



IS THERE IS A PLACE FOR PREMIXED INSULIN IN TYPE 1 DIABETES MELLITUS?

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ABSTRACT

Background: The management of patients with type 1 diabetes mellitus is challenging for most doctors because it involves a multi-disciplinary team. One of the challenges is insulin availability, but it's not the only problem. The aim of this study was to see the role of premixed human insulin in a cohort of type 1 diabetes from Basrah, Southern Iraq. **Methods:** a prospective 6 months study of patients with type 1 diabetes mellitus enrolled from Al-Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC). Group one with premixed human insulin (70/30) given in two equal divided doses before breakfast and before dinner. Group two given insulin as modified basal bolus. The modified basal bolus includes two regular human insulin before breakfast and lunch with premixed human insulin (70/30) at dinner or twice premixed and regular human insulin at lunch. The third group given insulin as a basal bolus. **Results:** In all age groups of type 1 diabetes, the premixed group achieved the best results, but not reached statistical significance. Toddlers and preschoolers have the lowest figures for achieving targets of glycemia though no statistically significant differences between the different age groups regarding the achievement of target HbA1c. Only 72 out of 566 patients (12.7%) of the whole cohort achieved the target HbA1c by six months. **Conclusion:** our patients, whether they are using premixed insulin twice or modified basal bolus thrice with premixed or multiple four injections of basal bolus insulin regimen, achieve no significant difference in glycemic control. One of the explanations of the results may be the absence of diabetic educator, carbohydrate counting, and social interventions.

KEYWORDS: type 1 diabetes mellitus, premixed insulin, glycemic control.

INTRODUCTION

Type 1 diabetes mellitus patients from developing countries suffer from a lot of limitations not present in the developed world. The lack of insulin supply, storage difficulties, nonavailability of meters and strips with the social stigma of being affected by type 1 diabetes mellitus are examples of obstacles that face type 1 diabetes in the third world.^[1] In Iraq, the social stigma becomes so severe that the marriage of those people becomes difficult. The management of patients is challenging for most doctors because it involves a multi-disciplinary team. One of the challenges is insulin availability, but it's not the only problem.

The basal-bolus concept, i.e. either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) using a pump, has been shown to give the best results in type 1 diabetes mellitus.^[2] But we have to put in our mind that insulin is only successful as part of a comprehensive diabetes management, including nutritional management, physical activity, education, rules for sick days, surgery, and psychosocial support.^[2]

In adults with type 1 diabetes, it is clearly established that multiple injection regimens (basal-bolus regimens) are superior to simpler injection regimens, preferably using rapid-acting analogs as the bolus insulin.^[3,4]

Premixed insulins are not recommended for pediatric use, but premixed insulins may be useful to reduce the number of injections when compliance (or adherence) to the regimen is a problem.^[5] Biphasic insulin as part 30 is similar in efficacy to biphasic human insulin in improving hemoglobinA1c (HbA1c) levels, with the advantage of a better postprandial glucose profile in the review of Cochrane Database and scientific literature (PubMed) study until 2008.^[4,6]

Insulin regimen used for patients with type 1 diabetes varies among countries. For example, in Australia, among patients with type 1 diabetes in the 0-15 years age group, 61.3% were treated with two injections per day, 23.1% with three injections per day, 12.1% with four or more injections daily, 3.2% with one injection and 0.2% with insulin pumps.^[7]

Most of the guidelines suggested that A basal-bolus regimen with regular and NPH insulin should be preferred to pre-mixed insulin preparations, and NPH insulin should be given twice daily in most cases.^[2,5]

The aim of this study was to see the role of premixed human insulin in a cohort of type 1 diabetes from Basrah, Southern Iraq.

METHODS

STUDY ORGANIZATION

This was prospective 6 months study of patients with type 1 diabetes mellitus enrolled from Al-Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC). This is the tertiary referring center in Southern Iraq.

STUDY PARTICIPANTS

Of 2,000 patients with type 1 diabetes registered in the FDEMC, only 650 patients agree by them self or their parents to be enrolled to three treatment groups. Type 1 diabetes diagnosis was, according to the guideline.^[8] Written informed consent was taken from the patients if they are 18 years of age or more and from their parents if they are less than that. In the end, 566 patients continued the study of 6months.As part of routine work, the patients visit the center each three months for drug refilling and investigations with a reevaluation of dietary advice and glycemic control.

Exclusion criteria include patients who passed into the stage of partial remission of diabetes^[9], those with serum creatinine 1.5 mg/dl and above, those admitted with diabetes ketoacidosis within one week, and pregnant women. On enrollment extensive lifestyle instruction given to each patient or their family with dietary advice, but no carbohydrate counting was done.

