ISPAD-JDRF FELLOWSHIP AWARD PROGRESS REPORT

Title : Comparative Efficacy of a Two Daily Mixed Insulin Injection Versus a Multiple Daily Injection With Human Insulin in a Limited Resources Setting : a Multicenter Open Randomized Crossover Clinical Trial

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1. Background

The goal of type 1 diabetes management is to re-create blood glucose levels as close to the non-diabetic range as possible. Insulin therapy is the only treatment available for type 1 diabetes. Indeed, the survival of affected patients is conditioned by this treatment, and it is accepted that a good glycemic balance can only be obtained with several daily injections of insulin, self-monitoring of blood sugar, complete diabetes education and advice from qualified health professionals[1][8].

Unfortunately, many patients around the world do not reach the set glycemic targets, mainly in developing countries[2] [9]. Several factors may explain this glycemic imbalance in these countries, including the lack of a therapeutic education strategy and the use of so-called inappropriate insulin therapy regimens[1].

While the efficacy of NPH insulin within the framework of basal bolus protocols has been demonstrated in type 1 diabetes in both children and adults in terms of glycemic control and reduction of complications[3–5], there is still no rigorous literature comparing it to the premixed insulin used in many developing countries.

One study in Belgium showed that lowest HbA1c values (approximate 7.3% or 56.3 mmol/mol) could be obtained with a twice-daily free-mixed regimen with additional supplemental fast insulins ad hoc[6]. In Haiti it have been shown that a rigorous patient self-management education significantly improved glycemic control in youth with diabetes treated with a premixed 70/30 human insulin regimen[7].

Some studies evaluating the glycemic control of children and adolescents with T1D in Africa have focused on insulin therapy regimens, but with contradictory results. Indeed, if for some like those in South Africa[8] and Tanzania[9] the basal bolus regimen was more associated with good glycemic control compared to the premix regimen, studies in Cameroon[10] and Kenya[11] seem to find no difference. In Burkina Faso, a recent studies has shown that premix insulin regimens provide better glycemic control, but the need for further prospective studies in the

context of appropriate therapeutic education and a continuous blood glucose monitoring system was identified to consider multiple factors of bias[12].

2. Aims

The goal of this clinical trial is to compare glycemic control and variability between children and adolescents with type 1 diabetes treated by a two daily injection of premixed human insulin (Humulin 30/70) and those who have a basal bolus scheme (Humulin N + Humulin R) in a resource limited setting.

3. Subjects and methods

Twenty participants will be randomized, 10 initially to premix insulin human isophane suspension and insulin human injection (Humulin 30/70) twice daily, and 10 persons to insulin human isophane suspension (Humulin N) twice daily plus regular human insulin (Humulin R) before meals. At the end of the initial 16-wk treatment (period 1), all patients will be crossed over to the alternate treatment arm for an additional 16 wk (period 2). Insulin doses will be adjusted weekly by the clinical site according to a prespecified insulin intensification algorithm to achieve target fasting [<110 mg/dl (6.1 mmol/liter)], bedtime [<130 mg/dl (7.2 mmol/liter)], and premeal [<110 mg/dl (6.1 mmol/liter)] glucose levels until HbA1c was below 7.0%.

Subjects will receive training on the FreeStyle Libre CGMS System, and self-monitoring of blood glucose (SMBG), including recording glucose, insulin doses, and symptoms of hypo- or hyperglycemia.

- Arm 1: Premix human isophane suspension plus insulin human injection. 10 subjects will receive premix insulin human isophane suspension and insulin human injection twice daily.
  Sequence (Premix first, then Humulin N + Humulin R): Subjects randomized to this sequence will receive premix insulin, twice per day for 16 weeks. After the first 16 weeks, subjects will cross over to the Humulin N plus Humulin R sequence for a further treatment of 16 weeks
- Arm 2: Humulin N plus Humulin R. 10 subjects will receive insulin human isophane suspension (Humulin N) twice daily plus regular human insulin (Humulin R) before meals
  Sequence (Humulin N + Humulin R first, then Premix): Subjects randomized to this sequence will receive basal bolus insulin scheme with Humulin N (twice daily) and Humulin R (before meals) for 16 weeks. After the first 16 weeks, subjects will cross over to the Premix sequence for a further treatment of 16 weeks

Inclusion Criteria:

- Male or female 5 - 18 years of age
- Be diagnosed for at least 1 year at the date of inclusion.
- Have been regular at consultations during the last 12 years preceding inclusion (at least 3 visits)
- Willing and able to inject insulin human isophane and multi-day dosing of rapid acting human insulin.

- Willing and able to perform continuous glucose monitoring (CGMS) during the study
- Have (patient or guardian):
    - Either a connected cellphone that can install the FreeStyle link application and use connected messaging app,
    - Either a connected computer to regularly download data from the Freestyle Libre mobile device
    - Either a connected smartphone using the Whatsapp application and being able to send photos of daily blood glucose scans from the Freestyle Libre device to the medical team

Exclusion Criteria:

- pregnant or lactating females
- opposition to participating in the study
- residing outside the towns where the care centers are located
- Any disease or condition (including abuse of illicit drugs, prescription medicines or alcohol) that in the opinion of the investigator or sponsor may interfere with the study compliance and completion of the study.

4. Status of first six months (January–June 2023)

Ethical clearance was obtained from the national ethic committee. The study was also registered on the ClinicalTrials.gov Protocol registration system with the registration number NCT05768191, dated 03/01/2023.

We received FreeStyle Libre CGMS sensors in April 2023. Recruitment of subjects for the study started on 20th May 2023, and so far, 19 subjects have been recruited after their baseline data was collected. the interim results will be presented as late breaker abstract at the 49th Annual Conference of the International Society for Pediatric and Adolescent Diabetes (ISPAD) in October 2023.

5. Next steps

The study will be continued (at least 1 more patient need to be recruited) so that each subject completes their 16 weeks of treatment in their initial arm before switching to the second treatment arm.

Estimated study completion date is scheduled for February 2024 and complete data analysis for March 2024.

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