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Original research

Basal insulin therapy is associated with beneficial effects on postoperative infective complications, independently from circulating glucose levels in patients admitted for cardiac surgery

P.M. Piatti [a,*], M. Cioni [c], A. Magistro [a], V. Villa [a], V.G. Crippa [a], E. Galluccio [b], B. Fontana [b], S. Spadoni [b], E. Bosi [a,b], L.D. Monti [b], O. Alfieri [c]

[a] Cardio-Metabolism and Clinical Trials Unit, Diabetes Research Institute, Department of Internal Medicine, IRCCS San Raffaele Institute, Milan, Italy
[b] Cardio-Diabetes and Core Lab Unit, Diabetes Research Institute, Department of Internal Medicine, IRCCS San Raffaele Institute, Milan, Italy
[c] Cardio-Surgery Division, IRCCS San Raffaele Institute, Milan, Italy

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ABSTRACT

Background: Although hyperglycemia is a strong predictor of postoperative infective complications (PIC), little is known about the effect of basal insulin therapy (BIT) *per se* on PIC.
Aim: To evaluate if there is an association between BIT, independent of glucose levels, and a possible improvement of PIC during the perioperative cardiosurgery period (PCP).
Methods: In 812 patients admitted for cardiac intervention and treated with a continuous intravenous insulin infusion (CIII) for hyperglycemic levels (>130 mg/dl), a retrospective analysis was performed during the PCP (January 2009–December 2011). Upon transfer to the cardiac surgery division, if fasting glucose was ≥130 mg/dl, a basal + premeal insulin therapy was initiated (121 patients, group 1); for <130 mg/dl, a premeal insulin alone was initiated (691 patients, group 2).
Findings: Compared with group 2, group 1 showed reductions in PIC (2.48% vs 7.96%, $p < 0.049$; odds ratio: 0.294; 95% CI: 0.110–0.780), C-Reactive Protein ($p < 0.05$) and white blood cell ($p < 0.05$) levels despite glucose levels and CIII that were higher during the first two days after surgery (179.8 ± 25.3 vs 169.5 ± 10.6 mg/dl, $p < 0.01$; 0.046 ± 0.008 vs 0.037 ± 0.015 U/kg/h, $p < 0.05$, respectively). Normal glucose levels were achieved in both groups from day 3 before the discharge. The mean length of hospital duration was 18% lower in group 1 than in group 2 (7.21 ± 05.08 vs 8.76 ± 9.08 days, $p < 0.007$), providing a significant impact on public health costs.
Conclusions: Basal + preprandial insulin therapy was associated with a lower frequency of PIC than preprandial insulin therapy alone, suggesting a beneficial effect of basal insulin therapy on post-surgery outcome.

Introduction

It is well recognized that inadequate perioperative glucose control is a predictor of postoperative infection rates, worse wound healing, recurrent ischemic events, increased duration of hospital stay and overall short- and long-term mortality [1–5].

The benefit of glucose control for patients undergoing surgery has been shown in many previous studies. Following cardiac surgery glucose control provides benefits even to patients without pre-existing diabetes mellitus (DM) [1,5,6]. However, intensive insulin therapy is consistently associated with increased risk for severe hypoglycemia, which may outweigh the potential benefits of reducing blood glucose [7].

According to the current published guidelines, a glycemic goal of 140–180 mg/dl is optimal in intensive care units (ICU) while tighter control of circulating glucose (110–140 mg/dl) may be appropriate in selected patients, as long as this can be achieved without a significant risk for hypoglycemia [8]. On the other hand, several studies have found an important association between

Abbreviations: PIC, postoperative infective complications; BIT, basal insulin therapy; PCP, perioperative cardiosurgery period; CIII, continuous intravenous insulin infusion; DM, diabetes mellitus; ICU, intensive care units; CRP, C-Reactive Protein; WBC, white blood cell.

* Corresponding author at: Cardio-Metabolism and Clinical Trials Unit, Diabetes Research Institute, IRCCS San Raffaele Institute, Via Olgettina 60, 20132 Milan, Italy.
E-mail address: piatti.piermarco@hsr.it (P.M. Piatti).

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hyperglycemia and susceptibility to bacterial infection [9,10], although the underlying molecular mechanisms are poorly understood. Animal studies have shown that insulin modulates the production and release of cytokines, the expression of adhesion molecules and neutrophil migration during the course of lipopolysaccharide-induced acute lung inflammation [11]. Therefore, it could be possible that an increase in circulating insulin levels by exogenous insulin therapy could be beneficial in the perioperative setting. According with the knowledge of physiologic insulin secretion, we evolved into the use of regimens that incorporate both the basal and bolus insulin therapy.

