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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

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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.

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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.