Efficacy and safety of an insulin infusion protocol during and after cardiac surgery

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Received 1st March 2009; received in revised form 20 May 2009; accepted 26 May 2009
Available online 25 January 2010

Abstract

Aim. – Perioperative tight blood glucose (BG) control using insulin therapy after major surgery is a difficult, time-consuming task that also raises some concerns over the risk of severe hypoglycaemia. The aim of the present prospective study was to evaluate the efficacy and safety of an insulin therapy protocol in use at our institution.

Methods. – A total of 230 consecutive patients (mean ± SD age: 67 ± 11 years; diabetic patients: n = 62) undergoing cardiac surgery (coronary artery bypass grafting: n = 137; 20% off-pump) or intrathoracic aortic (n = 10) surgery were included. BG control was managed according to an insulin therapy protocol, described by Goldberg et al. (2004) [11], in use for 6 months in our intensive care unit. Insulin infusion rate and frequency of BG monitoring were both adjusted according to: (1) the current BG value; (2) the previous BG value; and (3) the current insulin infusion rate. Efficacy was assessed by the percentage of time spent at the target BG level (100–139 mg/dL) intraoperatively and during the first 2 postoperative days (POD).

Results. – All patients received postoperative insulin therapy. Patients spent 57.3% and 69.7% of time within the BG target range on POD 1 and 2, respectively. The percentage of time was significantly higher in nondiabetics than in diabetics. Mean BG measurements per patient intraoperatively, on POD 1 and on POD 2 were 4 ± 1, 10 ± 2 and 7 ± 2, respectively. No patient experienced any severe hypoglycaemic events (BG < 50 mg/dL).

Conclusion. – This study showed that a BG target of 100–139 mg/dL can be safely achieved with an insulin therapy protocol that can be routinely used in everyday clinical practice.

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Keywords: Blood glucose; Insulin; Hyperglycaemia; Cardiac surgery; Hypoglycaemia

Résumé

Efficacité et sécurité d’un protocole d’administration d’insuline pendant et après chirurgie cardiaque.

Objectifs. – Le contrôle strict périopératoire de la glycémie après chirurgie majeure est une tâche difficile et consommatrice de temps de soignants, qui expose au risque d’hypoglycémie sévère. Le but de cette étude prospective était d’évaluer l’efficacité et la sécurité d’un protocole d’insulinothérapie en cours dans notre établissement.

Méthodes. – Deux cent trente patients consécutifs (âge moyen [± DS]: 67 ± 11 ans, diabétiques: n = 62) ayant bénéficié de chirurgie cardiaque (pontages: n = 137; chirurgie sans CEC: 20%) ou de chirurgie aortique intrathoracique (n = 10) ont été inclus. La glycémie était prise en charge au moyen d’un protocole d’insulinothérapie décrit par Goldberg et al. (2004) [11], utilisé depuis six mois dans notre unité de soins intensifs. La perfusion d’insuline et le rythme de surveillance de la glycémie étaient ajustés en fonction de (1) la glycémie actuelle; (2) la glycémie précédente; et (3) le débit de perfusion de l’insuline. L’efficacité du protocole était évaluée par le pourcentage de temps passé dans la cible de glycémie (100–139 mg/dL) dans les deux premiers jours postopératoires (J1 et J2).
1. Introduction

Hyperglycaemia is increasingly being recognized as a risk factor for adverse outcomes among patients admitted to the intensive care unit (ICU) following cardiac surgery [1,2]. For this reason, several controlled studies have proposed strict perioperative glycaemic control using intensive insulin therapy (IIT), although the results on patients’ outcomes are conflicting [3–7].

A randomized controlled trial by Van den Berghe et al. [6] showed that IIT reduced mortality in patients admitted to the surgical ICU from 8.0% with conventional treatment to 4.6%. Furnary et al. [4] reported a significant decrease in sternal wound infection with IIT, but their results were tempered by the fact that they were compared with historical controls. In addition, a recent large-scale, international, randomized trial showed that a strict blood glucose (BG) target (81–108 mg/dL) increased mortality among adults admitted to the ICU [7].