In agreement with this hypothesis, intensive insulin therapy reduces morbidity and mortality among critically ill patients [5,12] and may increase neutrophil activity and phagocytosis in patients following major surgery [13]. On the other hand, it is very difficult to differentiate the effect of insulin *per se* on the postoperative infective complications from the effects which insulin has in reducing these risks through lowering blood sugar levels.

Therefore, the aim of the present study was to perform a retrospective analysis to determine the association between a constant increase in insulin levels by the use of basal insulin therapy, independent of glucose levels, and a possible improvement of postoperative infective complications after cardiac surgery. This study selected patients admitted for cardiac interventions, where a continuous intravenous insulin infusion (CIII) for an acute increase of glucose levels was undertaken. On the day of the transfer of the patient to the cardiac surgery unit patients were divided into two groups: in one group, where fasting glucose was ≥130 mg/dl, a basal + premeal insulin was started. In the other group, where fasting glucose was <130 mg/dl, premeal insulin alone was administered. This allowed the comparison of the effect of a constant versus an intermittent increase in insulin levels on post cardiac-surgery infections.

Secondary outcomes included differences between treatment groups in daily circulating glucose concentration, the occurrence of mild or severe hypoglycemia, the length of hospital stay and the occurrence of any of the following post-surgery complications: stroke, acute renal failure, acute respiratory failure, myocardial infarction, pericardial effusion, heart failure, low cardiac output syndrome, acute atrial fibrillation, anemia or exitus.

Materials and methods

Elegible population

This was a retrospective chart review from a single cardiac surgery center. Patients who had undergone cardiac surgery were identified according to these inclusion criteria and they had to meet both 1 and 2:

1) patients with or without DM admitted for cardiac surgery due to mitral or aortic valve disease, affected by ischemic heart disease, or both;
2) patients, who during the cardiac surgery intervention period, required treatment with continuous intravenous insulin infusion (CIII) for an acute increase of circulating glucose levels (blood glucose ≥130 mg/dl on two assessments during surgery);

Exclusion criteria were:

1) Patients with cancer, undergoing chronically outpatient steroid therapy, or with type-1 DM.
2) Patients with clinically relevant hepatic disease, with serum creatinine >3.0 mg/dl, or with a history of hyperglycemia before admission during the last 3 months (HbA1c > 10%).

From January 2009 to December 2011, 2114 patients underwent surgery in the cardiac division (cardiac valve repair or replace surgery alone in 1637 patients, cardiac revascularization surgery alone in 284 patients or both cardiac revascularization surgery and cardiac valve repair or replace surgery in 193 patients).

Among these, 812 patients satisfied the inclusion criteria and were analyzed and the clinical characteristics of this population are presented in Table 1.

Study design

All subjects underwent cardiac surgeries including mitral valve replacement/repair, aortic valve replacement/repair, cardiac revascularization surgery or a combination of the aforementioned surgeries.

Consultation with a diabetologist was performed daily throughout the pre-operative, perioperative and post-surgery period to optimize the insulin therapy.

During the surgery period, if the blood glucose was ≥130 mg/dl on two assessments, a CIII was initiated and continued after transfer to the cardiovascular intensive care unit. Glucose was assessed hourly by arterial blood gases intra-operatively and every 30–120 min while in the cardiovascular intensive care unit. The same insulin infusion protocol was continued postoperatively, using the same criteria with a blood glucose target of ≤120 mg/dl. If the blood glucose reached ≤80 mg/dl, the infusion was halted and restarted only if the threshold of 130 mg/dl was reached again.

On the day of transfer from the cardiovascular intensive care unit to the cardiac surgery division, patients were fasting and the insulin infusion was stopped, if present. After 3–4 h, if the capillary fasting glucose levels were ≥130 mg/dl a basal + premeal insulin therapy was started. This occurred with 121 patients (isophane, i.e., protophane every 12 h, in 69 patients, detemir every 12 h in 50 patients and glargine every 24 h in 2 patients; group 1). The initial insulin dose of basal insulin was determined as 50% of the estimated insulin requirements of the previous 24 h, during the cardiovascular intensive care unit period (usually between 0.2 to 0.5 U/kg body weight). Conversely, if the capillary fasting

Table 1
Clinical characteristics and medical history of patients requiring continuous intravenous insulin infusion during the cardiac surgery period for an acute increase of circulating glucose levels (blood glucose was ≥130 mg/dl on two assessments during surgery) from 01 March 2009 to 30 November 2011.

