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Pre-mixed insulin has a similar efficacy to basal-bolus insulin in reducing HbA1c levels in type 2 diabetics

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ABSTRACT A clinical decision report using:

Fulcher G, Roberts A, Sinha A, Proietto J. What happens when patients require intensification from basal insulin? A retrospective audit of clinical practice for the treatment of type 2 diabetes from four Australian centres. *Diabetes Research and Clinical Practice*, 2015;108(3):405–413. https://doi.org/10.1016/j.diabres.2015.03.004

for a patient with uncontrolled type 2 diabetes.

Keywords: *insulin, diabetes, type 2 diabetes, basal-bolus*

Clinical-Social Context

Mr. Frank Herbert (pseudonym) is a 55-year-old African American man with a history significant for type 2 diabetes mellitus, hypertension, seizure disorder, and end stage renal disease (ESRD) on dialysis, who presented to his primary care physician's office for a follow up evaluation of his lab work. The patient had an A1c taken a few days prior and he had come in to discuss the results; his A1c was 9.7%. In looking at the patient's previous A1c values, we noted a severe fluctuation – his A1c values from the past 2 years: 15.3%, 6.6%, 13.9%, 7.3%, 10.5%, 8.3%, 5.2%, and 6.6%. When discussing the most recent increased A1c value with the patient, he noted that his diet had "not been great over the past few months." He had been attempting to eat healthier last year, however, since starting dialysis earlier in the year (February 2020) he had been too tired to cook at home, even though he enjoyed cooking, and would end up eating fast food at least 2 times per week. He also relayed that he had been exercising at least three times a week but since starting dialysis, he was too tired to exercise and had been feeling generally fatigued. The patient also noted numbness and tingling in his feet that had developed over the past few months. We asked the patient for his usual fasting and post prandial blood glucose levels and he relayed, "My glucometer has been broken the past couple of months. I should get a new one, but it's been hard with the dialysis." He told us that his wife had been extremely supportive and had been noting down his blood glucose levels taken at dialysis, but he had not brought her notebook with him to clinic nor did his remember any values. He went to dialysis Tuesdays, Thursdays, and Saturdays from 5:30am to 10:30am.

For his diabetes, the patient only took Basaglar (Glargine) 26 units in the morning. Based on his current A1c, previously fluctuating values, and recently developed peripheral neuropathy, we concluded that the patient had uncontrolled type 2 diabetes that needed to be addressed and another agent likely needed to be added to his basal only insulin regimen.

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Usually, insulin regimens consist of a basal (long acting) and a bolus dose (short acting). Insulin regimens can also be supplemented with other diabetes medications, like Metformin. However, given the patient's ESRD and dialysis, Metformin and SGLT2 inhibitors would be contraindicated. When discussing insulin options with the care team and with the patient, the patient stated that he did not want basal-bolus therapy as it would require multiple injections and close monitoring every day. He also seemed overwhelmed with dialysis. Another option we considered was a premixed insulin regimen that would only require 1-2 injections per day; this option would disrupt the patient's life the least. However, given the patient's uncontrolled diabetes, we were unsure if a premixed insulin regimen would provide the same efficacy in decreasing the A1c as the standardized basal-bolus regimen in an uncontrolled diabetic patient.

Clinical Question

Do premixed insulin regimens provide the same effectiveness in decreasing the A1c as basal-bolus regimens in patients with uncontrolled type 2 diabetic?

