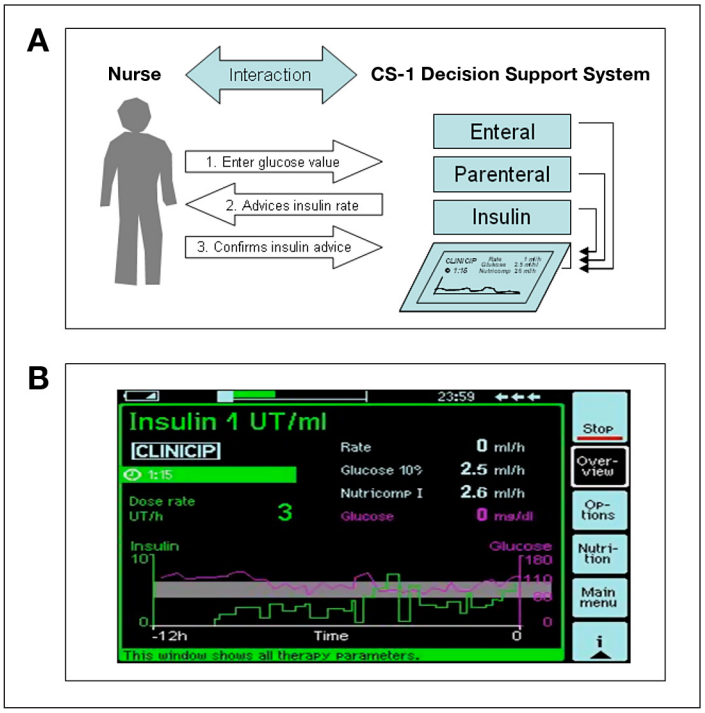

Figure 1. (A) Workflow to establish tight glycemic control using the CS-1 decision support system. (1) The glucose value is entered via the user interface. (2) The algorithm calculates advice for the new insulin infusion rate and suggests the time until the next BG measurement. (3) The suggested insulin rate needs to be confirmed by changing the infusion rate. **(B)** User interface of the CS-1 decision support system.

For glucose measurement, a certified device for ICU application was used (Accu-Check Inform, Roche Diagnostics GmbH, Mannheim, Germany). Actrapid HM (Novo Nordisk, Baegsvard, Denmark) was used in a 1-IU/ml 0.9% sodium chloride concentration for infusion.

All trial-related activities were carried out until the end of the ICU stay or for a period of 3 days using the glucose reading next to 72 hours as the last data point. Nurses who were actively participating in the study were asked to fill out a questionnaire and to make comments and suggestions for improvement.

Statistical Analysis

Statistical analysis was performed on an intention to treat basis. The percentage of values in the target range (80–110 mg/dl) was defined as the primary end point for the assessment of glucose control. Data are reported as mean ± standard deviation (SD) if not otherwise indicated. Normality of data was checked by Kolmogorov–Smirnov and Shapiro–Wilk tests. For comparison of glucose data with results from historical data, Kruskall–Wallis and subsequent Mann–Whitney *U* tests with Bonferroni correction for group comparisons were applied. Data analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL).

Results

Ten patients were recruited from April to June 2007. The duration of inclusion was 66 hours (57–71) [median (interquartile range)]. Treatment was discontinued ahead of schedule in 6 patients, because of technical problems (repetitive error messages by the CS-1 system) in 3 patients and because of clinical events in another 3 patients. In 2 patients, the arterial line for arterial glucose sampling was removed in preparation for referral to a general ward. In 1 patient who was admitted with acute heart failure and developed a multiorgan failure under therapy, the decision to withdraw intensive life support to avoid futile medical treatment was made by the treating physicians.

Glucose Control

As indicated by the mean and individual blood glucose profiles in **Figure 2a**, tight glycemic control could be established following the advice of the CS-1 decision support system. The percentage of glucose values within the target range (80 to 110 mg/dl) was 47.0% (±13.0). The average BG concentration was 109 mg/dl (±13), and the hyperglycemic index[19] was 10 mg/dl (±9). No hypoglycemic episode (<40 mg/dl) occurred during the evaluation period. The percentage of values below 60 mg/dl and above 150 mg/dl was 0.53% (±0.88) and 6.65% (±8.79), respectively.

