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# Insulin infusion therapy in critical care patients: Regular insulin vs short-acting insulin. A prospective, crossover, randomized, multicenter blind study☆,☆☆

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ABSTRACT

*Introduction:* The aim of this multicenter, prospective, randomized, crossover trial is to compare, in critical care patients receiving insulin infusion therapy (IIT), the pharmacodynamic of Humulin insulin (Hlin), currently used as "standard of care," and Humalog insulin (Hlog), a shorter acting insulin formulation. This was measured as extent and duration of the carryover effect of insulin treatment, with the latter calculated as ratio between blood glucose concentration (BGC) reduction during and after IIT.

*Materials and methods:* Twenty-eight patients treated in an intensive care unit and receiving full nutritional support were randomly assigned to Hlin or Hlog as first treatment. Insulin was infused at a constant rate in patients presenting with BGC greater than or equal to 180 mg/dL (0.04 U/kg per hour) and was discontinued when BGC was less than or equal to 140 mg/dL (therapeutic BGC drop). Further reductions in BGC after discontinuation of insulin infusion were recorded (postinfusional BGC drop). During the study period, whole blood BGC was measured every 30 minutes. A minimal 6-hour washout interval was maintained between treatments with the 2 types of insulin. The primary end point was the extent (calculated as ratio between the therapeutic BGC drop and the postinfusional BGC drop) and duration of the carryover effect.

*Results:* Treatment with Hlog, as compared with Hlin, was associated with a less profound carryover effect as well as a briefer duration of carryover (median, 0.40 vs 0.62; $P < .001$; median, 1 vs 1.5 hours; $P < .001$).

*Conclusions:* The use of constant Hlog infusion for IIT, when compared with Hlin at the same dose, is associated with a less profound carryover effect on BGC after discontinuation of IIT, a briefer duration of carryover, a faster BGC drop during infusion, and a quicker BGC rise after discontinuation. These characteristics suggest that Hlog IIT may be preferable for use in critically ill patients.



## 1. Introduction

Insulin infusion therapy (IIT) is widely used as "standard of care" to treat hyperglycemia in critical care patients [1,2]. This therapeutic approach leads to reduced morbidity and to a higher survival rate in some subgroups of critical care patients but is also associated with a substantial risk of inducing hypoglycemia [3-5]. Various strategies have been used to minimize the risk of iatrogenic-induced hypoglycemia during IIT including wider glycemia target ranges, sliding scale insulin titration, increased frequency of blood glucose concentration (BGC) measurements, and a higher caloric intake [6-8]. Whether these therapeutic measures do indeed provide greater safety margins remains controversial as does their impact on clinical benefit of IIT [9,10].

Clinical application of IIT is usually accomplished with regular human insulin (Hlin) (HumulinR; Eli Lilly, Indianapolis, IN) continuous infusion [11,12]. Shorter acting insulin formulations, such as lispro insulin (Hlog) (Humalog; Eli Lilly) have faster onset and offset kinetics than Hlin and may thus be more suitable for IIT in critical care patients [13-15]. The molecular structure of Hlog is characterized by a change in the amino acid sequence of the insulin B chain—with proline in position 28 and lysine in position 29 inverted Lys(B28),Pro(B29). This pharmacokinetic profile, which resembles that of endogenous insulin, leads to a faster rise in plasma concentration, a higher peak concentration, and a shorter duration of action than Hlin [12,13,16,17]. The use of Hlog in patients receiving chronic insulin therapy is associated with a faster BGC reduction when infusion is started and a reduced "residual effect" when infusion is stopped [18]. In the critical care setting, a similar effect may be

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potentially beneficial due to a decreased risk of hypoglycemia in the carryover phase, after insulin infusion is discontinued. However, controlled clinical data on the use of shorter acting insulin formulations in critical care patients are lacking.

We describe the effect of short-acting insulin on blood glucose during continuous infusion and after discontinuation of infusion in critically ill patients, compared with that of regular insulin (the current standard of care).

## 2. Materials and methods

This prospective, randomized, crossover, multicenter, clinical trial received institutional review board approval for human research from the University of Rome "La Sapienza," Italy (approval March 28, 2013, protocol no. 390/13, Chairman: Prof. Aldo Isidori) and from the Valencia University Hospital Institutional Review Board (President Dr Antonio Pelaez) and was registered at the clinicaltrials.gov (NCT 02165566). Written informed consent was obtained from the patients or their next of kin (when the patient was sedated or unable to sign by themselves or when someone from the family was nominated as legal guardian). The study took place in 2 academic centers, the neurosurgical postoperative intensive care unit (ICU) at the "La Sapienza" University of Rome, Italy, and the Surgical ICU at the Hospital Clinic Universitari of Valencia, Spain.