Research Article

Fulcher G, Roberts A, Sinha A, Proietto J. What happens when patients require intensification from basal insulin? A retrospective audit of clinical practice for the treatment of type 2 diabetes from four Australian centres. *Diabetes Research and Clinical Practice*, 2015;108(3):405–413. https://doi.org/10.1016/j.diabres.2015.03.004 [1]

Description of Related Literature

A review of the literature was performed by using PubMed with the following criteria: "pre-mixed insulin" and "type 2 diabetes". There was a total of 33 results that were generated on PubMed and sorted by best match. The search was additionally narrowed to articles published in the last 10 years, to ensure up to date and accurate information. This resulted in a total of 21 articles. Abstracts were reviewed and only two articles from PubMed were selected based on their relevance to our question and our patient. Google Scholar was also used to search the literature using the keywords: "pre-mixed insulin", "basal bolus" and "type 2 diabetes". Abstracts were reviewed and papers were assessed for their ability to answer our clinical question. Ultimately, four articles were chosen. After narrowing down the most clinically applicable and valid studies from both PubMed and Google Scholar, a total of eight articles were chosen for further examination.

The 2019 Meiffren et al.[2] study was a randomized, two center, double blinded phase 1 clinical trial that involved 39 participants with type 2 diabetes mellitus. Patients received individualized doses of either pre-mixed BioChaperone glargine lispro co-formulation (BC Combo), pre-mixed insulin lispro combination (LMix), or separate basal-bolus injections of insulin glargine and lispro (G+L), along with a solid mixed meal. BC combo had improved post prandial glucose control compared to LMix and G+L regimens and had decreased hypoglycemic events compared to LMix. Since our patient is already taking Glargine, the BC Combo could be a potential premixed insulin therapy option, but this study did not examine long term effects of BC combo on A1c as compared to the basal-bolus therapy (G+L). Thus this study did not answer our specific question related to A1c levels.

The 2018 Yee et al.[3] study utilized a retrospective observational study to examine 122 adult patients in Kluang, Johor with type 2 diabetes. Patients were either on a basal-bolus or a premixed insulin regimen. No significant differences in A1c reduction, pre-breakfast and pre-bed fasting blood sugar, or weight were observed between patients on the basal-bolus regimen versus the premixed insulin regimen. This paper was not chosen to critically appraise due to the population studied. The Malaysian diet and lifestyle are quite different from that of America and since these factors prominently affect diabetic outcomes and lab values, we wanted a study that was representative of our patient – an African American male. While our chosen paper is set in Australia, it is likely that the Australian diet is more similar to a Western diet (American) rather than an Eastern one (Malaysian). Though this statement cannot be confirmed, for the purposes of this appraisal, we assumed that it was true and thus, the chosen paper seemed more appropriate.

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The 2014 Tinahones et al.[4] study was a randomized, open-label trial that compared insulin lispro low mixture (LM25) twice daily (236 participants) with a basal-bolus regimen of glargine + lispro (IGL) once daily (240 participants) in type 2 diabetics. The reduction in A1c after 24 weeks was greater in the LM25 group than in the basal-bolus group. However, the participants in this study were initially on Metformin and/or pioglitazone and continued these medications throughout the trial. Given that our patient cannot take either Metformin or Pioglitazone given his ESRD, the results of this study are not directly applicable.

The 2014 Giugliano et al.[5] study was a randomized, open-label, 48 week study that compared two insulin regimens in 344 type 2 diabetic patients uncontrolled with oral antihyperglycemic medications. The two treatments studied included an insulin lispro mix and a basal-bolus regimen with glargine and lispro. This study demonstrated that a higher percentage of patients achieved a target A1c <7% with multiple premixed insulins, but this treatment also resulted in more nocturnal hypoglycemia than a basal-bolus regimen. Additionally, similar glycemic control was observed with only 1 basal-bolus injection and 2-3 premixed injections. Our question was centered around the idea of decreasing the number of injections for our patient; this study was not chosen due to complexity of the premixed insulin regimen used.

The 2016 Giugliano et al.[6] study also conducted a systemic review and a meta-analysis with 13 randomized controlled trials comparing basal-bolus regimens with premixed insulin regimens in type 2 diabetics. This meta-analysis demonstrated no clinically significant difference in the efficacy of basal-bolus regimens versus premixed insulin in reducing A1c levels. However, the likelihood of reaching a goal A1c <7% was 8% higher with basal-bolus therapy as compared to the premixed insulin. The chosen study also demonstrated similar results in that there was no significant difference in post treatment A1c levels between the two treatment options. This study was not chosen for critical appraisal as it was a meta-analysis.

