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Pulsatile intermittent intravenous insulin therapy for attenuation of retinopathy and nephropathy in type 1 diabetes mellitus

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Abstract

Many hormones are secreted in a pulsatile fashion that is more efficient than continuous secretion when tested in vivo. A trial of multiple daily insulin doses with or without the addition of weekly pulsatile insulin infusion therapy was designed to determine if deterioration of renal and retinal function could be blunted. Sixty-five study subjects were evaluated prospectively in 7 centers. Thirty-six patients were randomly allocated to the infusion group and 29 to the standard therapy group. Mean serum creatinine was 1.6 mg/dL in both groups. Subjects were excluded if clearance was less than 30 mL/min. There were no significant differences between the groups with respect to age, duration of diabetes, sex distribution, glycohemoglobin, blood pressure, angiotensin-converting enzyme inhibitor use, proteinuria, or baseline diabetic retinopathy (DR) severity level (all eyes exhibited DR; 8 were deemed technically not amenable to evaluation). Progression of DR was noted in 31.6% of 57 patients (32.3% treated, 30.8% control; $P = 1.0$) with both eyes evaluable. For patients with 12 or more months of follow-up, 27.9% of 43 patients demonstrated progression of DR (32.0% treated, 22.2% control; $P = .57$). There were no significant differences between study groups with respect to progression or marked progression, nor was there any influence of duration of follow-up. Progression of DR was noted in 18.8% of 122 eyes that could be adequately evaluated (17.9% of 67 treated, 20% of 55 controls; $P = .39$). Serum creatinine increased to 1.7 mg/dL in the treatment group and to 1.9 mg/dL in the control group ($P = .03$). Statistically significant preservation of renal function by pulsatile insulin infusion was not matched by a statistically significant prevention of DR progression compared with standard diabetes care. Inadequate statistical power or duration of the study, or lack of further benefit of pulsatile insulin infusion on the retina in the presence of angiotensin-converting enzyme inhibition may be responsible.

1. Background

Pulsatile secretion of insulin from β-cells follows a pattern of oscillations of intracellular calcium. Increased efficiency of equimolar amounts of hormones administered in pulsatile fashion when compared with continuous infusion has been demonstrated for insulin [1,2], glucagon [3], and growth hormone [4]. Disruption of organized pulsatile secretion of insulin in type 2 diabetes mellitus and in aldosterone secreted from adrenocortical adenomata [5] has been noted. Pulsatile secretion of hormone is retained by the isolated β-cell [6] and the remnant parathyroid gland [7] despite separation from changes in plasma glucose or calcium.

The addition of pulsatile infusion to multiple daily subcutaneous injections has been reported to decrease elevated glycohemoglobin while diminishing hypoglycemic

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events [8], to correct postural hypotension by autonomic activation [9], and to blunt progression of renal microvascular disease in type 1 diabetes mellitus [10].

Release of oxygen from hemoglobin is blunted by elevation of glycohemoglobin. Relative hypoxia in the eye and kidney, which require high concentrations of oxygen for proper function, may contribute to apoptosis. We tested the hypothesis that intermittent delivery of high doses of insulin would attenuate progressive deterioration of the eye and kidney by increased tissue oxygen delivery by hemoglobin. We measured respiratory quotient (carbon dioxide produced per oxygen utilized) as an index of conversion from oxidation of fat to oxidation of carbohydrate as a more efficient means of generating high-energy phosphate by skeletal and cardiac muscle mitochondria [11]. It was anticipated that correction of the disordered carbohydrate metabolism would result in improved cardiovascular, autonomic nervous, and retinal function by reversing toxicity of glucose at intracellular sites [12].

2. Patients and methods

This prospective, randomized, multicenter study (designated the *Pulsatile Intravenous Insulin Trial* or PIVIT Study; ClinicalTrials.gov trial no. NCT00594152) was designed to compare the Diabetes Control and Complications Trial standard 3 to 4 (basal plus bolus) injection per day of insulin for diabetes management to a program that in addition to the Diabetes Control and Complications Trial standard incorporated a single day per week of computerized intravenous pulsatile insulin accompanied by oral boluses of carbohydrate to determine if such therapy decreased the progression of diabetic renal disease [10]. Inclusion criteria required type 1 diabetes mellitus with C-peptide less than 0.05 ng/mL, creatinine clearance greater than 30 mL/min, 24-hour urine protein greater than 300 or albumin greater than 100 mg, and absence of acute illness at baseline. Patients were randomized to study group based on renal and diabetic parameters; and no attempt was made to match study groups by degree of retinopathy, autonomic neuropathy or left ventricular function, morphology, or size. Prespecified areas of follow-up did include each of the systems. There were no differences between study groups with respect to retinopathy distribution.

