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Utilization of an abbreviated diabetes impact management scale to assess change in subjective disability during a trial of pulsatile insulin delivery demonstrates benefit

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Abstract

A prospective interventional study of pulsatile intravenous insulin infusion therapy has demonstrated reduction of left ventricular mass and blunting of progression of diabetic nephropathy. We anticipated that improvements in objective parameters would be associated with similar improvement measurable by the self-administered Diabetes Impact Management Scale (DIMS). The DIMS was administered at baseline and 12 months for 19 participants randomized to receive either standard insulin treatment of 3 to 4 injections of insulin daily or insulin treatment plus an additional day per week of 3 intravenous pulses over an 8-hour period. For standard vs pulsed intravenous insulin therapy, mean baseline scores were similar for the 12 total questions as well as the groups of 7 questions with emotional content and 5 with physical (neurologic) content. Mean study group scores at 1 year and changes over 1 year were not significantly different for the 7 questions with emotional content ($P = .3143, .7574$). Score results for the 5 questions related to neurologic status at 1 year and changes over 1 year were significantly different between patients with standard and with pulsed insulin therapy ($P = .0144, 0.0004$). Pulsatile intravenous insulin, when added to standard multiple-dose insulin therapy, was demonstrated to improve subjective perception of neurologic disability on repeated use of an abbreviated form of the DIMS.

1. Introduction

Physiologic secretion of several hormones occurs in pulsatile fashion, including insulin [1], glucagon [2], somatostatin [3], and growth hormone [4]. When equimolar amounts of hormones have been compared with continuous infusion, increased efficiency of physiologic response has been found for insulin, glucagons, and growth hormone. The intent of this study was to assess quality of life as determined by the Diabetes Impact Management Scale (DIMS) in a prospective randomized study involving pulsatile intravenous insulin infusion [5] added to standard care in patients with type 1 diabetic nephropathy followed for 12 months. We hypothesized that repeated use of a simple subjective impact evaluation tool would give information that would correlate with objective changes in clinical and laboratory patient status particularly improvement in carbon dioxide to oxygen production ratio [6,7].

A prospective interventional study of pulsatile intravenous insulin infusion therapy has demonstrated reduction of left ventricular mass and blunting of progression of diabetic nephropathy. Such findings would not be expected to bring about improvements in patient's perception of their quality of life. We considered that improvements in objective parameters, however, might be associated with similar improvement measurable by a self-administered DIMS and were worthy of investigating in a trial to assess methods of insulin delivery to patients with type 1 diabetes mellitus.

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2. Methods

Investigators participating in a multicenter study, with the goal of optimizing glycemia and blood pressure control, saw patients with type 1 diabetes mellitus weekly for 1 year. Individual patients were randomized to either a control group or a treated group. Both groups of patients received 3 to 4 subcutaneous insulin injections per day. The treated group received, in addition, a pulsed intravenous insulin infusion consisting of three 1-hour infusions in a pulsatile fashion over one 8-hour period each week. A description of the complete protocol has been previously published [8]. Laboratory investigations included levels of and changes in serum creatinine, creatinine clearance, total urinary protein per 24 hours, hemoglobin, glycohemoglobin, and advanced glycated end products. Additional measurements were calculated for left ventricular mass, serum fibrinogen, fibrinolytic activity, factor VII level, plasminogen activator inhibitor 1, von Willebrand factor, diastolic function (by E/A ratio), systolic function (fractional fiber shortening, ejection fraction), mean arterial pressure, day to night mean arterial pressure ratio, and measures of time and frequency spectral analysis of 24-hour ambulatory electrocardiographic monitoring (all results not shown) [9-11].

A subgroup of 19 patients seen at the Joslin Diabetes Center (12 men, 7 women) participated in this study [7,9-11]. The patients were randomly assigned to a control group (n =9) or an intravenous pulsed insulin infusion group (n =10). Baseline characteristics and clinical profile are shown in Table 1.