Enrolled patients underwent basal anthropometric evaluation during each visit with blood pressure measurement. The human insulin and syringes are given to each patient free of charge each three months. No glucometer or strips are given to patients.

STUDY PROCEDURES

The study conducted for the period of January 2013 to April 2014.Of 566 patients enrolled, they were divided into three groups (figure-1). To start with, all patients or their families, advised that the primary treatment for all type one should be multiple daily injections with at least four injections daily according to the guidelines. Most of the patients refused to take more than two injections per day, and almost all use syringes. That's why we are left with three lines of treatment. Those who agree on four injections per day constituted a group, those who agree on three injections per day constitutes another group and those who agree on two injections per day constituted the other group regardless the pre-enrollment treatment regimen. Unfortunately, most of those patients were on single injection daily or not at all before enrollment, and

most of them severely catabolic with frequent hospital admissions for diabetic ketoacidosis.

Group one with premixed human insulin (70/30) stated dose of 0.5 units per kilogram daily, given in two equal divided doses before breakfast and before dinner. Group two given insulin as modified basal bolus. The modified basal bolus includes two regular human insulin before breakfast and lunch with premixed human insulin (70/30) at dinner or twice premixed and regular human insulin at lunch. The third group given insulin as basal bolus, the total daily insulin calculated as 0.5 units per kilogram of which 50% given as basal and 50% bolus in three divided doses, with correctional dose of insulin calculated for regular insulin according to premeal glucose, were 1500 divided by total dose of insulin needed according to body weight.

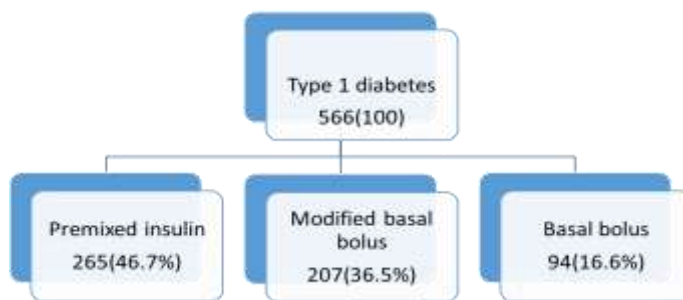


Figure 1. Study flow diagram.

The enrolled patients were either new or old type 1. The family history of diabetes was defined as having diabetes (either type 1 or 2) in any of the following family members: parents, grandparents (either paternal and maternal), siblings grandchildren, aunts, uncles, nephews, nieces or half-siblings.

Height and weight were measured without shoes and heavy clothes. BMI was calculated as weight in kilograms divided by the square of height in meters. Self-monitoring blood glucose (SMBG) was considered positive in those who do the test by themselves or by their parents at least once weekly.

During the first visit blood test for glycosylated hemoglobin (HbA1c) was done for each patient. The second HbA1c was done six months later. Target HbA1c was, according to the American Diabetes Association (ADA) standards of medical care in diabetes for 2014, including different cutoff for each age group.^[10] For toddlers and preschoolers (aged 0–5 year) the target HbA1c was < 8.5%, school age (aged 6–12 year), adolescents and young adults (aged 13–19 year), and adults >19 years, <7%.^[10] Insulin is supplied free of charge from the Center with check of HA1c each 4 months, but the glucometers and their strips are not supplied routinely.

The Center lacks the availability of diabetes educators, where are information supplied to patients and or their parents by doctors. Carbohydrate counting is not feasible for parents, and social support ignored award because of the crowds.

Almost all our patients with basal bolus used NPH once daily which is against the consensus recommendation.^[11]

STATISTICAL ANALYSIS

Numerical data were presented as mean \pm standard deviation while categorical variables were demonstrated as frequency and percentage (%). Comparisons were made by one-way analysis of variance (ANOVA) and Student t tests for continuous variables. The Chi-square analysis or Fisher's exact test was used to compare categorical variables. A p value of <0.05 was considered statistically significant. All statistical analysis was performed using the SPSS 15.0 software package.

RESULTS

The males constitute 53.5% with a mean age of 19.8 ± 10.3 year. The duration of diabetes was 7.5 ± 6.0 year. Family history was positive in 50.7% with 62.7% used SMBG. Insulin regimen was premixed human insulin in 46.8%, modified basal bolus in 36.6% and basal bolus in 16.6%. The enrollment HbA1c was 11.3 ± 2.5 percentage and after six months 10.4 ± 2.7 percentage. The overall reduction in HbA1c % was 0.8 ± 3.2 . A comparative analysis between the three treatment groups is presented in Table 2. New patients

were more likely to use premixed human insulin (P value = 0.002). There was no statistical difference between all treatment groups regarding gender or age, but the duration of diabetes was shorter in the promised group (P value <0.0001). Again, those with positive family history were more likely to use premixed human insulin (P value = 0.001).