### 2.1. Study population

All patients who were older than 18 years and receiving full nutritional support who presented with a BGC greater than or equal to 180 mg/dL were included. Moribund patients and patients enrolled in other studies were excluded as were patients with type 1 diabetes, patients with insulin-dependent diabetes, and patients with glycated hemoglobin greater than 6.5% because of the potential of underlying insulin resistance. Simplified Acute Physiology Score II was recorded at ICU admission. In both centers, BGC was measured using a point-of-care blood gas analyzer: in Rome, GEM Premier 4000 Instrumental Laboratories, Barcelona, Spain; in Valencia, Blood Gas Analyzer 825 FLEX, Radiometer, Denmark.

### 2.2. Study end points

The primary outcome measure was the extent of Hlog and Hlin "carryover effect," expressed as the ratio between BGC reduction during insulin infusion (therapeutic BGC drop) and BGC reduction after infusion discontinuation (postinfusional BGC drop). Secondary outcome measures were the rate of BGC reduction during insulin infusion (milligrams per deciliter per hour), the duration of the carryover effect (ie, the time elapsing between IIT discontinuation and the lowest BGC value), and the rate of BGC increase after IIT discontinuation—from the lowest BGC value to the first BGC value greater than or equal to 140 mg/dL (Fig. 1, segments 1-3, slope m1, m2).

### 2.3. Study protocol

All insulin infusions were prepared by diluting 50 U of Hlin or Hlog in 500 mL of saline and infused through a volumetric pump. Patients who fulfilled inclusion criteria were prospectively enrolled and randomly assigned to start treatment with either Hlog or Hlin at a dose of 0.04 U/kg per hour [19]. Bolus injection of insulin was not allowed.

After full nutritional support was established, continuous IIT was initiated provided the BGC was greater than or equal to 180 mg/dL (upper BGC threshold). Insulin infusion therapy was kept constant until the BGC was less than or equal to 140 mg/dL (lower BGC threshold). Insulin infusion was discontinued once the BGC reached less than or equal to 140 mg/dL. Crossover involved treatment of the same patient with both types of insulin (Hlog and Hlin) with a washout interval of at least 6 hours between the 2 treatments when BGC values were greater than 180 mg/dL. Throughout the duration of IIT and after insulin infusion was discontinued, the BGC was measured once every 30 minutes in whole blood until BGC values returned to target values (140-180 mg/dL). Two operators were used to achieve blinding: The operator in charge of BGC measurements was not aware of the type of insulin being used. The operator responsible for insulin administration was unaware of the values being measured. We defined severe hypoglycemia as BGC less than 90 mg/dL.

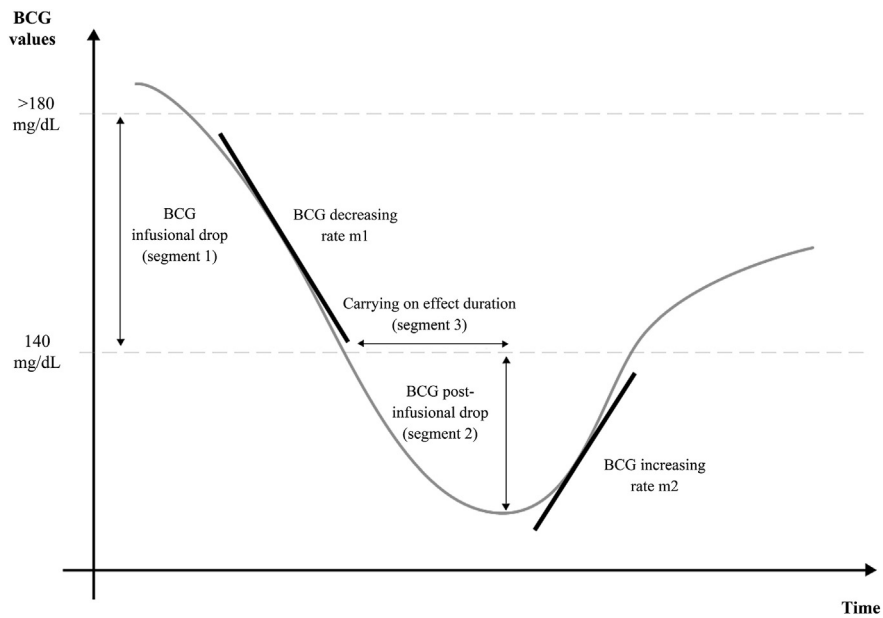


**Fig. 1.** The primary outcome measure was the extent of carryover effect (segment 2/segment 1). Secondary end point measures were rate of BGC reduction during insulin infusion (slope m1), duration of the carryover effect (segment 3), and the rate of BGC increase from lowest BGC value to the first BGC value greater than or equal to 140 mg/dL (slope m2).

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