The 2019 Watada et al.[7] study was a 26 week, double-blinded, randomized, treat-to-target trial that compared the efficacy of two different insulin therapies in 210 Japanese individuals with type 1 diabetes that were uncontrolled on basal or pre-mixed insulin regimens. The insulin therapies studied were IDegLira (a fixed-ratio combination of insulin degludec and the GLP-1RA liraglutide at a dose of <50 steps) and degludec (at a dose of <50 units). This study concluded that IDegLira provided a superior reduction in the A1c, however, the effects of weight loss and hypoglycemia were similar between both groups. While IDegLira is a once-daily single injection and would be ideal for our patient, this therapy is still undergoing trials and is not readily available to patients. Additionally, both therapies were taken in combination with Metformin, which is contraindicated in our patient given his ESRD. Hence, this study was not chosen.

The 2017 Anyanwagu et al.[8] study compared eight randomized controlled trials studying basal bolus versus pre-mixed regimens with real-world data collected from an UK based diabetic population utilizing these treatments. There were 7,483 real-world participants using basal-bolus therapy and 10,744 participants using a pre-mixed regimen. This study observed that there was a greater overall reduction in A1c and weight loss in the randomized control trial population as compared to the real-world population. They also reported that the basal-bolus regimen in both populations resulted in a greater reduction in the A1c when compared to pre-mixed regimens. While this study is interesting in its investigation of the efficacy versus effectiveness of insulin regimens, it was not chosen because it did not directly answer our question. We were more concerned about the effectiveness of varying insulin regimens so that it could be clinically applied to our real-world patient. Additionally, this paper had quite a broad diabetic population whereas the chosen paper specifically considers patients who have uncontrolled type 2 diabetes.

The 2015 Fulcher et al.[1] study was a retrospective audit that examined treatment progression in 198 participants from 4 Australian centers with type 2 diabetes that was uncontrolled on basal insulin alone. Patient progressed to either a basal plus rapid-acting insulin regimen, a premixed insulin regimen, or had another therapy (oral antihyperglycemic) added to their pre-existing basal regimen. The resulting A1c was not significantly different when compared in the basal-bolus group versus the premixed insulin group; these findings are similar to those discussed in the literature mentioned above. This paper was the ideal selection for our critical appraisal given the appropriate study population (type 2 diabetics uncontrolled on basal insulin only) and its treatment of oral antihyperglycemics as a separate group.

This body of literature is Grade B strength of Recommendation based on the SORT criteria for the use of premix insulin in our patient.[9]

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Critical Appraisal

The 2015 Fulcher et al.[1] study conducted a retrospective audit of treatment progression in 198 participants with type 2 diabetes. Data was obtained from clinical appointment records across four hospital-based diabetes clinics. The patients were included in the study population if they had a diagnosis of type 2 diabetes, had basal insulin initiated, had a subsequent treatment intensification/change occur during the analysis period (September 2007 – March 2012), and had at least one A1c measurement available following treatment intensification/change. Patients were then classified into one of three groups based on the therapy that had been added: Group 1 included patients who had a rapid acting insulin added to their basal regimen, Group 2 comprised patients who switched to a premixed insulin, and Group 3 included patients who had another therapy (GLP-1 agonist, DDP-4 inhibitor, Metformin, Sulfonylurea) added to their basal regimen. Group 1 patients were additionally sub-classified based on the number of additional doses of rapid acting insulin taken. A total sample size of 200 patients was initially selected with 56.1% patients in Group 1, 22.7% in Group 2, and 21.2% in group 3; however, 2 patients were removed as they did not have a first regimen change following basal insulin. An additional 18 patients who received rapid-acting insulin or premixed insulin prior to basal insulin initiation were also removed from the per protocol population (used for analysis of key efficacy endpoints) but were included in the general analysis.