There was no statistically significant difference between the three groups regarding SMBG, BMI, enrollment HbA1c, and HbA1c after six months. No significant difference in the achievement of target HbA1c $<7\%$ or reduction in mean HbA1c in the three treatment groups by six months (Figure-2).

Table-3 shows target HbA1c achieved according to ADA standards of medical care in diabetes for 2014. Only 15.3% of children aged 1-5 year achieved the ADA target of glycemia. For the age group 6-12 and the 13-19-year glycemic target was achieved in 27.8%. In adults, aged more than 19 years, 29.9% achieved the target. In all age groups of type 1, the premixed diabetes group achieved the best results, but not reached statistical significance.

Toddlers and preschoolers have the lowest figures for achieving targets of glycemia though no statistically significant differences between the different age group regarding the achievement of target HbA1c. Only 72 out of 566 patients (12.7%) of the whole cohort achieved the target HbA1c by six months.

Table -1-baseline characteristics, insulin regimen and HbA1c changes.

| | | |
|---|---------------------------------|-----------------|
| New type 1 No. (%) | | 181(32) |
| Male No. (%) | | 303(53.5) |
| Age (year) | | 19.8 ± 10.3 |
| Duration of diabetes (year) | | 7.5 ± 6.0 |
| Family history No. (%) | | 287(50.7) |
| SMBG No. (%) | | 355(62.7) |
| BMI (kg/m^2) | | 20.1 ± 4.9 |
| Insulin regimen | *Premixed 1 (Regimen 1) No. (%) | 265(46.8) |
| | **MBB 2 (Regimen 2) No. (%) | 207(36.6) |
| | ***BB 3 (Regimen 3) No. (%) | 94(16.6) |
| Enrollment HbA1c No. (%) | | 11.3 ± 2.5 |
| HbA1c after 6 months No. (%) | | 10.4 ± 2.7 |
| Reduction of HbA1c % | | 0.8 ± 3.2 |
| *Premixed denote premixed human insulin (70/30) | | |
| ** MBB denote modified basal bolus | | |
| ***BB denote basal bolus | | |

Table -2-comparative analysis of the three lines of treatment used.

| | Premixed human insulin (Regimen 1) | Modified basal bolus human insulin (Regimen 2) | Basal bolus human insulin (Regimen 3) | P value |
|-----------------------------|---|---|--|--------------------------------|
| New type 1 No. (%) | 104(39.2) | 50(24.2) | 27(28.7) | 0.002 |
| Male No. (%) | 139 (52.5) | 117 (56.5) | 47 (50.0) | 0.512 |
| Age (year) | 19.3 ± 10.1 | 19.9 ± 9.3 | 20.8 ± 12.6 | 0.487 |
| Duration of diabetes (year) | 6.0 ± 4.9 | 9.0 ± 5.9 | 8.81 ± 7.7 | <0.0001 |
| Family history No. (%) | 147(55.5) | 108(52.2) | 32(34.0) | 0.001 |

| | | | | |
|--------------------------|-----------|-----------|----------|-------|
| SMBG No. (%) | 154(58.1) | 140(67.6) | 61(64.9) | 0.094 |
| BMI (kg/m ²) | 20.0±4.9 | 20.3±5.1 | 19.6±4.4 | 0.568 |
| Enrollment HbA1c % | 11.2±2.3 | 11.0±2.4 | 11.9±2.8 | 0.007 |
| HbA1c after 6 months% | 10.5±2.9 | 10.2±2.4 | 10.6±2.9 | 0.368 |
| HbA1c reduction % | 0.7±3.2 | 0.7±2.9 | 1.3±3.4 | 0.3 |

Table-3-target HbA1c achieved according to ADA recommendation.

| Age group | ADA HbA1c target | Total No. (%) | Premixed human insulin (Regimen 1) | Modified basal bolus human insulin (Regimen 2) | Basal bolus human insulin (Regimen 3) | P value | ADA total achieved target No. (%) |
|-----------|------------------|---------------|------------------------------------|--|---------------------------------------|---------|-----------------------------------|
| 1-5 (1) | < 8.5% (1) | 25(4.4) | 6(54.5%) | 3(27.3%) | 2(18.2%) | 0.64 | 11 (15.3) |
| 6-12 (2) | <8 (2) | 131(23.1) | 11(55.6%) | 5(25.0%) | 4(20.0%) | 0.56 | 20(27.8) |
| 13-19 (3) | <7.5(3) | 152(26.9) | 9(45.0%) | 6(30.0%) | 5(25.0%) | 0.271 | 20(27.8) |
| >19 (4) | <7(4) | 258(45.6) | 15(71.4%) | 5(23.8%) | 1(4.8%) | 0.564 | 21(29.2%) |
| Total | | 566(100) | 41(56.9%) | 19(26.4%) | 12(16.7%) | | 72(100.0) |