No. of patients	812
Period of hospitalization	01 March 2009 to 30 November 2011
Age (years)	62.50 ± 11.50
Sex (Males/Females)	511/302
No. of patients with valve disease (VD)	633
No. of patients with ischemic heart disease (IHD)	96
No. of patients with VD and IHD	83
Co-morbidities:	
Diabetes mellitus	95
Hypertension	674
Chronic obstructive pulmonary disease	85
Chronic atrial fibrillation	195
Body weight (kg)	73.04 ± 14.03
Body mass index (kg/m^2)	25.62 ± 4.15
Fasting glucose (mg/dl)*	100.3 ± 23.7
Glycated Hemoglobin (%)*	5.52 ± 1.38
Creatinine (mg/dl)*	0.92 ± 0.37
BUN (mg/dl)*	46.92 ± 18.85
Plasma albumin (mg/dl)*	41.49 ± 3.84
Hemoglobin (g/dl)*	13.58 ± 1.62

(**)75 subjects were treated with hypoglycemic agents, 13 subjects with diet alone and 9 subjects with subcutaneous insulin therapy.
* samples were withdrawn at the entrance to the ward in the fasting state, prior to surgery.

glucose was <130 mg/dl, a premeal insulin alone administration was started (691 patients; group 2). The doses of premeal insulin (aspart insulin) therapy were adjusted according to a prespecified protocol (breakfast: 0.05–0.10 U/kg, lunch: 0.10–0.30 U/kg; dinner 0.10–0.20 U/kg).

The decision to start insulin therapy if baseline blood sugar levels were above 130 mg/dl in these patients was contained in the internal guidelines established since 2008 from doctors diabetologists and physicians of surgical departments, endorsed by the Institute's Health Department. The ability to start insulin sc therapy at levels ≥130 mg/dl was based on the daily valuation of diabetologists who interacted with nurses and doctors of the department so as to optimize insulin therapy and reduce the possible hypoglycemic episodes.

There were no significant differences between the 2 groups regarding age, gender, BMI, creatinine, BUN, plasma albumin, hemoglobin and other co-morbidities except for the presence of DM in group 1, which was significantly higher than in group 2 (19.8% vs 9.6%, $p < 0.01$). However, fasting glucose levels and glycated hemoglobin were not significantly different, being 100.1 ± 22.1 mg/dl and 5.55 ± 1.23% in group 1 and 100.9 ± 23.8 mg/dl and 5.51 ± 1.41% in group 2 ($p = 0.93$ and $p = 0.69$, respectively, Table 2).

Capillary blood glucose concentrations were obtained by nurses four times per day throughout the cardiac surgery unit period. All blood glucose check times were standardized and occurred at 7:30 am (fasting, before breakfast), 12:00 pm (before lunch), 6:00 pm (before dinner) and 12:00 am.

Outcome measures

The primary outcome of the study was the difference between treatment groups in the composite of major postoperative infective complications according to Cardiothoracic Surgical Trials Network Criteria determined by chart review for each patient [14]: deep incisional surgical infection, mediastinitis, infection endocarditis, cardiac device infection, pneumonia and bloodstream infection.

Table 2
Clinical Characteristics and co-morbidities of patients. Group 1, patients with fasting glucose ≥ 130 after surgery, treated with basal + premeal insulin therapy. Group 2, patients with fasting glucose < 130 after surgery treated with premeal insulin therapy.

Characterization of patients	Group 1	Group 2	P value
No. of patients	121	691	
Age (years)	62.00 ± 11.30	62.80 ± 11.60	0.47
Sex (Males/Females)	81/40	428/262	0.35
No. of patients with valve disease (VD)	88 (72.7%)	545 (78.9%)	0.16
No. of patients with ischemic heart disease (IHD)	16 (13.2%)	67 (9.7%)	0.31
No. of patients with VD and IHD	17 (14.0%)	79 (11.4%)	0.36
Co-morbidities:			
Diabetes mellitus	24 (19.8%)	71 (9.6%)	0.01
Diet alone	10	6	0.01
Oral agents	11	62	0.09
Insulin therapy	3	3	0.06
Hypertension	102 (84.3%)	572 (82.9%)	0.78
Chronic obst. pulmonary disease	12 (9.9%)	73 (10.65%)	0.96
Chronic atrial fibrillation	28 (16.5%)	167 (24.2%)	0.90
Body weight (kg)	74.62 ± 13.71	72.70 ± 14.11	0.17
Body mass index (kg/m^2)	26.02 ± 4.20	25.51 ± 4.13	0.21
Fasting glucose (mg/dl)*	100.1 ± 22.1	100.9 ± 23.8	0.93
Glycated Hemoglobin (%)*	5.55 ± 1.23	5.51 ± 1,41	0.69
Creatinine (mg/dl)*	0.90 ± 0.25	0.93 ± 0.38	0.29
BUN (mg/dl)*	44.95 ± 15.60	47.26 ± 19.36	0.15
Plasma albumin (mg/dl)*	41.50 ± 3.86	41.48 ± 3.83	0.96
Hemoglobin (g/dl)*	13.74 ± 1.55	13,56 ± 1.63	0.23

* Samples were withdrawn at the entrance to the ward in the fasting state, prior to surgery.