The protocols used to control BG, and the degree of BG control achieved with insulin therapy, have varied from one study to another. However, whatever the BG target, lowering BG during the perioperative period remains a difficult and time-consuming task. In the study by Van den Berghe et al. [6], for instance, the protocol necessary to achieve the target BG of 79–110 mg/dL (4.4–6.1 mmol/L) was different from the way physicians generally make insulin therapy adjustments. Furthermore, the amount of time that patients were able to maintain the achieved target glycaemia with the study protocol and the nurses’ adherence to the protocol have rarely been described. Lecomte et al. [8] reported on the effectiveness of tight glycaemic control using an algorithm for insulin therapy both during and after cardiac surgery. However, the algorithm required a mean of 29 BG measurements per patient during the study period (all within the first 24 h), a task that is difficult to achieve in routine clinical practice.

On the other hand, there are serious concerns regarding the consequences of severe hypoglycaemia when insulin therapy is used to achieve tight BG control [9,10], as the optimal degree of glycaemic control is, as yet, undetermined. In addition, the precise causes of the increased mortality reported in intensively BG controlled patients in some studies, such as the recently published NICE-SUGAR trial [10], are still unconfirmed, although the increased frequency of severe hypoglycaemia is a likely culprit. Such strict BG monitoring as reported by Lecomte et al. [8] may help to reduce the incidence of hypoglycaemia although, in their study, a BG < 50 mg/dL (2.78 mmol/L) was nonetheless observed in 0.6% of the patients.

Overall, the complexity of most IIT protocols and their potential for hypoglycaemia may render them less acceptable to medical teams in cardiac ICUs outside of clinical trials.

For this reason, the protocol by Goldberg et al. [11] is of great interest, as the main characteristic of this protocol is that both the frequency of BG measurements and changes in insulin infusion rates depend upon the rate of change in BG levels. The target BG is 100–139 mg/dL (5.5–7.7 mmol/L) and the protocol, evaluated in 118 patients admitted to the cardiothoracic ICU, has proved to be effective and safe. However, implementation of the protocol has not been extensively evaluated in other institutions.

The aim of the present study was to evaluate in both diabetic and nondiabetic patients undergoing cardiac or intrathoracic aortic surgery: (1) the compliance of the ICU team to the insulin therapy protocol based on that of Goldberg et al.; (2) the quality of glucose control achieved; and (3) the safety of the protocol as assessed by the incidence of induced hypoglycaemia.

2. Patients and methods

This prospective study took place from December 2005 to April 2006 in the thoracic and cardiovascular surgery department of a university hospital. The study was conducted according to the French bioethics law (Article L. 1121-1 of the French common law number 2004-806, August 9, 2004). All patients gave their informed consent to participate in the study and, as the study was only observational and did not modify the current diagnostic or therapeutic strategy used at our institution, authorization was given to waive putting the informed consent into writing. All consecutive patients who underwent cardiac or intrathoracic aortic surgery and were admitted to the ICU during the study period were eligible for the study. According to the presence or absence of a past medical history of diabetes mellitus (DM) – whatever the type of diabetes – patients were included in either the DM or non-DM group. Patients with diabetic ketoacidosis or diabetic non-ketotic hyperosmolar coma were excluded. Demographic data, the type of surgery and outcome data were collected. Outcome parameters included postoperative mechanical ventilation for > 48 h, renal failure requiring dialysis, deep sternal infection, neurological complications lasting > 24 h, duration of hospital stay and in-hospital death.

2.1. Insulin therapy protocol

BG control was managed in all patients according to a unique insulin therapy protocol (Appendix 1) that was slightly modified
from that of Goldberg et al. [11]. The protocol was developed by an endocrinology consultant (A.P.) and an anaesthesiologist (W.S.) together with a team of senior anaesthesiologists, intensivists and nurses. The protocol was initiated in the unit 6 months before the start of the study to allow time for staff training and to resolve any practical problems.