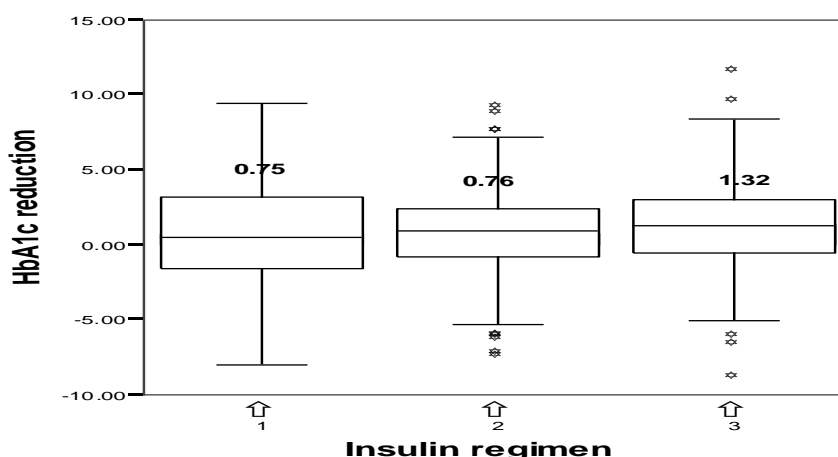


Figure-2-mean reduction of HbA1c in the three treatment groups.

DISCUSSION

Using multiple daily insulin injections in developing country is quite challenging. Simply because it's not only the insulin therapy that determine the achievement of target glycemia. The treatment of type 1 diabetes should be team work involving dietitian, psychologist, especially during the transition period, diabetic educationist, besides the social workers and availability of drugs specially the new insulin analogs which should be affordable for all with glucometers and their strips and their proper storage.^[12-16]

In this cohort, only 12.7% achieved the target glycemia recommended by the ADA, according to age group. The similar finding also seen before from the same Center.^[17]

Only 94 (16.6) patients were on four injections daily. Their achievement of target glycemia is not different from those with fewer injections. No sufficient, scientific evidence showed that treating type 1 diabetic subjects with four daily insulin injections will improve glycemic target, but the fact that the quality of life for the patients is improved makes this regimen preferably compared with two daily insulin injections.^[4,18]

Meta-analysis shows that CSII treatment provides the greatest reduction in HbA1c without inducing more hypoglycemic events, and basal-bolus therapy has not been shown to improve HbA1c but provides flexibility for the patients.^[18]

Premixed insulin is still used in developing countries for treating type 1 diabetes mellitus with some success.^[19] Furthermore, despite the clear benefits of CSII, but, this device use is not easy, the parents and patients should accept it, and it should be affordable for patients.^[20]

The story in type 2 diabetes mellitus may be not different. In a large systemic review study, biphasic and basal bolus regimens were equally effective in reducing HbA1c in insulin-naïve patients with type 2 diabetes, and both regimens are equally effective for initiating insulin in Type 2 diabetes.^[21]

The picture of real life treatment for type 1 diabetes mellitus is heterogeneous. For example, in, Saudi Arabia, a majority of children with type 1 started twice insulin doses daily, with human insulin (both regular and NPH).²² While in an Omani cohort of 144 patients with

type 1 diabetes, insulin was used twice in 16%, multiple daily injections in 76%, and insulin pump in 10%.^[23] But among 2,961 cohorts of type 1 diabetic from Brazil, 90.2% were on multiple daily injection basal-bolus insulin regimen with human insulin of intermediate type and regular as the commonest regimen used.^[24]

Most of the recommendations on that topic were loose. For example, the last NICE recommendation for patients with type 1 diabetes was to consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal-bolus insulin regimen is not possible.^[25]

STUDY LIMITATION

The study was an open label, and the enrollment of treatment groups was, according to patients and their family wishes.

CONCLUSION

our patients whether they are using premixed insulin twice or modified basal bolus thrice with premixed or multiple four injections of basal-bolus insulin regimen achieve no significant difference in glycemic control. One of the explanations of the results may be the absence of diabetic educator, carbohydrate counting, and social intervention.

CONFLICT OF INTERESTS: None

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DATA SHARING STATEMENT

No additional data available

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AUTHOR CONTRIBUTIONS

Both authors contributed equally to the study.

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