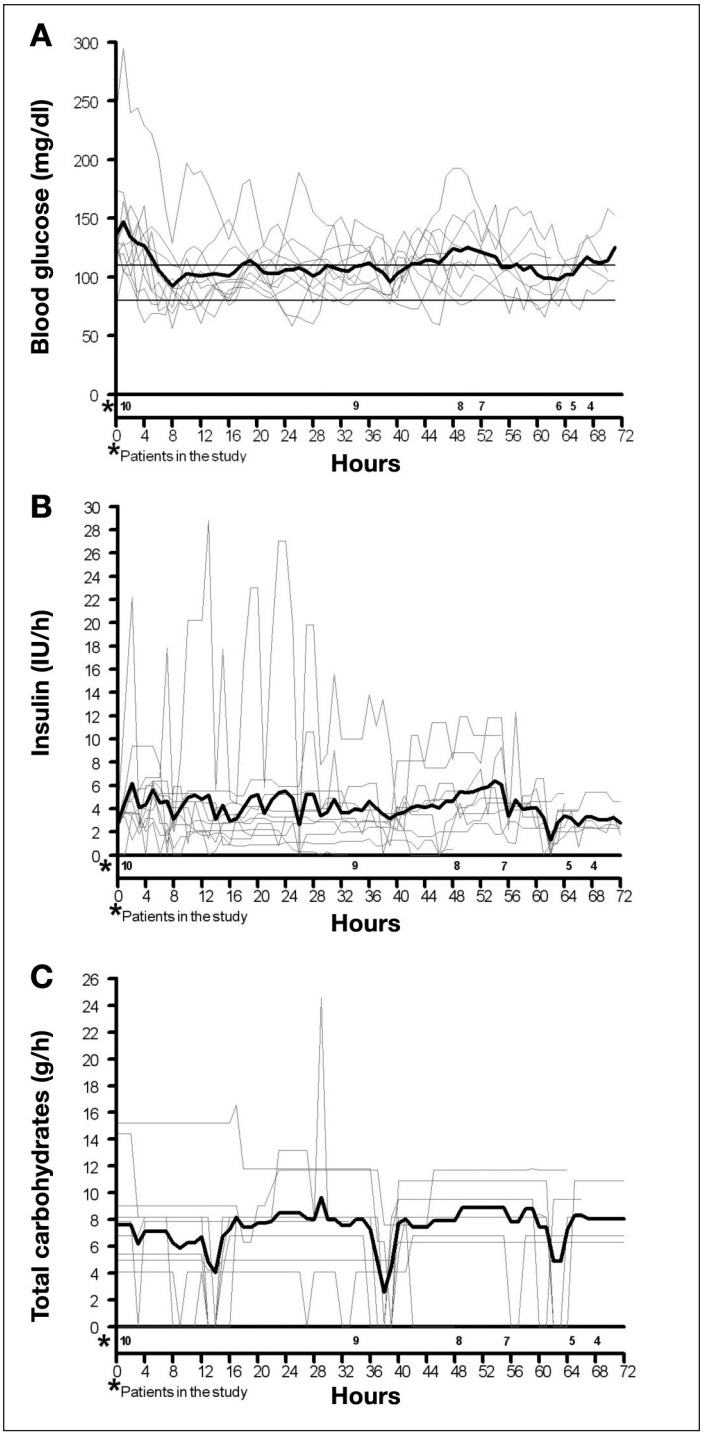

Figure 2. Average (bold) and individual (thin) profiles for the CS-1 system to support tight glycemic control for **(A)** glucose, **(B)** insulin dose, and **(C)** carbohydrate intake from hours 0 to 72.

Insulin and Carbohydrates and Sampling Frequency

Mean and individual profiles of insulin and carbohydrate content of nutrition are given in **Figures 2b and 2c**,

respectively. The mean insulin rate was 4.2 (±2.8) IU/h, and the total carbohydrate administration was 7.5 (±2.0) g/h. The sampling interval, defined as input of glucose values into the CS-1 system, was 86.3 (±26.0) minutes.

Usability, Technical Failures, User Interventions

Twenty-one actively participating nurses completed a questionnaire. As indicated by the results in **Table 2**, the efficacy and potential capacity of the CS-1 decision support system were reported by the nursing staff. However, it was noted that the use of the current version of the system increased nurses' workload.

