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Premix Insulin Analogues in Steroid-Induced Hyperglycaemia: A Prospective Randomized Trial Comparing Insulin Aspart 30/70 and Insulin Lispro 50/50 in Hospitalized Patients

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Abstract

Background: Glucocorticoids are widely prescribed for acute and chronic conditions but frequently cause hyperglycaemia, which increases infection risk, delays recovery, and prolongs hospital stay. Insulin is the treatment of choice, but optimal regimens in steroid-induced hyperglycaemia remain uncertain. Premixed insulin analogues may offer practical advantages, yet evidence comparing different premix ratios is limited.

Aim: To evaluate and compare the efficacy and safety of biphasic Aspart 30/70 versus biphasic lispro 50/50 in managing glucocorticoid-induced hyperglycaemia in hospitalised patients.

Methods: This prospective, randomised, open-label trial enrolled 60 hospitalised patients with glucocorticoid-induced hyperglycaemia (random blood glucose >200 mg/dL after ≥3 days of prednisolone or dexamethasone). Participants were randomised 1:1 to receive biphasic Aspart 30/70 or biphasic Lispro 50/50, with individualised titration to achieve pre-specified targets (<120 mg/dL pre-meal, <180 mg/dL post-meal). The primary endpoint was mean daily blood glucose; secondary endpoints included pre- and post-meal glucose, HbA1c, insulin dose, and hypoglycaemia.

Results: Baseline characteristics were comparable between groups. Mean HbA1c was 8.22% in the biphasic Aspart 30/70 group and 8.84% in the biphasic lispro 50/50 group (p=0.07). biphasic Aspart 30/70 achieved significantly lower fasting glucose (130.3 vs 161.3 mg/dL, p=0.003), pre-meal glucose (161.3 vs 197.4 mg/dL, p=0.0003), post-meal glucose (227.7 vs 250.4 mg/dL, p=0.05), and mean daily glucose (187.1 vs 221.8 mg/dL, p=0.001). Insulin requirements were lower with biphasic Aspart 30/70 (47.2 vs 59.1 units/day, p=0.03). The incidence of hypoglycaemia was comparable in both arms.

Conclusion: Biphasic Aspart 30/70 provided superior glycaemic control with lower insulin requirements compared to biphasic lispro 50/50 in hospitalized patients with glucocorticoid-induced hyperglycaemia. These findings suggest that premix formulations with a higher basal component may be better suited to address the metabolic profile of steroid-induced hyperglycaemia.

Keywords: Hyperglycaemia; Glycaemic; Glucose; Glucocorticoids

Introduction

Glucocorticoids are widely used for acute and chronic medical conditions but often cause disturbances in glucose metabolism. They may unmask diabetes in previously normoglycemic individuals or exacerbate hyperglycaemia in those with known diabetes. Steroid-induced hyperglycaemia is common in hospitalized patients and is associated with increased infection risk, prolonged recovery, and longer hospital stay [1,2].

The pattern of glucocorticoid-induced hyperglycaemia is distinctive: fasting glucose is relatively preserved, while postprandial and afternoon excursions are exaggerated, particularly following morning steroid dosing. These changes reflect increased hepatic gluconeogenesis, peripheral insulin resistance, and reduced glucose uptake. The risk and severity vary with dose, duration, and steroid potency; dexamethasone, in particular, produces sustained hyperglycaemia [3].

Insulin remains the treatment of choice in this setting. While basal–bolus and NPH-based regimens are guideline-supported, they require multiple injections and intensive monitoring [4,5]. Premixed insulin analogues, combining both basal and prandial components, may better match the glycaemic profile of glucocorticoid therapy and simplify inpatient management. However, limited evidence exists comparing different premix formulations in this context. This study was designed to compare the efficacy and safety of biphasic Aspart 30/70 versus biphasic lispro 50/50 in achieving glycaemic targets among hospitalized patients with glucocorticoid-induced hyperglycaemia.