The secondary outcomes determined by chart review for each patient included differences between treatment groups in daily capillary blood glucose concentrations, the occurrence of mild or severe hypoglycemia (<70 mg/dl and <40 mg/dl, respectively, 15), the length of hospital stay and the occurrence of any of the following post-surgery complications: the occurrence in temperature ≥38.5 °C at least 3 days after surgery [16] associated with increase in WBC ≥ 10.0×10^3/mm^3 [17] and CRP ≥114 mg/l [18] six days after surgery as indirect index of infection complication, stroke, acute renal failure, acute respiratory failure, myocardial infarction, pericardial effusion, heart failure, low cardiac output syndrome, acute fibrillation, anemia or exitus.

Statistical methods

Continuous variables were expressed as the mean ± SD median and were compared using the unpaired *t*-test. Categorical variables were expressed as number with percentage and were compared using the Chi-Square test. A multivariable logistic regression model was used to estimate odds ratios and 95% confidence intervals (CIs) of group 1, with patients of group 2 as a reference. All analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL).

Calculation of the sample size

The calculation of the sample size was calculated analyzing previous studies in which 7.1% of subjects submitted to basal insulin (either as CIII or sc therapy), and 23.7% of subjects treated with sliding scale regular insulin sc therapy, showed infective complications after cardio or general surgery [15,19,20]. In the present study, we aimed to detect a minimal difference of 50% in the primary outcome between treatments with a 2-sided type error protection of 0.05 and a power of 0.80. Therefore, we estimated that the required sample size was at least 115 subjects for each group; we optimized the power of the study with a ratio of 1:6.

Ethics statement

The study protocol was approved by the Ethics Committee of IRCCS San Raffaele Institute, and the study was conducted in accordance with the Declaration of Helsinki.

Results

Evaluation of clinical outcomes

As shown in Table 3, the composite of postoperative infective complications was found in 2.48% and in 7.96% of the patients in group 1 and in group 2, respectively ($p < 0.049$). The risk of presenting with these complications was reduced by almost 70% in group 1 compared with group 2, with an odds ratio of 0.294 (95% CI; 0.111–0.780). The most common organisms identified in the bloodstream infection cultures were Staphylococcus aureus, Staphylococcus epidermidis, psedomonas, Escherichia coli, enterococcus faecalis. In confirmation of this result, the risk of presenting with temperature ≥38.5 °C at least 3 days after surgery associated with increase in WBC ≥ 10.0×10^3/mm^3 and CRP ≥ 114 mg/l six days after surgery was decreased by 70% (1.65% vs 5.21%) in group 1 compared to group 2, with an odds ratio of 0.306 (95% CI; 0.094–0.999).

No significant differences were found when evaluating the other secondary outcomes in the two groups, except for the length of hospital stay and the presence of mild hypoglycemic episodes. The mean length of hospital stay was 18% lower in group 1 than in group 2 (7.21 ± 05.08 vs 8.76 ± 9.08 days, $p < 0.007$) despite the

Table 3
Composite hospital complications and outcomes.