All patients (65 patients) received subcutaneous insulin (3-4 injections per day). The infusion group (36 patients) received a pure carbohydrate diet over 8 hours on a single day each week during which three 1-hour courses of pulsed insulin (7-10 pulses per hour to approximate normal portal insulin concentrations) were infused according to a computerized program and were compared with a noninfusion control group (29 patients). CO_2 production/O_2 utilization (respiratory quotient) was measured with each infusion.

Ninety patients enrolled in the renal study; 19 patients dropped out before 12 months. Six patients who completed 12 months did not obtain both baseline and follow-up scheduled retinal photography. Durations of follow-up ranged from 6 to 22 months for the 65 patients whose results are the subject of this report. Six of these patients had a single eye that was not able to be evaluated by retinal photography at either baseline or follow-up; 2 patients had 1 eye that could not be technically evaluated at either baseline or follow-up.

A demographic description of the patients is included in Table 1. All hypertensive patients were initially treated with angiotensin-converting enzyme inhibitor (ACEI) unless intolerant, in which case diltiazem was used. Goal blood pressure control of less than 135/80 was documented and maintained with the aid of monthly ambulatory 24-hour monitoring sessions in all patients. Glycohemoglobin was checked monthly. The initial study duration was planned to be 12 months; however, patients were offered the possibility to extend the duration of the study to 18 months.

Repeated standardized retinal photographs with 7 stereoscopic 30° field analyses over 18 months were read at a core reading center (Fundus Photograph Reading Center, University of Wisconsin–Madison, Madison, WI). Readers were masked as to study group enrollment. The photographs were graded according to a standard Early Treatment Diabetic Retinopathy Study protocol [13] and categorized as showing no diabetic retinopathy, nonproliferative (mild, moderate, or severe) diabetic retinopathy, or proliferative retinopathy. Patients in this study were matched with respect to kidney function and not severity of retinopathy. Clinical decision for treatment of retinopathy was left to the judgment of the treating ophthalmologist.

Deterioration of retinal function was defined by a 2-step increase in severity level of retinopathy using Early Treatment Diabetic Retinopathy Study criteria (progression), or a 3- or greater step increase in severity level of retinopathy (marked progression) by the same criteria. Similar definitions were used for apparent improvement of retinopathy (regression). Results were tabulated by individual eye, by individual patient, and by time of follow-up.

Distributions of patients according to regression, no change, or progression of retinopathy between treated and control groups, and duration of follow-up were tested for statistical significance by Fisher exact test. Study group means of demographic variables were compared using unpaired *t* test. Comparison of mean follow-up times according to diabetic retinopathy regression, no change, or progression within study groups was done using a general

Table 1
Baseline demographics (N = 65)

Baseline data	PIVIT	Control	*P* value
Age (y)	41.5 ± 1.6	39.1 ± 1.7	.3132
Age onset of DM	14.1 ± 1.5	14.3 ± 1.5	.9188
Duration of DM	27.2 ± 1.5	25.1 ± 1.4	.3055
Sex (M, F)	19, 17	18, 11	.6148

Table 2
Clinical measurements by treatment modality (N = 65)

	Treatment group	Baseline	End[a]	Δ	*P* value
Serum creatinine	PIVIT	1.62 ± 0.09	1.71 ± 0.12	0.09 ± 0.06	.1439
	Control	1.55 ± 0.09	1.93 ± 0.15	0.39 ± 0.12	.0038
	P value	.6101	.2463	.0346	
Creatinine clearance	PIVIT	58.2 ± 4.1	53.1 ± 3.8	−5.1 ± 2.8	.0757
	Control	63.5 ± 4.0	53.6 ± 5.2	−9.9 ± 3.8	.0153
	P value	.3635	.9351	.3033	
Urine protein	PIVIT	1977 ± 358	2226 ± 464	249 ± 225	.2767
	Control	1784 ± 226	2003 ± 445	219 ± 298	.4676
	P value	.6502	.7345	.9355	
Glycohemoglobin	PIVIT	8.9 ± 0.3	7.6 ± 0.2	−1.3 ± −0.3	.0001
	Control	9.3 ± 0.4	8.3 ± 0.3	−1.0 ± 0.3	.0026
	P value	.4047	.0870	.4636	

[a] Measurement taken from available patient visit with date closest to last eye photograph.

linear models procedure followed by Duncan multiple range test. Statistical analyses were done using a PC version of SAS (Cary, NC) Version 8. A P value < .05 was considered statistically significant, and the standard error of the mean was used as a measure of dispersion.

3. Results

Table 2 summarizes baseline and follow-up renal function measurements made during the 6- to 22-month duration of the study in the 65 patients who had satisfactory retinal photography. Glycemia management was equally effective in the 2 study groups. Serum creatinine increased significantly in the control group, but not in the group receiving weekly pulsatile insulin infusion. Creatinine clearance decreased in both groups, although the decrease was not significant in the group receiving weekly pulsatile insulin infusion.