All patients completed the 44-question DIMS at baseline and 12 months. Validation of the methodology and scoring of this instrument in a standardized manner has been previously published [12-14]. Each patient's DIMS response at 12 months was compared with his/her individual baseline response to minimize interindividual variability. All patients had at least a 75% question response rate on both the baseline and 12-month questionnaires. Because missing data occurred for different questions in the 2 study groups, we created a data set for analysis where each missing value was replaced with the mean response for that question for the total group [15,16]. Thirty-two of the 44 questions showed no significant change between baseline and 12 months for the total group ($P \geq .10$) and were therefore excluded from further analysis. Of the 12 remaining questions, 5 predominantly reflected physical issues (Did burning, tingling, pain, or numbness bother you in your hands? Have you been bothered by blurring of vision? How often did you have diarrhea? How often were you able to function sexually as well as you wanted to? Have you been bothered by feeling faint/dizzy on sitting up/standing up?) and 7 reflected emotional issues (How much of the time were you lacking enough energy? Have you felt optimistic about your diabetes? How well have you slept? Have you felt depressed? Have you eaten what you wanted to? Have you participated in and enjoyed family life? How often have you been able to function well in your usual occupation?) regarding the prior months' activities and sensations. Responses were based on a 6-point scale (worst case response being 6 points, best case receiving 1 point): never, rarely, sometimes, often, usually, and always. The neuropathy question was scored on responses including no discomfort, mild, moderate, severe, nearly unbearable, and unbearable (worst case response being 6 points, best case receiving 1 point).

Annual changes of individual patient scores were calculated for each of the 2 response question groups, and results were then correlated with treatment and changes in laboratory values measured during the study. It should be understood that a decrease in DIMS score or any of its components represents a subjective improvement of symptoms reported for the prior month.

Data analyses were performed using SAS Version 8.2 (SAS Institute, Cary, NC). Significance of annual responses from zero was determined by Student paired *t* tests. Tests of significance between study groups were determined by Student unpaired *t* tests. Frequency data were compared using Fisher exact test. Pearson product moment correlations were used to determine the relationships between variables. Values are reported with standard error of the mean as a measure of dispersion. A *P* value not exceeding .05 was considered statistically significant.

Table 1
Demographics: baseline variables

Variables	Insulin pulsing by IV insulin		
	Yes (n = 10)	No (n = 9)	*P* value
Age (y)	40.3 ± 2.4	40.2 ± 3.8	.9860
Duration DM	27.0 ± 1.4	26.6 ± 1.9	.8528
Body weight (kg)	73.2 ± 3.7	72.8 ± 2.4	.9400
Serum creatinine (mg/dL)	1.8 ± 0.2	1.8 ± 0.2	.9725
Creatinine clearance (mL/min)	58.1 ± 7.0	57.8 ± 6.0	.9729
24-h proteinuria (g/d)	2449 ± 735	3974 ± 794	.1764
Hemoglobin (g%)	13.4 ± 0.7	13.8 ± 0.5	.6557
Hemoglobin A_{1c} (%)	8.9 ± 0.5	9.7 ± 0.5	.2724
Advanced glycated end products	11.5 ± 3.3	12.6 ± 1.8	.7867

IV indicates intravenous; DM, diabetes mellitus.

3. Results

Using standardized scoring of the DIMS questionnaire, we found that changes, over the year, in the 12-question scores (Table 2) were significantly different between the study groups. There were no statistically significant relationships between change in the baseline and 1-year DIMS scoring for 44 questions and type of insulin delivery or resultant diabetes control (all *P*s = not significant). It appeared that virtually all of the difference between the insulin groups was accounted for by the physical and not the emotional content questions.

During the yearlong course of the trial, the patients receiving pulsed weekly insulin had more stable serum creatinine (baseline, 1.8 mg/dL; 12 months, 1.8) than those

Table 2
The DIMS question scores over 1 year: relationship to method of insulin administration (mean ± SEM)

	Insulin pulsing by IV insulin		*P* value
	Yes (n = 10)	No (n = 9)	
12-Question score (total)			
Baseline	32.01 ± 1.72	31.23 ± 1.38	.7323
1 y	27.18 ± 1.41	33.16 ± 2.22	.0331
Change	−4.83 ± 1.79	1.92 ± 1.72	.0150
5-Question score (physical)			
Baseline	13.10 ± 0.82	11.33 ± 0.60	.1078
1 y	8.48 ± 0.91	12.96 ± 1.41	.0144
Change	−4.62 ± 0.87	1.62 ± 1.16	.0004
7-Question score (emotional)			
Baseline	18.91 ± 1.16	19.90 ± 1.09	.5455
1 y	18.70 ± 1.03	20.20 ± 1.00	.3143
Change	−0.21 ± 1.30	0.30 ± 0.92	.7574

on standard insulin therapy (baseline, 1.8; 12 months, 2.3; difference between study groups, $P = .0233$). Likewise, creatinine clearance in the pulsed group was more stable (58 to 59 vs 58 to 41 mL/min, $P = .0528$); as was hemoglobin (13.4 to 12.6 vs 13.8 to 11.8, $P = .0075$). Control of glycemia as measured by glycohemoglobin A_{1c} was not statistically different at baseline or at 1 year but improved less in the pulsed care group (8.9% to 8.4% vs 10.0% to 8.0%, $P = .0520$); as measured by advanced glycated end products (11.5 to 8.3 vs 12.6 to 7.2, $P = .6666$), there were no differences between study groups. These findings are similar to those previously reported in the multicenter study [3].