	All (%)	Group 1 (%)	Group 2 (%)	P value	Odd Ratio (IC 95%)
PostoperativeInfection complications	58 (7.14)	3 (2.48)	55 (7.96)	0.049	0.294 (0.110–0780)
Wound infection	10 (1.23)	1 (0.83)	9 (1.30)		
Mediastinitis	5 (0.62)	0 (0.00)	5 (0.72)		
Endocarditis	3 (0.37)	0 (0.00)	3 (0.43)		
Cardiac device infection	2 (0.25)	0 (0.00)	2 (0.29)		
Pneumonia	9 (1.11)	0 (0.00)	9 (1.30)		
bloodstream infection	29 (3.57)	2 (1.65)	27 (3.91)		
Temperature $\geq$ 38.5 °C + WBC $\geq$ 10.0x10^3/mm^3 + CRP $\geq$ 114 mg/dl*	38 (4.68)	2 (1.65)	36 (5.21)	0.14	0.306 (0.094–0.999)
Acute atrial fibrillation	237 (29.19)	42 (34.71)	195 (28.22)	0.18	1.350 (0.989–1.848)
Low cardiac output syndrome	140 (17.24)	17 (14.05)	123 (17.80)	0.38	0.755 (0.478–1.191)
Pericardial effusion	52 (6.40)	4 (3.31)	48 (6.95)	0.19	0.458 (1.188–1.116)
Stroke	5 (0.62)	1 (0.83)	4 (0.58)	0.75	0.431 (0.191–10.743)
Myocardial infarction	4 (0.49)	1 (0.83)	3 (0.43)	0.89	1.912 (0.363–10.050)
Anemization	201 (24.75)	28 (23.14)	173 (25.04)	0.22	0.742 (0.504–1.093)
Acute respiratory failure	113 (13.92)	19 (15.70)	94 (13.60)	0.63	1.183 (0.756–1.850)
Heart failure	163 (20.03)	17 (14.05)	146 (21.13)	0.09	0.610 (0.383–0.971)
Acute kidney failure	133 (16.38)	22 (18.18)	111 (16.06)	0.65	1.161 (0.758–1.780)
Mortality**	9 (1.11)	1 (0.82)	8 (1.16)	0.43	
Mild hypoglycemia (<70 mg/dl)	46 (5.67)	18 (14.88)	28 (4.05)	0.0001	4.140 (2.626–6.522)
Severe hypoglycemia (<40 mg/dl)	5 (0.61)	1 (0.83)	4 (0.58)	0.75	1.430 (0.272–7.526)
Length of stay (days)	8.54 ± 8.62	7.21 ± 5.08	8.76 ± 9.08	0.007	

* Temperature $\geq$ 38.5 °C at least 3 days after surgery (15) + WBC $\geq$ 10.0 $\times$ 10^3/mm^3 (16) + CRP $\geq$114 mg/l (17) six days after surgery.
** Death in group 1: cardiogenic shock in one patient death in group 2: sepsis in 5 patients and cardiogenic shock in 3 patients.

risk of presenting with mild hypoglycemia being increased by almost four times in group 1 compared with group 2 (odds ratio 4.140, 95% CI; 2.626–6.522) However, no differences were found in evaluating the risk for severe hypoglycemic episodes between the two groups (odd ratio 1.430; 95% CI; 0.272–7.526).

Inflammatory markers during the perioperative period

Before the surgery, C-Reactive Protein (CRP) and white blood cell (WBC) levels were 6.19 ± 14.86 mg/l and 6.85 ± 2.10 $\times$ 10^3/mm^3 in group 1 and 5.38 ± 10.68 mg/l and 6.75 ± 1.91 $\times$ 10^3/mm^3 in group 2 (N.S.).

After surgery, CRP and WBC increased, with the highest levels being at day 2, after which the levels decreased but remained higher than baseline levels in both groups (Table 4). Conversely, CRP and WBC levels were lower in group 1 than in group 2 from day 2 to the day of discharge (Table 4, $p < 0.05$ two days and six days after surgery and discharge for both).

Glucose levels and insulin requirement during the during the perioperative period (Fig. 1)

Surgery period

Before surgery, glucose levels were 100.1 ± 22.1 and 100.3 ± 23.8 mg/dl in group 1 and group 2, respectively (N.S.). The mean glucose levels during surgery were 137.9 ± 41.5 and 116.0 ± 27.9 mg/dl, respectively ($p < 0.01$) despite the CIII being significantly higher in group 1 than in group 2 (0.10 ± 0.11 vs 0.04 ± 0.03 U/kg/h, $p < 0.01$).

Table 4
Inflammatory marker profiles during the perioperative period

	Group 1	Group 2	P value
C Protein Reactive (mg/l)			
Before the surgery	6.19 ± 14.86	5.38 ± 10.68	0.57
2 days after surgery	178.18 ± 73.49	193.05 ± 76.03	<0.05
4 days after surgery	146.70 ± 79.43	156.38 ± 125.20	0.41
6 days after surgery	95.40 ± 59.44	111.23 ± 73.55	<0.05
Discharge	81.34 ± 56.02	94.39 ± 67.25	<0.05
White Blood Cells (10^3/mm^3)			
Before the surgery	6.85 ± 2.10	6.75 ± 1.91	0.62
2 days after surgery	14.97 ± 6.01	16.40 ± 5.80	<0.05
4 days after surgery	9.80 ± 3.08	9.90 ± 3.62	0.75
6 days after surgery	8.97 ± 3.24	9.71 ± 3.99	<0.05
Discharge	8.87 ± 2.78	9.52 ± 5.07	<0.05

Cardiovascular intensive care unit period

During this period (from immediately after surgery until day 1 post-surgery), glucose levels remained significantly higher in group 1 than in group 2 (maximum glucose level: 179.8 ± 25.3 vs 169.5 ± 10.6 mg/dl, respectively, $p < 0.01$) despite the CIII remaining significantly higher in group 1 than in group 2 (0.046 ± 0.008 vs 0.037 ± 0.015 U/kg/h, $p < 0.05$).

