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Institution of Multiple Daily Insulin Regimen Compared with Twice Daily Pre-Mixed Insulin Regimen for Children with Type 1 Diabetes Mellitus

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Abstract Children and young adults with type 1 diabetes mellitus are usually commenced on either a multiple daily insulin (MDI) regimen or twice daily pre-mixed insulin regimen at diagnosis. The MDI regimen is thought to more closely mimic the normal secretory patterns of endogenous insulin production to improve glycaemic control compared to twice daily or thrice-daily insulin regimens. This study aims to look at the effect on glycaemic control and growth over an 18-month period in children with type 1 diabetes mellitus on a twice-daily pre-mixed bis die (BD) insulin therapy compared to MDI regimen. This is a retrospective study comparing glycaemic control (HbA1c) and growth parameters (height SDS, weight SDS and BMI SDS) at intervals over an 18-month period between children with type 1 diabetes mellitus started on a twice-daily pre-mixed insulin regimen compared to those children started on MDI regimen. No significant difference was found between the two groups. Multiple regression analysis examining independent variables (age at diagnosis, insulin regimen, gender) affecting HbA1c values at 3, 6, 12 and 18 months confirmed that there were no independent factors affecting glycaemic control at any time point A twice-daily insulin regimen and an MDI insulin regimen were equivocal in efficacy of HBA1c control and measures of growth parameters within an 18-month period in paediatric diabetic patients with type 1 diabetes mellitus. Future prospective studies are warranted to address the issues described.

Keywords: *Insulin, diabetes, paediatric*

1. Introduction

Paediatric diabetes is one of the commonest chronic diseases in childhood. Children and young adults with type 1 diabetes mellitus are commenced on multiple daily insulin (MDI) regimen or twice daily pre-mixed insulin regimen at diagnosis. MDI regimen consists of a long-acting insulin with a flat action profile given at night-time with rapid-acting insulin given before each meal. This regimen is thought to more closely mimic the normal secretory patterns of endogenous insulin production (a constant background "basal" level of secretion and food-associated "boluses"), compared to a biphasic regimen.[1,2,3,4,5,6,7] As such, it is plausible to theorise that MDI regimen may improve glycaemic control in diabetic patients compared to twice daily or thrice-daily insulin regimens [8,9]. A recent study showed that for children with "long-standing" (>1 year before change of insulin regimen) type 1 diabetes mellitus, a change to MDI regimen does not have a significant effect on glycaemic control [10]. Therefore, any potential benefits of MDI regimen might be thought to occur only if it is instituted at or soon after diagnosis. In addition to the concerns regarding the microvascular and macrovascular complications of diabetes and hyperglycaemia common to all diabetic patients, paediatric patients also present the challenge of a period of growth and development to glycaemic control [11].

In the United Kingdom (UK), the current National Institute for Clinical Excellence (NICE) guidance (CG15) for insulin regimens in children with type 1 diabetes mellitus under 11 years merely states that the "most appropriate insulin regimen be used to optimise glycaemic control". In this younger age group of under 11 years, MDI regimen is not favoured as it is with older patients, and children with type 1 diabetes mellitus are often started on a twice-daily *bis die* (BD) pre-mixed insulin regimen as this was thought to be easier for the family to adopt at the time of diagnosis. However, children are encouraged to change onto MDI regimen to further optimise their glycaemic control after a period of time.

This study aims to look at the effect on glycaemic control and growth over an 18-month period in children with type 1 diabetes mellitus on a twice-daily BD pre-mixed insulin therapy compared to MDI regimen.

2. Methods

A retrospective analysis of all children aged under 11 years with type 1 diabetes mellitus diagnosed between January 2000 and January 2011 at Southport and Ormskirk NHS Trust hospital were analysed. The child's height, weight and HbA1c value were collated from their medical records at 3 months, 6 months, 12 months and 18

months after the start of treatment. In the BD regimen, patients were started on 0.6units/kg/day of insulin and dose adjusted accordingly to achieve a blood glucose of between 4 to 8mmol/L pre-meals and between 4-9mmol/L post meals. In the MDI regimen, the dosing of rapid-acting insulin were adjusted according to the carbohydrate counting and adjusted accordingly to achieve a blood glucose of between 4 to 8mmol/L pre-meals and between 4-9mmol/L post meals.