From a technical point of view, shortcomings of the present version of the device were identified. Communication errors between the newly developed hardware for control of the therapy (SpaceControl) and the hardware platform for the eMPC (SpaceCom) led to repetitive error messages of the device and missing data to calculate the insulin advice. Because of these technical failures of system integration, treatment had to be stopped ahead of schedule in three patients.

Eleven times (1.5% of all given advice) the nurses did not follow and, thus, overruled the advice of the CS-1 system. Advice was overruled once in three patients and three and five times in two other patients, respectively. Advice was overruled almost exclusively during states of higher insulin infusion rates.

Glucose Control in Comparison to Historical Data

When comparing results of the present investigation to a previous study,[16] which was performed at the same intensive care unit, glucose control as established by the CS-1 decision support system was as tight as using a laptop-based version of the eMPC algorithm [BG 108 mg/dl (±13)]. In comparison to the standard management protocol (BG 140 mg/dl (±29) as reported in the study by Pachler and colleagues,16 a significant improvement of glucose control could be demonstrated using the CS-1 system (**Figure 3**).

Discussion

Our investigation demonstrated that in patients at a medical ICU, tight glycemic control could be established following the advice of the CS-1 decision support system. In comparison to a previous investigation studying the efficacy of a laptop version of the eMPC in a randomized controlled trial, the CS-1 decision support system was as effective as the eMPC in controlling glycemia.

The increased rate of hypoglycemia has often been described as the limiting factor for the establishment of tight glycemic control.[10,11,18,20,21] Hence, the prevention of hypoglycemic episodes in conjunction with the establishment of tight glucose control as indicated using the CS-1 system is a positive and promising finding.

Table 2.
Results from Conducted Survey[a]

Overall efficacy of BG control by the CS-1 system was	4	9	6	1	1
	Excellent		Moderate		Poor
Workload applying the CS-1 system in comparison to regular protocol was	2	17	2	0	0
	Increased		Equal		Decreased

	Yes (*n*)	No (*n*)
Do you think BG control of your patient was more efficient to handle than using the regular protocol?	19	2
Did you feel confident using the eMPC algorithm?	21	0
Do you think mistakes in BG control can be avoided using the eMPC algorithm?	20	1
Do you think that an updated version of the CS-1 system can be used in the daily routine of an ICU?	21	0

[a] Each actively participating ICU nurse completed the standardized questionnaire. The number of responses is shown for each question asked.

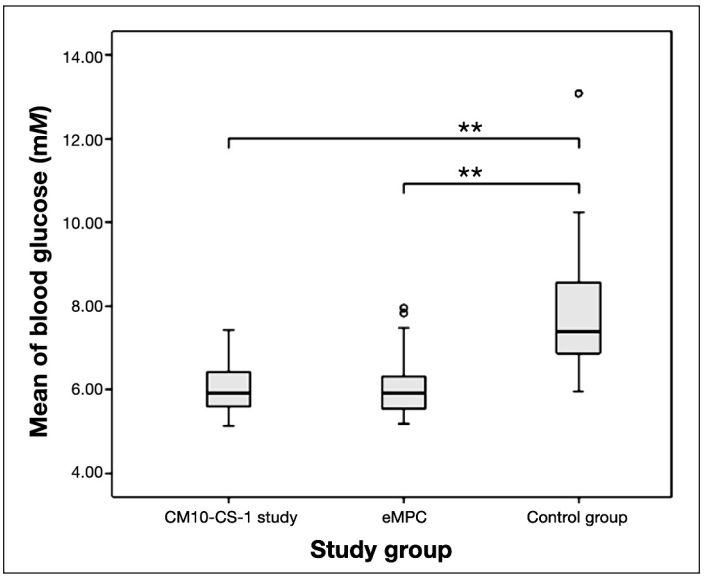

Figure 3. Arterial blood glucose distribution between CS-1 system and historical data from the same ICU using a laptop-based eMPC algorithm or standard treatment. Boxes indicate median (thick line), 25 and 75% percentiles (box), 95% confidence intervals (error bars), and outliers (open circles). $^{**}p < 0.001$.