Briefly, insulin therapy was based primarily on the rate of glycaemic changes and used three measurements to adjust intravenous insulin infusions: (1) the current BG value; (2) the previous BG value; and (3) the current insulin infusion rate. The target BG level was 100–139 mg/dL (5.5–7.7 mmol/L), and the study period began upon the arrival of the patient to the operating room (OR), with the first BG measured after the introduction of an indwelling arterial catheter (mostly in the radial artery). The arterial line was flushed with saline, and medications were diluted in glucose-free solutions unless there were specific recommendations otherwise.

All BG data were obtained from glucose meter readings (MediSense® OptiumTM; MediSense UK Ltd, Abingdon, Oxon, UK), measured from arterial blood (not finger-stick) samples. Glucose meters were calibrated monthly, according to the manufacturer’s specifications. BG measurements were taken hourly during the intraoperative period and after admission to the ICU until a stable BG level, defined as three consecutive values within the BG target range, was obtained. BG was then checked every 3 h. However, hourly BG monitoring was resumed if any of the following occurred: (1) change in insulin infusion; (2) change in clinical condition; or (3) initiation or cessation of vasopressor therapy or renal replacement therapy. No intravenous (IV) glucose was administered intraoperatively. In the ICU, IV glucose infusion levels were kept stable at a rate of 4.0–4.5 g/h, using highly accurate volumetric infusion devices, in both DM and non-DM groups. Depending on the patient’s clinical condition, oral intakes were initiated as soon as possible postoperatively. The study period ended when either oral feeding was initiated (IV insulin therapy replaced by subcutaneous insulin) or 2 days postoperatively.

2.2. Blood glucose control

The main criterion to assess the efficacy of the insulin therapy protocol was the percentage of time spent by the patient at the target BG level during the study period, defined as the time spent at the target BG level in relation to the total time of the protocol × 100. It was assumed that BG values would follow a linear trend between each successive measurement.

Secondary criteria of efficacy were: (1) percentage of time spent at the target BG intraoperatively; (2) percentage of time spent at the target BG per 24-h period; and (3) daily mean BG, calculated as the mean of all BG measurements during each 24 h period.

We also evaluated the number of patients who experienced at least one episode during the study period of: (1) mild hypoglycaemia, defined as a BG 50–75 mg/dL (2.78–4.20 mmol/L), or severe hypoglycaemia, defined as a BG < 50 mg/dL (< 2.78 mmol/L); and (2) clinical symptoms that may have been related to hypoglycaemia, including confusion, coma or convulsion. In cases of BG < 50 mg/dL (< 2.78 mmol/L) or hypoglycaemia-related symptoms, IV insulin was stopped and replaced by an IV 3 g bolus of dextrose.

A rise in BG to > 200 mg/dL (> 11.1 mmol/L) and lasting at least 2 h was considered a severe hyperglycaemic event and recorded.

2.3. Adherence to study protocol

One of the main difficulties in applying complex protocols is the compliance of the medical and nursing staff to protocol requirements. To assess whether BG monitoring and changes in insulin infusion rate were being carried out by the nursing team according to the protocol, we used a randomization table to randomly select 25 of the 230 patients’ charts. The number of BG measurements taken and changes in insulin infusion rate actually made by the nurses was recorded by an investigator (C.S.), and expressed as a percentage of the number of BG measurements and changes required by the protocol.

2.4. Statistical analysis

All data analyses were conducted using SPSS software for Windows® (SPSS Inc., Chicago, IL, USA). Data are expressed as either means ± standard deviation (SD) or as medians (interquartile range) where appropriate. Intergroup comparisons were carried out using chi² and Student’s t tests for qualitative and quantitative variables, respectively, and P < 0.05 was considered significant.

3. Results

Altogether, 251 patients underwent surgery during the study period. As medical charts were incomplete for 21 patients, a total of 230 patients–62 in the DM group (93.5% type 2 DM)–were finally included. The flow chart of patients during the study period is shown in Fig. 1. Patients’ baseline characteristics and main outcomes in both DM and non-DM groups are given in Table 1.