The children's BMI was calculated from their height and weight and the Standard Deviation Score for the height, weight and BMI were calculated using the British 1990 Growth Reference [12]. This allows meaningful comparisons of growth to be made when the groups involved include children of different ages.

The statistical package used to analyse the data was SPSS 20. Distributions of continuous outcomes were checked. P-values were calculated using a t-test or Mann Whitney U test as appropriate.

3. Results

There were 73 patients included in the study. There were no difference in mean age at diagnosis, sex, presentation of diabetic ketoacidosis and growth parameters between both groups (Table 1). Table 2 shows the comparison of children with type 1 diabetes mellitus on a twice-daily pre-mixed insulin therapy compared to MDI regimen with regards to HbA1c control (mmol/mol,%) and growth parameters at each time interval from start of diagnosis. The analysis of the difference in glycaemic control as measured by HbA1c between the two groups showed that there was no significant difference at any of the time points. There was also no significant difference in the SDS growth parameters (height, weight, BMI) at the start of treatment, at 3, 6, 12 or 18 months from diagnosis.

Table 1. Demographics and characteristics of children with T1DM on twice daily (BD) insulin therapy compared to MDI regimen

	Twice daily regimen N=45	MDI regimen N=28	P Value
Sex (males)	19 (42%)	13 (46%)	0.45
Mean Age at Diagnosis	8.20 (2.7)	9.00 (1.8)	0.86
Height SDS at start of treatment	0.63(1.03)	0.53(0.92)	0.68
Weight SDS at start of treatment	0.79(1.07)	0.89(1.00)	0.71
BMI SDS at start of treatment	0.68(1.24)	0.86(1.11)	0.55

Data expressed as mean (SD) for continuous outcomes, x(%) for categorical outcomes.

Multiple regression analysis examining independent variables (age at diagnosis, insulin regimen, gender) affecting HbA1c values at 3, 6, 12 and 18 months confirmed that there were no independent factors affecting glycaemic control at any time point.

Table 2. Comparison of children with T1DM on a twice-daily (BD) insulin therapy compared to MDI regimen

Outcome		BD group	MDI group	Difference (95%CI)	P-value
HbA1c at 3 months	mmol/mol %	59 (14.64) 7.52 (1.34)	60 (10.98) 7.63 (1.00)	-1.22 (-7.64,5.21) -0.11 (-7.00,0.48)	0.71 0.71
HbA1c at 6 months	mmol/mol %	60 (14.54) 7.60 (1.33)	61 (8.32) 7.69 (0.76)	-0.93 (-6.51,4.66) -0.08 (-0.60,0.43)	0.74 0.74
HbA1c at 12 months	mmol/mol %	65 (15.88) 8.14 (1.45)	67 (12.33) 8.26 (1.13)	-1.34 (-9.27,6.59) -0.12 (-0.85,0.60)	0.74 0.74
HbA1c at 18 months	mmol/mol %	70 (18.34) 8.59 (1.68)	67 (10.27) 8.29 (0.94)	3.23 (-6.49,12.95) 0.30 (-0.59,1.19)	0.50 0.50
Height SDS at 3 months		0.61(1.33)	0.67(0.96)	-0.06 (-0.62,0.50)	0.82
Weight SDS at 3 months		1.04(1.01)	1.00(1.01)	0.04 (-0.47,0.54)	0.89
BMI SDS at 3 months		1.03(1.16)	0.88(1.08)	0.15 (-0.41,0.71)	0.59
Height SDS at 6 months		0.77 (0.97)	0.60 (1.00)	0.17 (-0.34,0.68)	0.51
Weight SDS at 6 months		1.10(0.93)	0.99(1.05)	0.10 (-0.42,0.62)	0.69
BMI SDS at 6 months		0.99(1.03)	0.94(1.04)	0.05 (-0.48,0.58)	0.85
Height SDS at 12 months		0.68(1.07)	0.76(1.06)	-0.08 (-0.71,0.55)	0.80
Weight SDS at 12 months		1.00(0.94)	1.17(1.06)	-0.16 (-0.77,0.44)	0.59
BMI SDS at 12 months		0.90(1.00)	1.08(1.01)	-0.18 (-0.78,0.42)	0.55
Height SDS at 18 months		0.84(1.03)	0.93(0.81)	-0.08 (-0.75,0.59)	0.80
Weight SDS at 18 months		1.09(0.96)	1.43(1.00)	-0.34 (-1.11,0.44)	0.37
BMI SDS at 18 months		0.95(0.99)	1.30(1.01)	-0.36 (-1.14,0.43)	0.35

Data expressed as mean (SD) for continuous outcomes

A longitudinal analysis showed a trend for poorer glycaemic control as time progressed in patients on either BD or MDI insulin regimes (Figure 1). The MDI group did not show a significantly slower decline in HbA1c control compared with the BD group during the time period (p=0.07).