The institutional implementation of a glucose management protocol is a complex and long process.[22–25] In our investigation, efforts for the CS-1-related training activities for the nursing staff required 1 hour per person. In our opinion, this is an acceptable time for implementation of a standardized process regarding tight glucose control.

While results suggest that using the eMPC algorithm can reliably establish tight glycemic control when integrated into a standard infusion system and being operated via nursing staff, some matters must be viewed with caution. As observed, treatment had to be stopped ahead of schedule in 3 out of 10 patients because of technical problems. Several technical malfunctions of the device, such as repetitive error messages and missing data in the data log due to communication problems between the new hardware components, are shortcomings of the present version of the device and limited the eMPC performance. It is imperative to improve the stability of the system by solving these technical failures for the next phase of the development process.

The intended use of the device is to act as a decision support system for the ICU staff. According to results, the advice of the CS-1 system was overruled 11 times (1.5%) by the nurses during the evaluation period. Taking into consideration that published literature regarding adherence of ICU staff to insulin infusion protocols reports deviations from the protocol up to 50%,[26–28] present data indicate a high adherence to the proposal given by the CS-1 system. When reviewing the patients' charts retrospectively, in 9 out of 11 cases, overruling of the devices' advice was probably not necessary in terms of preventing an endangering situation as only a slight modification of the suggestion of the device was performed. However, in 2 cases the intervention of nurses is likely to have avoided the occurrence of a hypoglycemic episode. Again, missing data following communication problems between the new hardware components are likely to have contributed to the false advice given by the eMPC in such cases. In general, because the CS-1 system cannot control for all glucose-relevant factors (e.g., fever indicating increasing insulin resistance, steroid administration), the system architecture has been designed to allow overruling of the insulin dose advice.

It is a fact that safe establishment of tight glycemic control requires frequent glucose monitoring. The sampling interval, which has been defined as the input of glucose values entered into the CS-1 system, was significantly shorter in comparison to a previous laptop-based eMPC study (86 minutes vs 120 minutes) that used the same algorithm implemented in the CS-1 system.[14] In general, this would indicate that the work demand for the ICU nursing staff would be increased markedly when using the CS-1 system instead of the laptop-based algorithm. However, the factors contributing to this result need to be addressed. First, adherence to the optical and acoustical prealarm (–10 minutes) for the glucose input was extremely high and therefore shortened the interval in comparison to the previous laptop-based trials where this feature was not installed. Second, several technical malfunctions required a repetitive input of glucose values into the system, which also lowered the sampling interval. Therefore, the sampling interval as calculated using the CS-1 system requires careful interpretation. Further investigations using a technically improved version of the CS-1 system may demonstrate a sampling frequency that is more conceivable in clinical care. This interpretation is confirmed by results of the nurse questionnaire. Tight glycemic control when established using the CS-1 decision support system requires an increased workload compared to standard treatment. However, the CS-1 system has the potential to be used efficiently in a daily routine.

During the EC-funded project CLINICIP, we have been able to demonstrate since 2004 that the eMPC algorithm can establish tight glycemic control in the ICU (medical and surgical) as well as in the perioperative setting[14–16] with a very low incidence of hypoglycemic episodes. Regarding the increased sampling frequency and workload as observed within the present investigation, we are optimistic that both will be reduced in the technically revised system, which is currently under development. In addition, the increasing number of patients treated with the eMPC allows further improvement of the algorithm itself. In a recently published abstract of a laptop-based study in Leuven, Belgium, the sampling interval could be extended to a mean interval of ~3 hours.[29] Moreover, the measuring time for blood glucose with ICU-licensed point of care devices is constantly decreasing, which further reduces the workload for the nursing staff. Finally, the system architecture of the CS-1 decision support system will allow interaction with continuous glucose measurement devices once a robust performance can be guaranteed.

In conclusion, our investigation demonstrated that tight glycemic control in patients at a medical ICU can be established following the advice of the newly developed CS-1 decision support system. Accordingly, and with

technical improvement required, the CS-1 system has the capacity to be a reliable tool for routine establishment of glycemic control for critically ill patients.

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Disclosure:

Doris Röthlein, Matthias Wufka, and Norman Kachel are employees of B. Braun, the manufacturer of the CS-1 decision support system. Roman Hovorka is a consultant for B. Braun and has applied for a patent related to this work. Martin Ellmerer is a consultant for B. Braun.

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