Aims and Objectives

To evaluate and compare the efficacy of two premix insulin analogues (biphasic Aspart 30/70 and biphasic Lispro 50/50) in managing steroid-induced hyperglycaemia in hospitalized patients, to compare the proportion of glucose values within predefined targets (<110 mg/dL pre-meal, <180 mg/dL post-meal), to assess mean daily blood glucose, pre-meal and post-meal glucose levels in patients treated with Aspart premix 30/70 versus Lispro premix 50/50. Aim also was to evaluate safety outcomes, including hypoglycaemia, in both groups.

Methodology

Study Design and Ethics

This was a prospective, randomised, open-label clinical trial conducted in hospitalised patients with glucocorticoid-induced hyperglycaemia. The protocol was approved by the Institutional Ethics Committee and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participants prior to enrolment.

Participants

Eligible patients were adults receiving glucocorticoid therapy (prednisolone or dexamethasone) who developed hyperglycaemia, defined as random blood glucose >200 mg/dL, and had received at least 3 consecutive days of glucocorticoid treatment during hospitalisation. Both patients with pre-existing diabetes and those without prior diabetes were included. Most participants were admitted for management of cancer-related conditions.

Randomisation and Interventions

Patients meeting the inclusion criteria were randomised in a 1:1 ratio into two treatment arms. One group received biphasic Aspart 30/70, and the other received biphasic Lispro 50/50 as the study intervention. The study was open label, treat to target, and both participants and investigators were aware of treatment allocation.

Insulin Titration and Glycaemic Targets

Insulin dosing was individualised based on patient glycaemic profiles and daily requirements. Titration was guided by pre-specified glucose targets of <110 mg/dL for pre-meal values and <180 mg/dL for post-meal values.

Outcomes

The primary outcome was mean daily blood glucose during hospitalization. Secondary outcomes included pre-meal and post-meal glucose levels and HbA1c. Safety endpoints included episodes of hypoglycaemia.

Results

A total of 60 patients were included, with 30 assigned to the biphasic Aspart 30/70 group and 30 to the biphasic Lispro 50/50 group. The mean age was 50 years in the biphasic Aspart 30/70 group and 54 years in the biphasic Lispro 50/50 group. Both groups included patients with and without pre-existing diabetes; among those with diabetes, prior therapy consisted of either oral agents or insulin. The majority of patients were admitted for oncology-related illnesses. The mean cumulative steroid dose (hydrocortisone equivalent) was 307 mg in the biphasic Aspart 30/70 group and 250 mg in the biphasic Lispro 50/50 group (p=0.305).

At the end of the study, the mean HbA1c was 8.22% in the biphasic Aspart 30/70 group and 8.84% in the biphasic Lispro 50/50 group (p=0.07). Fasting glucose levels were

significantly lower with biphasic Aspart 30/70 (130.3 mg/dL) compared with biphasic Lispro 50/50 (161.3 mg/dL, p=0.003). Mean pre-meal glucose was 161.3 mg/dL versus 197.4 mg/dL (p=0.0003), while mean post-meal values were 227.7 mg/dL versus 250.4 mg/dL (p=0.05). Overall mean daily glucose was also lower in the biphasic Aspart 30/70 group at 187.1 mg/dL compared with 221.8 mg/dL in the biphasic Lispro 50/50 group (p=0.001).

Insulin requirements differed significantly, with patients on biphasic Aspart 30/70 requiring a mean of 47.2 units per day compared with 59.1 units per day for biphasic Lispro 50/50 (p=0.03). The six-point glucose profile demonstrated more consistent control across both pre-meal and post-meal values in the biphasic Aspart 30/70 group (Figure 1 & Table 1)

The incidence of hypoglycaemia was comparable in both arms, three and two episodes, all were mild and managed successfully without ill consequences.

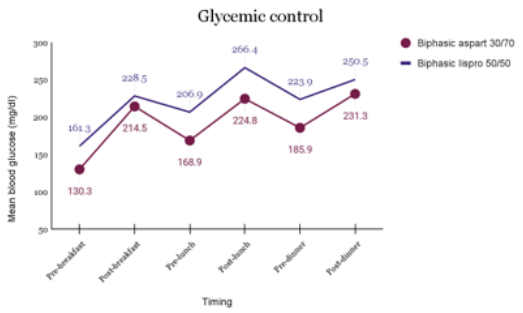

Figure 1: Six-point glucose control profile of biphasic Aspart 30/70 and biphasic Lispro 50/50.