Compliance with the study protocol was evaluated in 25 selected charts, and showed that 72% of the BG assays were performed according to the timeframe stated in the insulin therapy protocol. A time lag of > 3 h between the two BG measurements was observed in 11 cases. Changes in insulin infusion rate were carried out according to the protocol in 82% of cases.

A total of 898 and 3870 BG measurements were taken during the intraoperative period and the first two postoperative days (POD), respectively. The mean daily numbers of BG measurements per patient are presented in Table 2.

During the intraoperative period, intravenous insulin was administered to significantly more patients in the DM vs non-DM group (53% vs 11%; P < 0.001). However, all patients, regardless of group, received insulin therapy postoperatively.

Mean BG and percentage of time spent at the BG target in both DM and non-DM patients intraoperatively, and on POD 1 and POD 2, are shown in Figs. 2 and 3, respectively.
Throughout the study period, no patient experienced any severe hypoglycaemic events (BG < 50 mg/dL (<2.78 mmol/L)). Mild hypoglycaemia, defined as a BG level of 50–75 mg/dL (2.78–4.20 mmol/L) occurred 44 and 11 times in the non-DM and DM groups, respectively, during the study period. Mild hypoglycaemic events were significantly more frequent in the non-DM patients during the intraoperative period. Postoperatively, four patients in the non-DM group felt drowsy and received an IV bolus dose of glucose to restore normal BG. In the remaining cases, insulin therapy was stopped.

Table 1
Patients’ baseline characteristics and outcome in diabetes mellitus (DM) and non-DM groups.

<table>
<thead>
<tr>
<th></th>
<th>DM group</th>
<th>Non-DM group</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n [%])</td>
<td>62 (27)</td>
<td>168 (73)</td>
<td>230</td>
</tr>
<tr>
<td><strong>Baseline data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.3 ± 9.5</td>
<td>67.0 ± 12</td>
<td>67.1 ± 11.3</td>
</tr>
<tr>
<td>Males (%)</td>
<td>80.6</td>
<td>74.4</td>
<td>76.1</td>
</tr>
<tr>
<td>Body mass index* (kg/m²)</td>
<td>28.9 ± 4.1</td>
<td>26.8 ± 4.2*</td>
<td>27.3 ± 4.3</td>
</tr>
<tr>
<td>Insulin therapy (%)</td>
<td>29</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Oral antidiabetic treatment (%)</td>
<td>77</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>BG upon arrival at OR (mg/dL)</td>
<td>127 ± 35</td>
<td>92 ± 19**</td>
<td>102 ± 29</td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG (n [%])</td>
<td>48 (77.4)</td>
<td>89 (53.0)**</td>
<td>137 (59.6)</td>
</tr>
<tr>
<td>CABG on pump/off pump (n/n)</td>
<td>27/21</td>
<td>63/26</td>
<td>90/47</td>
</tr>
<tr>
<td>Valve replacement (n [%])</td>
<td>19 (30.7)</td>
<td>73 (43.5)</td>
<td>92 (40.0)</td>
</tr>
<tr>
<td>Thoracic aortic surgery (n [%])</td>
<td>2 (3.2)</td>
<td>21 (12.5)</td>
<td>23 (10.0)</td>
</tr>
<tr>
<td>Emergency surgery (%)</td>
<td>7 (11.3)</td>
<td>24 (14.3)</td>
<td>31 (13.5)</td>
</tr>
<tr>
<td><strong>Postoperative period and outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed red cell transfusion (%)</td>
<td>46.7</td>
<td>46.4</td>
<td>46.5</td>
</tr>
<tr>
<td>Steroid therapy (%)</td>
<td>4.8</td>
<td>4.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Use of vasopressor in ICU (%)</td>
<td>17.7</td>
<td>18.4</td>
<td>18.3</td>
</tr>
<tr>
<td>In-hospital death (%)</td>
<td>8.1</td>
<td>3.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Mechanical ventilation &gt;48 h (%)</td>
<td>8.1</td>
<td>5.4</td>
<td>6.1</td>
</tr>
<tr>
<td>Dialysis (%)</td>
<td>4.8</td>
<td>3.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Neurological complicationsb (%)</td>
<td>0</td>
<td>3.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Deep sternal infection (%)</td>
<td>3.2</td>
<td>1.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>13.4 ± 9.0</td>
<td>13.1 ± 8.6</td>
<td>13.2 ± 8.7</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD unless otherwise specified; *P<0.05; **P<0.001, DM group vs non-DM group; BG: blood glucose level; OR: operating room; CABG: coronary artery bypass grafting; ICU: intensive care unit.