There was no statistically significant difference in the distribution or grade of retinopathy between the treated and control groups at baseline. Progression of diabetic retinopathy was noted in 31.6% of 57 patients (32.3% treated, 30.8% control; P = 1.0) as summarized in Table 3. For patients with 12 or more months of follow-up, 27.9% of 43 patients demonstrated progression of diabetic retinopathy (32.0% treated, 22.2% control; P = .57). There were no significant differences between study groups with respect to progression or marked progression, nor was there any influence of duration of follow-up (Table 3).

Progression of diabetic retinopathy was noted in 18.8% of 122 eyes that were adequately evaluated (17.9% of 67 treated, 20% of 55 controls; P = .39) as summarized in Table 4. Progression of diabetic retinopathy was not significantly different for patients with less severe diabetic retinopathy at baseline than for those with more severe diabetic retinopathy at baseline. Progression of diabetic retinopathy was also not

Table 3
Patient (N = 65) diabetic retinopathy scores and mean follow-up (months)

	Score changed by 2 steps					
	Regression	Unchanged	Progression	Total scored	Not evaluable[a]	Total
PIVIT	3	18	10	31	5	36
Percentage	9.7	53.0	32.3			
Mean follow-up	15.9 ± 1.5	14.9 ± 0.9	15.0 ± 1.4		15.4 ± 2.6	
Control	2	16	8	26	3	29
Percentage	7.7	61.5	30.8			
Mean follow-up	15.4 ± 3.9	15.6 ± 1.0	12.8 ± 1.6		14.7 ± 3.6	
	Score changed by 3 steps					
	Regression	Unchanged	Progression	Total scored	Not evaluable[a]	Total
PIVIT	1	25	5	31	5	36
Percentage	3.2	8.0	16.1			
Mean follow-up	18.8	15.3 ± 0.9	12.9 ± 2.1		15.4 ± 2.6	
Control	1	21	4	26	3	29
Percentage	3.8	8.1	12.7			
Mean follow-up	11.5	15.4 ± 1.0	12.4 ± 2.4		14.7 ± 2.6	

All *P*s = not significant.

[a] Six patients (3 PIVIT, 3 control) had 1 eye technically not able to be evaluated at either baseline or follow-up. In 2 patients (both PIVIT), the same eye was technically not able to be evaluated at both baseline and follow-up.

Table 4
Eyes (n = 122) diabetic retinopathy score and mean follow-up (months)

	Score changed by 2 steps				
	Regression	Unchanged	Progression	Not evaluable	Total scored
PIVIT	6	49	12	5	67
Percentage	9.0	73.1	17.9		
Mean follow-up	16.6 ± 2.3	14.9 ± 0.8	15.1 ± 1.4	15.4 ± 5.0	
Control	9	35	11	3	55
Percentage	18.4	63.6	20.0		
Mean follow-up	14.0 ± 1.8	14.8 ± 1.2	15.2 ± 1.7	14.7 ± 5.0	
	Score changed by 3 steps				
	Regression	Unchanged	Progression	Not evaluable	Total scored
PIVIT	5	53	9	5	67
Percentage	7.5	79.1	13.4		
Mean follow-up	16.1 ± 1.9	15.0 ± 0.8	14.3 ± 1.7	15.4 ± 5.0	
Control	5	43	7	3	55
Percentage	9.1	78.2	12.7		
Mean follow-up	14.9 ± 3.1	14.6 ± 1.0	15.7 ± 2.5	14.7 ± 5.0	

All *P*s = not significant.

significantly different when based upon the duration of follow-up provided in this study.

4. Discussion

This is a pilot study of type 1 diabetes mellitus patients designed for the purpose of detecting small differences in the progression of renal dysfunction in patients with moderately severe nephropathy. Inclusion and exclusion criteria were not designed to match patients by degree, by prior treatment, or by stability of retinopathy. Given this limitation and the difference between the sensitivity of retinopathy grading (a categorical system) and changes in serum creatinine or creatinine clearance (continuous variables), it is not surprising that this short-term study was unable to discern a significant difference in treatment effect on the retina.

Although renal function deteriorates between a clearance of 90 and 30 mL/min, as seen in our patients, the disabilities encountered most often relate not to the level of blood urea nitrogen, creatinine, or potassium but rather to loss of energy (anemia, cardiac dysfunction), motor function (sensory and autonomic neuropathy, peripheral vascular disease), and visual acuity. Patients with creatinine clearance of 30 to 90 mL/min have a spectrum of visual compromises. In this study, all subjects had retinal manifestations of diabetes; no patients had uremic symptoms (mean creatinine clearance at baseline was 59 mL/min), and none were blind. Although retinopathy was not part of the inclusion/exclusion criteria, the spectrum of retinal pathology was similar to the spectrum of renal dysfunction in this cohort. As such, this study group represents a typical referral population for a diabetes renal clinic.