	Biphasic Aspart 30/70	Biphasic Lispro 50/50
Mean Pre-meal	161.2	197.4
Mean post-meal	227.7	250.4
Mean glucose	187	221.7

Table 1: Mean premeal & post meal glucose levels in biphasic Aspart 30/70 and biphasic Lispro 50/50 groups.

Discussion

Our prospective randomized trial demonstrated that biphasic Aspart 30/70 achieved superior glycaemic control compared to biphasic lispro 50/50 in hospitalized patients with glucocorticoid-induced hyperglycaemia. Patients receiving biphasic Aspart 30/70 showed significantly lower fasting glucose (130.3 vs 161.3 mg/dL, p=0.003), pre-meal glucose (161.3 vs 197.4 mg/dL, p=0.0003), and overall daily glucose levels (187.1 vs 221.8 mg/dL, p=0.001) with reduced insulin requirements (47.2 vs 59.1 units/day, p=0.03). The literature on premixed insulin formulation comparisons in steroid-induced hyperglycaemia remains limited. Most comparative studies have focused on either premixed versus basal-bolus regimens or different premix ratios (30/70 vs 50/50) in conventional diabetes management, with few addressing the unique challenges of glucocorticoid-induced hyperglycaemia in hospitalised settings.

A recent study by Ketaroonrut et al. specifically examined insulin management in hospitalized COVID-19 patients with steroid-induced hyperglycaemia and found that premixed insulin analogue formulations were associated with lower hypoglycaemia risk compared to human premixed insulin, supporting the use of premixed formulations in steroid settings. The authors noted that during the COVID-19 pandemic, premixed insulin was considered an alternative option for insulin therapy to reduce infection exposure for healthcare professionals while maintaining effective glycaemic control [6]. The literature comparing premixes 30/70 and 50/50 are limited. The few studies comparing different premix ratios were conducted in outpatient settings without steroid therapy. A Turkish study found that insulin lispro premix 50/50 administered three times daily provided superior postprandial glucose control compared to insulin Aspart premix 70/30 twice daily in insulin-naive type 2 diabetic patients (p<0.0001). However, this study involved ambulatory patients with conventional diabetes, different dosing frequencies (TID vs BID), and no concurrent glucocorticoid therapy [7]. Similarly, other comparative studies showing advantages of 50/50 formulations were conducted in stable outpatient populations without the acute metabolic stress and altered insulin sensitivity patterns characteristic of steroid-induced hyperglycaemia.

The superior performance of the 30/70 formulation in steroid-induced hyperglycaemia can be explained by the unique metabolic profile created by glucocorticoids. Steroid-induced hyperglycaemia is characterised by marked insulin resistance and increased hepatic gluconeogenesis. The 70% protamine component in biphasic Aspart 30/70 provides more sustained basal insulin action, better addressing the underlying insulin resistance and elevated hepatic glucose production induced by glucocorticoids. Additionally, the molecular mechanisms of glucocorticoid action involve impaired insulin signalling and decreased glucose transporter function, requiring more robust intermediate-acting insulin coverage which the 30/70 formulation better provides compared to the equal rapid/intermediate ratio in 50/50 formulations.

These findings suggest that in hospitalized patients with glucocorticoid-induced hyperglycaemia, premixed formulations with higher proportions of intermediate-acting insulin (such as 30/70) may be preferable to those with equal rapid and intermediate components (50/50), potentially leading to revised treatment protocols for this challenging clinical scenario.

Conclusion

Biphasic Aspart 30/70 demonstrated superior glycaemic control with lower insulin requirements compared to biphasic lispro 50/50 in managing steroid-induced hyperglycaemia, suggesting that the 30/70 formulation is more effective for addressing the specific metabolic derangements associated with glucocorticoid therapy in hospitalized patients.

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