a Calculated as weight (kg) divided by height² (metres squared).
b Including transient and permanent strokes.
Table 2

Data related to blood glucose (BG) control during the intraoperative period and the first two postoperative days in both diabetes mellitus (DM) and non-DM groups.

<table>
<thead>
<tr>
<th></th>
<th>Intraoperative period</th>
<th>Postoperative day 1</th>
<th>Postoperative day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DM  (n [%])</td>
<td>Non-DM   (n [%])</td>
<td>DM  (n [%])</td>
</tr>
<tr>
<td>Patients</td>
<td>62 (27.0)</td>
<td>168 (73.0)</td>
<td>61 (26.8)</td>
</tr>
<tr>
<td>BG assays per patient</td>
<td>3.7 ± 0.8 [1–5]</td>
<td>4.1 ± 1.1 [2–5]</td>
<td>10.4 ± 2.4 [5–18]</td>
</tr>
<tr>
<td>BG (mg/dL)</td>
<td>130 ± 27</td>
<td>101 ± 17**</td>
<td>150 ± 20</td>
</tr>
</tbody>
</table>

Hypoglycaemic events

<table>
<thead>
<tr>
<th></th>
<th>All events (n)</th>
<th>Mild hypoglycaemia (n [%])</th>
<th>Severe hypoglycaemia (n)</th>
<th>Hyperglycaemic events (n [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>36</td>
<td>5 (8.2)</td>
<td>0</td>
<td>16 (26.2)</td>
</tr>
<tr>
<td>Mild hypoglycaemia</td>
<td>3 (3.8)</td>
<td>33 (19.6)*</td>
<td>5 (8.2)</td>
<td>22 (37.3)</td>
</tr>
<tr>
<td>Severe hypoglycaemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycaemic events</td>
<td>9 (14.5)</td>
<td>12 (7.1)</td>
<td>17 (10.2)**</td>
<td>27 (16.5)**</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD unless otherwise specified; *P < 0.05; **P < 0.001, DM group vs non-DM group; mild hypoglycaemia: BG 50–75 mg/dL; severe hypoglycaemia: BG < 50 mg/dL; hyperglycaemic event: BG > 200 mg/dL.

Fig. 2. Percentage of time spent within the BG target range (100–139 mg/dL) on postoperative day 1 (POD 1) and 2 (POD 2). DM: diabetes mellitus; *P < 0.05; **P < 0.001, DM group vs non-DM group.

and BG levels returned to normal values within 1 h. No clinical sequelae were noted with these episodes.

The number of hyperglycaemic episodes, defined as BG > 200 mg/dL (> 11.1 mmol/L) and lasting for at least 2 h, were significantly more frequent in the DM compared with non-DM patients (Table 2).

4. Discussion

The key finding of the present study was that intraoperative and early postoperative BG control using an insulin therapy protocol in fasting patients was feasible as part of the everyday practice at a cardiac surgery unit, and did not induce severe or symptomatic hypoglycaemia.