Cardiac surgery division period

Glucose levels were significantly higher in group 1 than in group 2 only during day 2 post-surgery: (capillary fasting glucose: 170.4 ± 43.7 vs 120.4 ± 13.9 mg/dl; $p < 0.001$, respectively) while from day 3 to the day of discharge glucose levels were almost normalized either at fasting or postprandially in both groups (Fig. 1). During this period, the amount of premeal insulin was similar in both groups, ranging between 0.21 ± 0.18 and 0.34 ± 0.35 U/kg/day in group 1 and between 0.18 ± 0.14 and 0.34 ± 0.37 U/kg/day in group 2 (Fig. 1). Basal insulin therapy, administered only in group 1, ranged between 0.26 ± 0.18 and 0.35 ± 0.20 U/kg/day.

During the stay in the cardiovascular intensive care unit and in the cardiac surgery division, there were 18 and 28 episodes of mild hypoglycemia (glucose levels <70 mg/dl) in group 1 and 2, respectively, ($p < 0.0001$) while there was only 1 episode of severe hypoglycemia (glucose levels <40 mg/dl) in group 1 and 4 episodes of severe hypoglycemia in group 2 ($p = 0.75$). In the present study we reported the total number of hypoglycemic episodes and not the number of patients that showed hypoglycemic episodes. This implies that there may have been more patients who experienced more than one episode of hypoglycemia.

Discussion

Basal insulin therapy and postoperative infective complications

This study was designed to evaluate whether a constant increase in circulating insulin levels due to a basal insulin administration *per se*, independent of glycemic levels, could influence the