A beneficial renal response to weekly pulses of insulin plus carbohydrates has previously been demonstrated in this patient cohort with annual deterioration of creatinine clearance (2 mL/min treated, 7 mL/min control; $P = .03$) [9]. It required 18 months to establish a statistically significant benefit. Angiotensin-converting enzyme inhibitors were used equally in both the treatment and control groups. Therefore, even the control group experienced improved preservation of renal function when compared with a historical experience of greater than 14 mL/(min y) loss [14]. Future generations in which insulin and ACEI resistance due to obesity accompanies type 1 diabetes mellitus might not anticipate such a good result. A relevant study in type 1 diabetes mellitus patients before the development of either proteinuria or background retinopathy has demonstrated equal effectiveness of ACEIs and angiotensin receptor blockers with respect to progression of retinopathy, but no protection from the development of proteinuria [15]. This is an important area for future research of intensive insulin therapies in addition to angiotensin active medications.

The renal benefit noted was matched by improvement in all of the subjective neuropathic components of the Diabetes Impact Management Scale [16]. It is reasonable from these observations to hypothesize that similar benefits might also be seen at the retinal level. Studies have demonstrated that improvements of glycemic control (appropriate lowering of glycohemoglobin and nonspecific glycated end products) are associated with reduction in left ventricular mass, improvement in left ventricular function [17,18], and normalization of the hemostatic profile (plasminogen activator inhibitor, factor VII, fibrinogen) [19]. These results seem to be related to the status of the autonomic nervous system [20-23]. The relationship between retinal blood flow and macular edema is an area of active investigation in which platelet hyperreactivity could be a confounding mechanism. We have previously found a statistically nonsignificant diminution in the hypercoagulable state of type 1 diabetes mellitus

patients with nephropathy treated with intensive glycemia control for 6 months [24].

The pulsatile weekly insulin infusions used in this and other studies did not result in a statistically significant difference in glycohemoglobin A_{1c} when compared with control. Glycemic control as measured by glycohemoglobin or nonspecific advanced glycated end products may not be statistically related to microvascular blood flow. Specific glycated end products such as carboxymethyl lysine vs methyl glyoxal [25] are currently under investigation for discrimination of protective/injurious properties in the genesis of diabetic complications. Greater oxidative stress is hypothesized to be required in the generation of certain glycation end products like carboxymethyl lysine as opposed to methyl glyoxal or carboxyethyl lysine [26].

In our study, there were only 9 patients that progressed by 3 grades on the retinopathy scale (5 in the treatment group, 4 in control group). Sixteen eyes markedly progressed significantly during the study (9 in the treated group, 7 in the control group). Thus, most of the observed changes in retinopathy score would not be considered clinically significant. There appeared to be no reduction in retinal deterioration noted with the addition of pulsatile intravenous insulin to standard care. Based on these observations, a study to test the hypothesis of a beneficial retinal effect of this therapy would require many more patients followed for a much longer duration of time, a prohibitively expensive project in the private sector. Until such a study is performed, we consider this treatment to be investigational for purposes of retinal stabilization.

5. Limitations

The primary focus in this prospective study being protection from loss of kidney function, it was more difficult to achieve follow-up retinal photographs than scheduled appointments for insulin infusion and renal function testing. Similar problems were also noted in the prospective study of type 1 diabetes mellitus patients without retinopathy or proteinuria [15] in which a second renal biopsy was achieved in 90% of study subjects vs 82% for follow-up retinal photographs.

This study only involved type 1 diabetes mellitus patients. With the rising incidence of obesity described among US preadolescents and adolescents [27,28], predictions of number of patients and duration of study required to demonstrate an effect of this treatment on retinopathy based upon the population herein described may not apply to the type 1 diabetes mellitus patients that we will be seeing in the next decade. We have no experience with insulin resistance in our infusion patients and cannot make any definitive statements about the efficacy, benefits, or risks of infusion superimposed upon multiple insulin injections in obese type 1 diabetes mellitus or any type 2 diabetes mellitus hyperinsulinemic patients. This study does not include observations related to changes in retinal macular edema that may be as important as retinopathy in tests of visual acuity [29]. Another weakness of this retinopathy study is the inability to assess retinal neurodegeneration associated with mitochondrial oxidative stress in the setting of diabetes and hypertension involving treatment with angiotensin inhibiting medications [30].

6. Conclusion

In this small study, statistically significant preservation of renal function by pulsatile insulin infusion was not matched by a statistically significant blunting of the progression of diabetic retinopathy compared with standard diabetes care.

These findings may be due to inadequate power or duration of the study, or to a lack of further benefit of pulsatile insulin infusion on the retina in the presence of angiotensin-converting enzyme inhibition.

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