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Randomized clinical trial of the efficacy and safety of insulin glargine vs. NPH insulin as basal insulin for the treatment of glucocorticoid induced hyperglycemia using continuous glucose monitoring in hospitalized patients with type 2 diabetes and respiratory disease

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ABSTRACT

Aims: To investigate the clinical efficacy and safety of insulin glargine compared with NPH insulin as basal insulin for the management of corticosteroid-induced hyperglycemia in hospitalized people with type 2 diabetes (T2DM) and respiratory disease.

Materials and methods: Randomized, two-arm parallel group, clinical trial undertaken from February 2011 to November 2012 on the pneumology ward of the Hospital Regional Universitario de Málaga (Spain), involving 53 participants with T2DM treated with medium/high doses of intermediate-acting corticosteroids. Participants were randomly assigned to receive one single dose of insulin glargine or NPH insulin in three equally divided doses before each meal as basal insulin within a basal–bolus insulin protocol. The intervention lasted six days or until discharge if earlier.

Results: No significant differences were seen between groups during the study in mean blood glucose (11.43 ± 3.44 mmol/l in glargine vs. 11.88 ± 2.94 mmol/l in NPH, $p = 0.624$), and measures of glucose variability (standard deviation 3.27 ± 1.16 mmol/l vs. 3.61 ± 0.99 mmol/l, $p = 0.273$; coefficient of variation 1.55 ± 0.33 mmol/l vs. 1.72 ± 0.39 mmol/l, $p = 0.200$). Results from CGM were concordant with those obtained with capillary blood glucose reading. The length of hospital stay was also similar between groups (8.2 ± 2.8 days vs.

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9.8 ± 3.4 days, $p = 0.166$) There was a non significant trend for lower episodes of mild (4 vs. 8, $p = 0.351$) and severe hypoglycemia (0 vs. 3, $p = 0.13$) in the glargine group.
Conclusions: The results of this study showed that insulin glargine and NPH insulin are equally effective in a basal–bolus insulin protocol to treat glucocorticoid-induced hyperglycemia in people with T2DM on a pneumology ward.
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1. Introduction

Glucocorticoids are drugs widely used in medicine to treat many conditions. There exist several compounds of glucocorticoids with different pharmacokinetics, as well as different dosing regimens, depending on the particular treatment indications. One of the best-known adverse effects of glucocorticoid therapy is the deleterious effect on carbohydrate metabolism, worsening hyperglycemia in almost all person who already have diabetes or precipitating ''steroid diabetes'' in that people with no prior diabetes [1]. Glucocorticoid-induced hyperglycemia is an important and prevalent clinical problem, and the need for treatment can and should be anticipated in these individuals [2]. As this hyperglycemia is sometimes considered to be transitory, its diagnosis and treatment is often underestimated. Proof of this is the scarce literature on the topic, consisting mainly of opinion articles or reviews [2,8] or retrospective studies [7,15] though with virtually no data from randomized clinical trials evaluating treatment regimens for these patients.

Basal–bolus insulin therapy is now the preferred regimen in hospitalized people with diabetes [4–6]. However, basal–bolus insulin protocols commonly used in clinical practice may not adequately cover steroid-induced hyperglycemia [3].

The pharmacokinetic properties of neutral protamine hagedorn (NPH) insulin suggest that it is appropriate for the treatment of hyperglycemia induced by oral prednisone and prednisolone. The hyperglycemic effect of these corticosteroids occurs between 4 and 8 h after their intake and the duration of action is approximately 12–16 h, mirroring the activity of NPH insulin. Thus, NPH insulin has been widely used for the treatment of corticosteroid-induced hyperglycemia. Insulin glargine is a long-acting insulin analog which is frequently used as a basal insulin in people with both type 1 and type 2 diabetes. It has a pharmacokinetic profile characterized by a flat profile with up to 32 h duration [9].

The aim of this study was to investigate the clinical efficacy and safety of insulin glargine in comparison with NPH insulin as a basal insulin in the treatment of corticosteroid-induced hyperglycemia in hospitalized people with type 2 diabetes and respiratory disease treated with a medium–high dose of intermediate-acting corticosteroids more than once daily.

2. Materials and methods

2.1. Study design

The study was a single center, randomized, two-arm parallel group, clinical trial. The maximum duration of the intervention was six days, or until discharge if this occurred before the sixth day after admission. The study was carried out from February 2011 to November 2012 on the pneumology ward of the Hospital Regional Universitario de Málaga (Spain).

2.2. Study population

Within the first 24-h after admission to the pneumology ward, people with type 2 diabetes aged 18–80 years who were treated with a medium or high dose of intermediate-acting corticosteroids were enrolled. The inclusion criteria required a history of type 2 diabetes treated with diet, hypoglycemic agents or insulin, and a prescription of medium or high dose intermediate-acting corticosteroids (methylprednisolone > 40 mg/day or deflazacort > 60 mg/day) more than once daily during the first 48 h after admission.

The exclusion criteria comprised subjects with type 1 diabetes or steroid diabetes, subjects who were receiving artificial nutrition, subjects with advanced liver disease or impaired kidney function (creatinine at admission > 265 μ‴ mol/l), psychiatric disorders, or failure to collaborate, considered as refusing to sign the informed consent document.

Fifty-three participants were enrolled (Fig. 1). The participants were randomly assigned in the order of admission to one of the two treatment groups in a 1:1 glargine:NPH allocation ratio.

2.3. Insulin protocol

Hospital insulinization was done following a local protocol based on the RABBIT2 trial [5]. The basal insulin was glargine or NPH insulin according to the intervention arm, and as a rapid-acting insulin analog, we used insulin glulisine for all participants.

In participants treated with diet or with oral hypoglycemic agents at home, the total insulin dose was calculated from the blood glucose measurement at admission: <8.32 mmol/l: 0.3 IU/kg; 8.32–11.10 mmol/l: 0.4 IU/kg; >11.10 mmol/l: 0.5 IU/kg. In participants previously treated with insulin, the total insulin dose was similar to that administered at home. In all participants, the insulin dose calculated using this protocol was multiplied by 1.5 (correction factor for corticoid therapy) [10].

In both groups, 50% of the total insulin dose was distributed as basal insulin and 50% as preprandial bolus. In the insulin glargine group, the basal insulin was given in a single dose at 09.00, and the bolus insulin was given in three equally divided doses before each meal (breakfast, lunch and dinner). In the NPH insulin group, both the basal insulin and the bolus insulin were given in three equally divided doses before each meal.

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