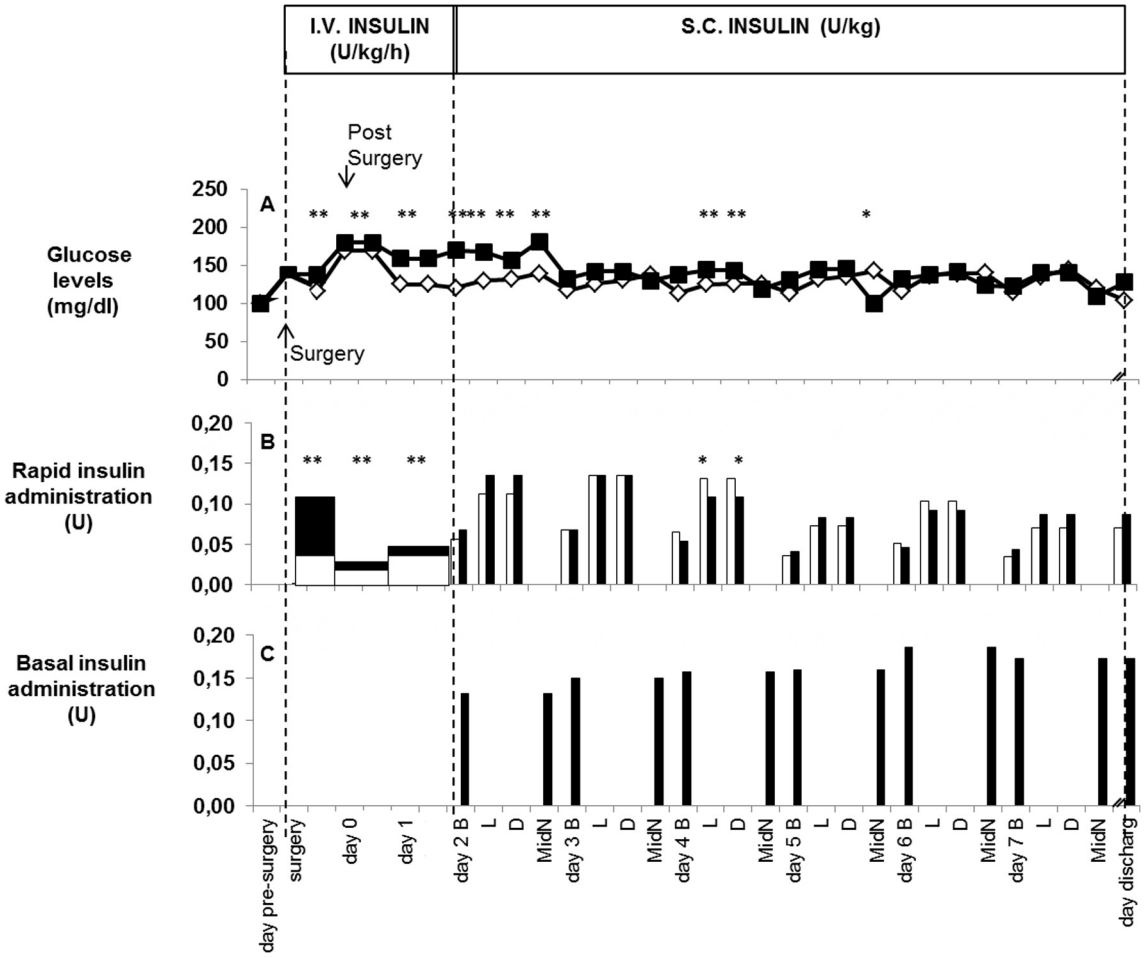

Fig. 1. Glucose levels and insulin therapy during the perioperative period. Glucose levels (A) were significantly higher in group 1 (basal + pre-meal insulin therapy, black lines and squares) than in group 2 (pre-meal insulin therapy, black lines and white diamonds) from immediately after surgery until day 2 post-surgery. Rapid insulin administration (B) during the surgery and on day 1 after the surgery, was performed intravenously (U/kg/hr) in the intensive care unit, with the amount being significantly higher in group 1 (black histograms) than in group 2 (white histograms). From day two after surgery to discharge, rapid insulin was administered subcutaneously (U/kg) and the amount was similar in both groups. Rapid insulin in the ICU was regular insulin while in the cardio-surgery ward was aspart insulin. Basal insulin administration (C, black histograms) started from day 2 after surgery until discharge in group 1. Basal insulin in the cardio surgery ward was isophane, i.e., protophane every 12 h, in 69 patients, detemir every 12 h in 50 patients and glargine every 24 h in 2 patients. (*): $p < 0.05$ group 1 vs group 2. (**): $p < 0.01$ group 1 vs group 2.

composite of postoperative infective complications [14] after cardiac surgery. We found that these complications after cardiac surgery were significantly decreased by the constant increase of circulating insulin levels (basal + premeal insulin therapy) compared with an intermittent insulin increase (premeal insulin alone therapy).). In fact, the risk of presenting with these composite infective complications was reduced by almost 70% in group 1 compared with group 2 with an odds ratio of 0.294 (95% CI; 0.110–0.780), although glycemic levels were significantly increased in the former group of patients during surgery and in the two days after surgery. It is also important to note that in both groups of patients, glucose levels were always below 180 mg/dl as suggested by the local and international guidelines [9]. In group 1, to achieve a rapid steady state, basal insulin was administered twice a day with isophane insulin (protophane insulin) or detemir insulin with a therapeutic goal obtained 24 h later. Conversely, as the biological half-life of insulin aspart is only 2–4 h, this therapy was unable to ensure an adequate constant increase of basal insulin levels when administered premeal three times a day.

Previous studies have demonstrated that continuous insulin, either CIII or sc therapy, improves daily glucose profiles and composite hospital infective complications compared with sliding scale regular insulin therapy [15,20].

Insulin effects on immune cells

Insulin exerts its effects on immune cells by binding to the insulin receptor, which is extensively expressed on immune cells, such as neutrophils and monocytes/macrophages, determines regulatory properties of insulin, both for the antimicrobial and for the inflammatory response in infection [21–23]. In fact, the presence of insulin resistance, with decreased insulin action is associated with increased susceptibility to invasive bacterial infections [9,10,24,25]. An immuno-modulatory effect of insulin has been experimentally demonstrated in a mouse model [26]. Moreover, Kenzel et al., [27] found in vitro that insulin specifically inhibited the chemokine response to Group B Streptococcus and other bacteria by modulating NF-kB binding to chemokine genes via activation of PI3 K. Insulin concentrations in several tissues are higher than in plasma [10]. Therefore, it is conceivable that high tissue insulin concentrations achieved by a constant increase in circulating insulin levels due to basal + premeal insulin therapy instead of premeal insulin alone therapy may interfere with polymorphonuclear leukocytes recruitment and affect tissue homeostasis [27]. The evaluation of CRP and WBC levels after surgery in the present study are in agreement with these insulin-induced molecular mechanisms (Table 4) .