Significant physical, but not emotional, score responses were evident only after pulsed insulin administration (Table 2) along with stability of renal function and reduction of left ventricular mass [17]. Changes in the 5-question responses over the course of the study were statistically correlated with changes in serum creatinine ($r = 0.6998$, $P = .0009$), creatinine clearance ($r = −0.4669$, $P = .0438$), and left ventricular mass ($r = 0.5189$, $P = .0394$).

4. Discussion

We hypothesized that correction of insulin deficiency by pulsatile intravenous insulin infusion in type 1 diabetes mellitus patients with nephropathy would be associated with a measurable improvement of the physical and emotional diabetes impact measurement scale when compared with a control group with conventional subcutaneous insulin dosing provided that there was similar glycemic control. We reasoned that questions relating to the subjective physical as opposed to emotional impact of diabetic nephropathy or its management might be more sensitive to the objective changes observed in individuals. Of the 5 physical questions, 3 relate directly to autonomic, 1 to peripheral, and 1 potentially to cranial nerve function [18]. We anticipated as well that changes in the individual responses to the DIMS would be associated with measurable changes in the kidney and the heart. Physical, but not emotional, responses corresponded nearly identically to pulsed insulin administration (Table 2), stability of renal function, and reduction of left ventricular mass. The response to physical status questions was not associated with any improvement in hemoglobin or control of diabetes as assessed by glycohemoglobin concentration or advanced glycated end products.

This study demonstrates that pulsatile insulin injections had a significant benefit in perceived neurologic function when compared with standard therapy corresponding to a slowing in the decline in kidney function and diminution in left ventricular hypertrophy. As it is quite unlikely that stability of renal function or decrease in left ventricular mass has a direct effect on subtle neurologic changes, 1 reasonable explanation may be that the delivery of insulin in a physiologic manner has diffuse metabolic effects at the cellular level.

The current pilot study was limited to type 1 diabetes mellitus patients with abnormalities in renal function. The findings cannot be generalized to type 1 diabetes mellitus patients with normal renal function or to individuals with type 2 diabetes mellitus. Our results, however, suggest that repeated use of abbreviated DIMS (rather than the standard long form) questionnaires might provide useful information in prospective interventional studies. At least in this study, the abbreviated test focused and magnified changes that would have been obscured by the use of the full tool. In the complete DIMS tool, there are many questions that related to morale. In the current study, patients were used as their own controls; and chronic depressive illnesses were neither diagnosed nor treated. Prior studies have demonstrated little relevant clinical value for the full DIMS tool. We believe that this is due to the static produced by questions that are only loosely associated with physical illness, though certainly related to perceived quality of life.

A large prospective study (n = 506) of individuals older than 70 years demonstrated significant differences in all-cause mortality and cardiovascular events in the presence or absence of subtle neurologic findings. In that study, patients were examined for tremor, rigidity, deficiencies of small movements, and postural balance in addition to changes in frontal lobe function, with notable difference in patient outcomes after 3 to 9 years [19]. Mechanism of brain dysfunction in the older adults was suggested to be direct subcortical injury, but the accompanying editorial suggests that the more basic underlying defect is in the microvasculature [20]. The current small pilot study using subtle subjective neurologic abnormalities in patients 3 decades younger with cardiorenal disease was able to identify significant differences in surrogate markers of vital organ function within the first 18 months. Because the findings in our study touch areas of microvasculature as well as direct neurologic change, the impact of physiologic insulin delivery to diverse target organs at the mitochondrial level would appear central [21].

We believe this to be a potentially important observation in the clinical evaluation of patients with progressive nephropathy, as the full DIMS tool may obscure some

important results with respect to the progressive changes of diabetes. If this finding is confirmed in larger data sets, it may lead to improvement in the precision and utility of the DIMS for further clinical research in patients with type 1 diabetes mellitus. Pulsatile intravenous insulin, when added to standard multiple-dose insulin therapy, was demonstrated to improve subjective perception of neurologic disability on repeated use of an abbreviated form of the DIMS.

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