4. Discussion

This study compared children and young adults with type 1 diabetes mellitus on a twice-daily insulin regimen compared with those on MDI regimen and looked at the differences in glycaemic control and growth over an 18-month period. No significant differences were found between the two groups in either HbA1c or SDS growth parameters. Multiple regression analysis did not find any independent factors affecting HbA1c.

The retrospective nature of the study design is a limitation. This study was not able to address other indicators of poor glycaemic control, such as hypoglycaemic episodes as this data was not reliably recorded in the medical notes. It is possible that an MDI regimen has benefits beyond improved HbA1c or growth,

such as fewer hypoglycaemic episodes. In addition, information on autoantibodies and residual insulin secretion were not available. A prospective study would be warranted to address these issues in the future.

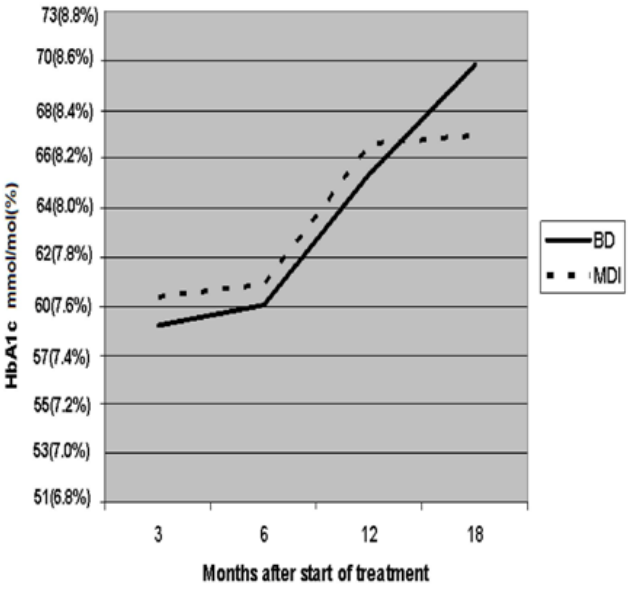

Figure 1. A longitudinal analysis of diabetes control comparing patients on either BD or MDI insulin regimes

Although the study did not find a significant difference in glycaemic control between insulin regimens over an 18-month period, a longitudinal comparison shown in Figure 1 showed a slower worsening of HbA1c control in the MDI group by 18 months post treatment. It is worth remembering that patients with diabetes often fail to find abstract things like HbA1c values to be of any significance in their day-to-day lives, despite the understood risk of microvascular and macrovascular complications. The increased flexibility of an MDI regimen with respect to flexible mealtimes is an advantage of MDI for which patients are likely to appreciate [6,7]. Even in the absence of any improvement in blood test values, different insulin regimens can be more or less appealing to patients dependent on factors such as quality of life, hypoglycemic episodes and flexibility of their insulin regimen[8,9]. Therefore, even though this study failed to find a significant improvement in glycaemic control as measured by HbA1c or growth parameter when using an MDI regimen, it confirmed that a BD regimen was at least equivalent in efficacy of control within an 18-month period. In the face of a lack of a current national recommendations for patients with type 1 diabetes mellitus under 11 years of one regimen over another, it will fall to the individual clinicians to decide on appropriateness of an insulin regimen to the individual. There is no evidence to date that that children who are started on a twice-daily pre-mixed regimen which, while "good enough" in the short-term, means that they will miss the potential long-term control benefits of MDI. The study by Adhikari et al [10] found that for children with type 1 diabetes mellitus, a change to MDI regimen from a BD regimen did not have a significant effect on glycaemic control.

In conclusion, this study did not find a significant difference in glycaemic control or growth parameters between a twice-daily insulin regimen and an MDI regimen in paediatric patients diagnosed with type 1 diabetes mellitus over an 18-month follow-up period. Future prospective studies are warranted to address the issues raised above and provide a framework for guidance to be issued on the desirability of starting all newly-diagnosed patients with type 1 diabetes mellitus on MDI.

Conflict of Interest

The authors declare no conflict of interest.

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