The study aimed to evaluate the difficulties of applying the results of well-controlled clinical trials to routine clinical practice. The protocol was automatically applied to all patients admitted to the OR and ICU in our cardiac surgery unit. The protocol was evaluated 6 months after its initial implementation to assess whether such a complex protocol could be adhered to over time. However, no particular attention or assistance was given to the staff, nor was the usual number of nurses (one patient per full-time-equivalent anaesthetist nurse in the OR, and three patients per full-time-equivalent nurse in the ICU) changed because of the study. It was found that 72 and 82% of BG assays and changes in insulin infusion rate, respectively, were performed within the time frame required by the protocol. However, comparisons with other studies are difficult, as validated tools to assess the adequacy of the algorithms for controlling BG in the ICU are lacking [12]. Nevertheless, one of the reasons for such reasonable compliance with the protocol may be that the interval between the two BG measurements was 1–3 h, depending on whether or not BG levels were stable, and the median number of BG measurements per patient was reduced between POD 1 and POD 2. Thus, any extra work due to BG monitoring was considered acceptable by the nurses, as it was limited to a specific time period and corresponded to a time when the patients already required special care. This is in contrast to the findings of Plank et al. [13] who, using a fully automated model of a predictive control algorithm that required hourly sampling, found that such a short sampling interval would markedly increase the work demands on the ICU nursing staff and would therefore not be feasible for routine care.

The present study evaluated an insulin therapy protocol using ‘softer’ BG targets [100–139 mg/dL (5.5–7.7 mmol/L)] than the stricter Leuven protocol [79–110 mg/dL (4.4–6.1 mmol/L)].
Berghe et al. [5,6] cannot be explained by more frequent hypoglycaemic events from two randomized controlled trials by Van den Berghe et al. This suggests that the lack of any survival benefit [5] remains hypothetical. As in the study by Van den Berghe et al. [11], is based on both the direction and velocity of glucose changes, and not on individual insulin sensitivity. Insulin resistance is, in fact, a major concern in acute medical or surgical situations and especially in diabetic patients. In the Lecomte et al. study, assessment of the efficacy and safety of the insulin therapy protocol using a less stringent BG target of < 140 mg/dL (<7.8 mmol/L). In contrast, post-hoc analysis of the original Leuven study indicated that moderate BG control [110–150 mg/dL (6.1–8.3 mmol/L)] conferred only moderate advantages compared with a target BG of 80–110 mg/dL (4.4–6.1 mmol/L) [5].

The BG targets chosen for the present study were also influenced by the previously reported difficulties of achieving strict BG targets without inducing severe hypoglycaemia, as was recently reported in the NICE-SUGAR trial [7]. Indeed, in the report by Kanji et al. [17], the target range of 80–110 mg/dL (4.4–6.1 mmol/L) was achieved 47% of the time by the protocol group only, and Shulman et al. [18], who developed a computerized decision-making support system, reported that such a target BG was achieved for a median of only 23% of the time.

Based on observational studies showing that intraoperative hyperglycaemia is an independent risk factor for perioperative complications or death, the protocol used in the present study aimed to control BG levels from the time of the patient’s arrival at the OR [2]. As a consequence, 53% and 11% of the DM and non-DM patients, respectively, received insulin therapy during the intraoperative period. Ouattara et al. [19] showed that poor intraoperative control of BG in diabetic patients was associated with a worsened hospital outcome after cardiac surgery. However, this finding needs to be reevaluated in light of the recent report from Gandhi et al. [20], who could find no improvement in cardiac surgery patients’ outcomes using strict intraoperative BG control compared with intraoperative initiation of insulin if BG levels remained > 11.1 mmol/L (200 mg/dL).

In the present study as in others, the success rates with the insulin infusion protocol were lower in diabetic patients than in nondiabetics [5,6]. Our insulin protocol, adapted from Goldberg et al. [11], is based on both the direction and velocity of glucose changes, and not on individual insulin sensitivity. Insulin resistance is, in fact, a major concern in acute medical or surgical situations and especially in diabetic patients. In the Lecomte et al. protocol [8], insulin dosage was adjusted according to the projected insulin sensitivity in relation to the intraoperative or postoperative period, not the individual insulin resistance of each diabetic patient. However, whether or not this explains the diabetic patients’ difficulty in achieving their metabolic objectives remains hypothetical. As in the study by Van den Berghe et al. [5], hypoglycaemic events were also less frequent in our diabetic patients. This suggests that the lack of any survival benefit with the IIT in patients with a previous history of diabetes in the pooled data from two randomized controlled trials by Van den Berghe et al. [5,6] cannot be explained by more frequent hypoglycaemic events. In fact, on the contrary, this observation could suggest that a too-rapid normalization of BG could be deleterious in high-cardiovascular-risk diabetic patients, as supported by the recent identification of the previously unrecognized dangers of intensive glucose-lowering in high-risk patients with type 2 diabetes in the ACCORD study [21]. It is worth noting that a large percentage of high-cardiovascular-risk patients can be found among diabetic patients in studies evaluating IIT in critically ill patients, as was also observed in the present study, where more than three-fourths of the DM patients had undergone coronary artery bypass grafting. The percentage of coronary disease was significantly higher among DM vs non-DM patients (77.4% vs 53.0%, respectively).