Insulin therapy and hypoglycemia

The basal + premeal insulin therapy is well tolerated with an acceptable rate of hypoglycemia. In this study, a glucose level <70 mg/dl was reported in 14.88% of patients in the basal + premeal insulin group and in 4.05% in the premeal insulin alone therapy group ($p < 0.0001$), without significant differences in the frequency of severe hypoglycemia. Similar results were reported during the Umpierrez et al. study[15], in which glucose levels <70 mg/dl were reported in 23.1% of patients in the basal-bolus and in 4.7% in the sliding scale regular insulin therapy group without differences in the frequency of severe hypoglycemia. On the other hand, mild hypoglycemic episodes in the present study were 36% and 38% lower than those find in the Umpierrez at al [15] and in Bellido et al. [28] studies**,** respectively, underlying the importance of a strict collaboration between surgery and diabetologist teams.

It is interesting to note that in both the Umpierrez et al. [15]. and in our study, the length of hospital stay was significantly decreased with basal + premeal insulin therapy. Moreover, in the present study, the length of hospital stay after surgery was 1.5 days less (decrease of 18%) than with premeal insulin alone therapy, providing a significant impact on public health costs. In agreement with these data, Greco et al. [29] found in a multicenter cohort study in 4316 cardiac surgery patients operated in 2010, although the presence of hyperglycemia (≥180 mg/dl) was associated with an additional cost of $3192, an additional length of hospital stay of 0.8 days and an increase in infections of 1.6%, this effect was counter-regulated by the insulin treatment in the presence of the same hyperglycemic levels (180 to 240 mg/dl). In fact, in these insulin-treated patients there was a cost reductions of $6225, a reduction of length of hospital stay of 1.6 days and a reduction of infections of 4.1%.

Limitations/Strengths

This study was limited by being a single-center retrospective observational nature and by the evaluation of an association between the use of basal insulin therapy and an improvement in postoperative infective complications. On the other hand, the strength of our study was to exclude patients with a clinically relevant history of hyperglycemic crises before admission. In fact, it is well known that diabetic subjects with higher HbA1c could have increased risk to develop postoperative infective complications and the intensive insulin therapy during the post surgery period reduced these risks. These data were elegantly presented by ref 6 e ref 30 et al. and this argument would also beyond the scope of the study. Therefore, we only studied individuals who needed insulin therapy from the onset of elevated blood glucose levels during cardiac surgery. Thus, we were able to evaluate the effect of basal insulin *per se* on postoperative infective complications and could exclude a possible legacy hyperglycemic effect on post-surgery outcomes [6,30]. This exclusion criterion might explain the almost normal HbA1c levels before surgery in both groups of subjects. In a previous study we found that in subjects submitted to cardiac surgery, before the surgery intervention the presence of impaired glucose tolerance or new diagnosis of type 2 diabetes was present in 56% of subjects affected by mitral or aortic valve disease and in 67% of subjects affected by ischemic cardiac disease [31]. This data are in agreement with previous epidemiological studies on patients affected by valve disease in which the prevalence of diabetes mellitus was at least doubled as compared to the general population aged between 20 and 79 years (10.9% vs. 5.5% in Canada and 13.4% vs. 7.9% in USA) [32–34] and with our previous studies on non-diabetic subjects affected by ischemic heart disease undergoing coronary stenting [35]. This high percentage of alterations in glucose metabolism in these subjects well explains how we selected almost 50% of subject hospitalized during this period and underlines the potential clinical relevance of the study. On the other hands, it is important to underline that nearly 90% of the patients in the study did not have diabetes and this should impact interpretation and application of the results. For instance data from the gLUCO-CABG study indicates that patients without DM may do better at lower BG targets than patients with DM [36].

Conclusion

In conclusion, the basal + premeal insulin regimen is associated with a reduced frequency of postoperative infective complications than the premeal insulin alone therapy, without increasing the number of severe hypoglycemic events. Therefore, these results suggest, for the first time, a beneficial effect of basal insulin therapy on post-surgery outcome independent of circulating glucose levels. Moreover, the present study suggests that the basal + premeal insulin regimen could be preferred over pre-meal insulin alone treatment in cardiac surgery patients requiring continuous intravenous insulin infusion for an acute increase in circulating glucose levels during the cardiac surgery period. However, although the present study included a relatively large number of subjects, a prospective, multicenter, randomized clinical trial on the effect of insulin *per se*, independent of glycemic control, on composite hospital infective complications in cardiac surgery setting is certainly needed.

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Disclosure statements

The authors declare that they have no conflicts of interest.

Author contributions

PMP and LDM share equal contribution in the design of the study. PMP, MC, AM, VV, VGC, EG, BF, SS performed data extraction and data interpretation. PMP and LDM performed statistical analysis. PMP, LDM wrote the manuscript. EB and OA contributed to the manuscript revision.

All authors have provided a final approval of the article contents.

Conflicts of interest

None.

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