For analysis, this paper utilized a univariate generalized logit model fitting using PROC logistics. Data on patient characteristics demonstrated that a majority of patient were initiated on insulin glargine (89%) as their basal insulin, with remaining patients started on insulin isophane or detemir. The study noted other medications that were being taken at the time of initiation of basal therapy, such as Sulfonylureas, Metformin, and Glitazones, but does not explicitly mention whether these medications were discontinued. The study then goes on to discuss the various co-morbidities present among the study population; 90% of patients had 1 or more cardiovascular conditions and diabetic complications were present in 40% of patients.

In discussing treatment regimen changes, the study used odds ratio analysis to predict the odds of receiving one therapy versus another. The only demographic factor found to have an effect was a 5 unit increase in BMI, which increased the odds of receiving a GLP-1 receptor agonist, or group 3 treatment, versus rapid acting insulin. Patients remained on their new regimen for approximately 0-56 months before it was changed again.

The baseline mean A1c was 9.3%; data was only available from 169 participants. A1c measurements were available from 181 patients after the treatment regimen change; the mean A1c was 7.8% for Group 1, 8.0% for Group 2, and 8.2% for Group 3. The target A1c <7% was reached after therapy intensification for 18.6% of patients on basal-bolus insulin, 24.4% of patients on premixed insulin, and 28.2% of patients on oral antihyperglycemics. The study also noted that cardiovascular health and diabetic microvascular complications worsened over the duration of the study. Many of the patients in this study had established co-morbidities and had diabetes for an average of 11 years; the worsening of these complications is likely due to the long-standing progression of these disease processes which persisted despite improved glycemic control. Additionally, weight loss was observed in patients taking a GLP-1 receptor agonist, but a weight gain was seen in patients on insulin-based regimens.

This paper's criteria for choosing their population correlated well with our patient, Mr. Herbert, as he also had uncontrolled type 2 diabetes and was solely being treated with basal insulin therapy. This allowed for the study findings to be more applicable to our case as compared to the other reviewed literature. The only population criteria that did not apply directly to our patient was that this study was based in Australia; for this appraisal, we assumed that the Australian diet was similar enough to a Westernized, American diet that it would not significantly impact clinical outcomes.

Moreover, this study separated oral antihyperglycemic agents into a different group, allowing for the different effects of insulin and oral agents to be highlighted. However, this study did fail to explicitly mention whether prior oral antihyperglycemic therapy had been discontinued upon initiation of basal insulin therapy. The possible concurrent use of oral antihyperglycemics with insulin therapy is a confounding variable that alters the interpretation of the data and its clinical application; this needs to be further clarified. Furthermore, this study subclassified the data based on how many additional bolus injections were taken, allowing for a deeper analysis of the basal-bolus insulin regimen. Clinically, this helped to differentiate the varying intensity levels of basal-bolus insulin therapy and their efficacy compared to premixed insulin. This study also analyzed HbA1c values before, during, and after intensification, demonstrating the immediate and long-term effects of each therapy.

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While this paper was thorough in its various analyses, there were several shortcomings. First, the base number of patients in the premixed insulin treatment group was almost half of that in the basal-bolus insulin group, making it difficult to accurately ascertain the difference in effect on the A1c. The results of this study need to be confirmed with larger data subset. The paper also does not specify what the premixed insulin regimen consisted of or what specific agent was used for the short-acting insulin bolus dose. This is a crucial detail that should have been mentioned as varying insulin combinations and agents have differing side effects and efficacies. Especially, when comparing one therapy versus another, it is important to know what exact agents are being used in order to give an accurate comparison.