Several stringent BG control protocols have resulted in a high incidence of severe hypoglycaemic episodes. In a study by Van den Berghe et al. [6], the incidence of hypoglycaemia-defined as a BG < 40 mg/dL—was 5.1 and 0.7% in the insulin treatment group and conventional treatment group, respectively. The VISEP study, a multicentre German trial, was stopped prematurely because of the significantly higher incidence of hypoglycaemia with insulin vs conventional therapy (12.1% vs 2.1%; P < 0.001) [14]. In a retrospective study of 5365 consecutive, critically ill, medical, surgical and cardiac patients, Krinsley and Grover found that intensive glycaemic monitoring and tight glycaemic control were independent risk factors for the development of severe hypoglycaemia (defined as a BG < 40 mg/dL) [16]. This is a serious complication, as it has been shown that a single episode of severe hypoglycaemia is an independent predictor of mortality for the entire cohort (odds ratio, 2.28; 95% confidence interval, 1.41–3.70; P < 0.0008). Treggiari et al. [10] recently reported a fourfold increase in the incidence of hypoglycaemia with an insulin therapy protocol aiming at a BG target of 80–110 mg/dL (4.4–6.1 mmol/L) in ICU patients. Although Lecomte et al. [8] found a lower incidence of severe hypoglycaemia (in the 0.6% range) during the first 24 h after cardiac surgery using a dynamic algorithm of insulin therapy, it should be noted that this was achieved using stringent BG monitoring (a mean of 29 BG measurements per patient during POD 1), a feat difficult to achieve in everyday practice.

Overall, these data suggest that hypoglycaemia-related complications and mortality may negate the survival benefits of tight glycaemic control in the ICU. We found that the protocol we adapted from Goldberg et al. [11] was safer, as it did not induce severe hypoglycaemia in a real-life context. However, the present study has several other limitations. First, the study period was limited to before the start of postoperative enteral feeding, a period reported to be at risk of wide variations in BG [22]. It should be noted that a minimum of three days of IIT was required to obtain a sizable outcome benefit in the studies by Van den Berghe et al. and Furnary et al. whereas, in our present study, assessment of the efficacy and safety of the insulin therapy protocol was performed only for 48 h [5,23]. Finally, evaluation of the efficacy of any therapeutic protocol depends on the criteria used. We chose to use the percentage of time spent within the BG target level, and our results are comparable to those of Kanji et al. [17] (11.3 ± 7.9 h/day). However, the recent literature reveals a lack of consensus on the primary indicator of perioperative glycaemic control. For instance, the average of all BG measurements obtained during the perioperative period was used in the studies by Estrada et al. and Furnary et al., while BG...
measured on admission and every morning postoperatively were taken into account in the Leuven studies [1,4–6]. Clearly, further research is required to identify the most effective protocol, and the best way to organize the ICU management of IIT. In addition, there is a clear need to standardize protocols for insulin therapy to address the differences in glycaemic targets, nutritional and glucose supplementation, and insulin-dosing strategy. For this reason, the glycaemic penalty index proposed by Van Herpe et al. [24] may be useful in the future evaluation of BG control algorithms. In accordance with the Goldberg et al. protocol [11], the present study also used the assumption – which is open to criticism – that BG values follow a linear trend between successive measurements. However, this was considered necessary to ensure that all insulin infusion changes contributed equally to the statistical analyses.

In conclusion, the present study found that a reasonable BG target of 100–139 mg/dL can be safely achieved using an insulin therapy protocol that can be included in the everyday clinical practice of a postoperative ICU in a university hospital.

Conflicts of interest

The authors have not declared any conflict of interest.

Appendix 1.

Insulin infusion protocol (adapted from Goldberg et al. [11]).

General statements

- Target blood glucose (BG) levels: 100–139 mg/dL
- Blood sampling for BG measurement: 2 mL of blood obtained via an indwelling arterial catheter, flushed with continuous infusion using glucose-free solution
- BG measurement: MediSense Optium
- Preparation of insulin infusion: 1 unit of regular human insulin in 1 cc of saline
- Administration of insulin infusion via infusion pump in increments of 0.5 U/h.

Initiating insulin infusion

Initial BG rounded to nearest 0.5 U for both bolus and initial infusion rate.

BG monitoring

Check BG hourly until BG is stable (3 consecutive BG values within target range)

Then check BG every 3 hours if:

- BG is stable
- No significant change in clinical condition, and
- No significant change in nutritional intake.

Consider temporary resumption of hourly BG monitoring if any of the following events occurs:

- Any change in insulin infusion rate
- Significant change in clinical condition
- Initiation or cessation of pressor or steroid therapy
- Initiation, cessation or rate change of nutritional support.

Changing the insulin infusion rate

If BG is <50 mg/dL:

- Stop insulin infusion, give 10 mL of D30 IV and recheck BG within 15 min
- When BG >1 g/L, wait for 1 h, then resume insulin infusion at 50% of original rate.

If BG is in the 50–74 mg/dL range:

- Stop insulin infusion
- If patient is symptomatic: give 10 mL of D30 IV and check BG again within 15 min
- If patient is asymptomatic: give 5 mL of D30 IV and check BG again within 15–30 min
- When BG is >100 mg/dL, wait for 1 h, then resume insulin infusion at 75% of original rate.

If BG is >75 mg/dL:

- **Step 1:** determine the CURRENT BG level-this identifies a COLUMN in the table
- **Step 2:** determine the RATE OF CHANGE from the prior BG level-this identifies a CELL in the table-then go to the right for INSTRUCTIONS.

<table>
<thead>
<tr>
<th>BG 75–99 mg/dL</th>
<th>BG 100–139 mg/dL</th>
<th>BG 140–199 mg/dL</th>
<th>BG ≥ 200 mg/dL</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG ↑ by &gt;25 mg/dL/h</td>
<td>BG ↑ by 1–50 mg/dL/h or BG UNCHANGED</td>
<td>BG ↓ by 1–25 mg/dL/h</td>
<td>BG ↓ by 26–75 mg/dL/h</td>
<td>NO INFUSION CHANGE</td>
</tr>
<tr>
<td>BG UNCHANGED or BG ↓ by 1–25 mg/dL/h</td>
<td>BG ↓ by 26–50 mg/dL/h</td>
<td>BG ↓ by 51–75 mg/dL/h</td>
<td>BG ↓ by 76–100 mg/dL/h</td>
<td>↓ INFUSION by Δ</td>
</tr>
<tr>
<td>BG ↓ by &gt;25 mg/dL/h</td>
<td>BG ↓ by 50 mg/dL/h</td>
<td>BG ↓ by &gt;75 mg/dL/h</td>
<td>BG ↓ by 100 mg/dL/h</td>
<td>HOLD × 30 min, then ↓ INFUSION by 2Δ</td>
</tr>
</tbody>
</table>
CHANGES IN INFUSION RATE ($\Delta$) are determined by the current rate.

<table>
<thead>
<tr>
<th>Current rate (U/h)</th>
<th>$\Delta$ = Rate change (U/h)</th>
<th>$2\Delta$ = 2 × Rate change (U/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;$ 3.0</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>3.0–6.0</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>6.5–9.5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>10–14.5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>15–19.5</td>
<td>Consult MD</td>
<td>Consult MD</td>
</tr>
<tr>
<td>$\geq$ 20–24.5</td>
<td>Consult MD</td>
<td>Consult MD</td>
</tr>
</tbody>
</table>

References