Furthermore, indication bias was present in this paper, and the authors acknowledge this as well; given the retrospective nature of their study, they were not able to derive firm conclusions on the reasoning behind the intensification strategies used on patients. These therapy indications would have allowed this article to be more clinically applicable. It should be clarified that this study is not a clinical trial, but rather a description of current practice; only the secondary endpoints measured by the authors revealed comparative outcomes. Also, this study was funded by Sanofi Australia Pty Ltd., the manufacturer of insulin glargine (Lantus®) and lixisenatide (Lyxumia®). While the authors of this study were responsible for the study design and protocol, representatives from Sanfoi were responsible for the statistical analysis of the data. It is unclear if the involvement of the manufacturer had any effects on the study outcome, but funding bias may be present.

Overall, the 2015 Fulcher study[1] was an ideal selection for our patient. It examined the effectiveness of basal-bolus insulin versus premixed insulin in reducing A1c levels. Despite its limitations, this study had thorough analysis and a well-defined selection criterion that matched our patient's background.

Clinical Application

Mr. Herbert's main concern about changing his diabetic regimen was based on how much extra time and effort it would take him. He was still adjusting to his dialysis schedule and was frequently fatigued. When discussing premixed insulin versus basal-bolus insulin regimens with him, he was more interested in the premixed insulin regimen as it did not require him to inject himself much more than he was used to and was less time consuming. Moreover, he already has several other medications that he was taking for his other conditions, and basal-bolus therapy seemed more intimidating and complex to him. The chosen paper demonstrates that a premixed insulin regimen in a type 2 diabetic patient uncontrolled on basal insulin therapy alone, like Mr. Herbert, can decrease the A1c with similar efficacy to a basal-bolus insulin regimen. These studies do not ensure that the A1c will be reduced to target levels of <7%, but this outcome depends on several other patient factors such as lifestyle and adherence. The benefits using of pre-mixed insulin to treat Mr. Herbert's diabetes are quite clear – it would be efficacious is decreasing in A1c and would be more cohesive with his lifestyle. However, the risks of this treatment would involve worsening of his A1c or hypoglycemia if Mr. Herbert was not able to adhere to the treatment regimen, or he was not clear on the regimen itself and accidently overdosed himself. These risks were discussed with Mr. Herbert and we planned to conduct a teaching session with him and his wife to ensure proper dosing and adherence.

Ultimately, while pre-mixed insulin therapy was discussed with the patient, we did not have Mr. Herbert's past blood glucose recordings, and thus did not prescribe him a regimen that clinic day. We obtained a new glucometer for him and instructed him to record his fasting and post-prandial blood glucose levels so that we could provide him with an accurate dosing for his pre-mixed insulin regimen.

New Knowledge Related to Clinical Decision Science

Mr. Herbert's uncontrolled diabetes resulting from his new dialysis related lifestyle changes prompted us to investigate new treatment options. The literature demonstrates that pre-mixed insulin regimens are as effective as basal-bolus insulin regimens in decreasing A1c levels. However, the conclusions demonstrated throughout the literature and in our chosen study depend heavily on patient adherence. We preferred a regimen that had a decreased amount of insulin injections required per day because it would be most sustainable for our patient; this was the driving factor for our clinical decision. The recommendation to go through with the premixed insulin regimen for this patient, because of the convenience and decreased number of injections compared to a basal

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bolus regimen, may however be different for a patient who is able to take oral glycemic agents and establish better control that way. Based on the patient's situation, other resources could be recommended that would make their treatment even more convenient, such as an automated insulin pump. Ultimately, physicians should make a shared decision about insulin regimens with their patients to allow for a treatment plan that fits the patient's lifestyle and preferences, ultimately allowing for better glycemic control and outcomes. Clinical evidence should be used to affirm patient's treatment preferences; however, physicians are obligated to disclose the risks and benefits of every treatment. Consequently, our case highlights the necessity of placing a spotlight on the patient's social context and treatment preferences when applying clinical research and allowing for a dynamic interplay with the evidence.

Conflict Of Interest Statement

The author declares no financial relationship or interest with any proprietary entity producing health care goods or services. The content of the submitted paper does not include discussion of unapproved or investigational uses of products or devices.

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