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Islet cell transplantation improves nerve conduction velocity in type 1 diabetes compared with intensive medical therapy over six years

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ABSTRACT

Background: Neuropathy is a common diabetic complication that can result in significant disability. Few treatment options exist to reverse this process.
Methods: We conducted a one-way crossover cohort study comparing intensive medical treatment and islet cell transplantation for type 1 diabetes on the change in nerve conduction velocity over six years.
Findings: For subjects with some neuropathy at baseline (Z score below −1), nerve conduction velocity significantly improved post-transplant (slope (0.073 ± 0.042) while it worsened in medically treated patients (−0.136 ± 0.081) ($p < .05$).
Interpretation: Islet cell transplantation improves nerve conduction velocity and could be further investigated as a treatment for neuropathy in type 1 diabetes.

1. Introduction

Diabetic neuropathy will develop in about 50% of individuals by 25 years after the diagnosis of diabetes [1,2]. It is most commonly a distal symmetric polyneuropathy causing pain and loss of sensation which can lead to ulceration, infection, amputation and a worsened quality of life [2–5].

Intensive medical treatment with insulin is effective in slowing the progression of neuropathy [6,7], but is difficult to achieve in practice and has an increased risk of hypoglycemia which can be dangerous as patients with neuropathy often have hypoglycemia unawareness [8]. Therefore, achieving good glycemic control with transplantation could be a useful alternative to medical treatment.

The Vancouver islet transplantation program has conducted a prospective, one-way crossover, cohort study comparing the effects of intensive medical therapy and islet cell transplantation (ICT) on the progression of microvascular complications of type 1 diabetes. We have published preliminary findings that showed stabilization of neuropathy in both groups [9], and now report our final results.

2. Methods

2.1. Subjects

The study design and patient characteristics have been described previously [9,10]. In brief, the 44 subjects (23 women) were 44 ± 8.6 years and had type 1 diabetes for 29 ± 8.9 years at study entry. Data was collected between 2003 and 2011 when the study ended. The median follow-up for 44 subjects in the medical group was 53 months and for the

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30 subjects who had received an islet infusion 74 months. Three subjects received one islet infusion, 12 received two infusions, 10 received three and 7 received four. The study is a one-way crossover design [11], with a patient crossing over from the medical to the ICT group at the time of the first islet infusion.

2.2. Neuropathy assessment

Nerve conduction studies are the most reliable method to study diabetic polyneuropathy in clinical trials [12–14]. While a number of parameters are assessed during the test, nerve conduction velocity (NCV) is the most reproducible and widely utilized measurement and is used in this report [14,15]. Testing of seven nerves (sensory: ulnar, median, sural; motor: ulnar, median, peroneal, tibial) every 12 months was performed in the same laboratory under standardized conditions. The reporting neurologist was not blinded as to whether a patient had received an ICT.

The primary endpoint was the rate of change in NCV in the medical and post-ICT groups, as has been the case for our previous reports on retinopathy and nephropathy [9]. Due to the nature of the one-way crossover design, necessitated by the nature of transplantation and the unpredictability of when a donor organ becomes available, there are very few individuals who have similar amounts of time in medical and post-ICT groups to allow for comparison of NCV changes before and after in an individual. However, we believe that the group analysis does answer our primary question of whether ICT has a different effect on diabetic neuropathy compared with medical treatment in a cohort of subjects with type 1 diabetes.

We believe the total burden of neuropathy is best measured by treating all nerves equally. There is a wide range of normal mean NCV in our laboratory ranging from tibial 49.6 m/s to ulnar motor 58.5 m/s. If actual NCV were used in the calculation, therefore, the more rapid conducting nerves would be given more weight than the slower conducting nerves. To avoid this issue, NCV were standardized into Z scores which allowed each nerve to be given equal value.

The NCV from each nerve for all subjects in the group were averaged to produce a single value for each year. We decided to treat nerves for which no signal could be obtained as a missing value. The issue is that a nerve could have a signal one year, be absent the next year and then reappear. This does not make physiological sense but rather represents the technical limitation of the recording equipment. The number of absent signals represents a very small fraction of the total data and we believe treating them as missing values is the most meaningful method of dealing with this issue.

The slopes of the Z values for each group were calculated by simple linear regression to produce an annual rate of change. Baseline (year 0) is constructed using the first observation of the 44 patients in the medical group and the last pre-transplant observation of the 30 patients in the ICT group.

Analysis was by intention-to-treat. Patients crossed over and began to be analyzed in the ICT group once they received their first islet infusion. Data for continuous variables with a normal distribution is presented as mean ± standard deviation and otherwise as median and interquartile range. Continuous variables with a normal distribution were compared using a two-tailed, unpaired t-test. Comparison of slopes was done by ANOVA.

All subjects gave written informed consent and the study was approved by the institutional review board of the University of British Columbia.

2.3. Role of funding source

The funding source had no role in the study design, collection, analysis or interpretation of the data, writing of the report or decision to submit the paper for publication. The corresponding author had full access to all the data in the study and final responsibility to submit for publication.

3. Results

Diabetes duration and age, factors known to influence the progression of neuropathy, did not differ between the two groups as reported before (data not shown) [9].

3.1. Glucose control

Glucose control was assessed by HbA1c measurements every 3 months in both groups. At study entry the mean HbA1c was 8.1 ± 1.3%. HbA1c level post-ICT was 6.6 ± 0.7%, which was significantly lower than the 7.5 ± 0.9% in the medical group ($p < .01$).

C peptide levels were undetectable in the medical group and averaged 366.2 ± 213.0 pmol post-ICT.

3.2. Nerve conduction

At entry into the study, medical therapy subjects presented with varying severity of DN. Table 1 shows the Z score of each nerve for the 44 subjects at baseline. There was significant heterogeneity among patients as shown by the large standard deviation. Not all nerves produced a recording in each subject. For example, a reading for the sural nerve could only be obtained in 31 of 44 subjects, presumably because of severe damage to that nerve in the others. For a particular subject, however, a specific nerve could have a signal one year, be absent the next year, and then be recordable again the following year, with no obvious trend or difference between treatment groups. Therefore, nerves for which no recording was available were not included in the analysis for that time point.

The mean Z score for all nerves was −1.30 ± 0.53. There was no significant difference in the Z scores of upper versus lower or sensory versus motor nerves (data not shown).

We combined the Z scores from each nerve in a subject into a single value for that person. The distribution of these values in the group, reflecting neuropathy severity, is shown in Table 2. Patients with a Z score of higher than −1 are considered to have normal nerve conduction, from −1 to −2 mild neuropathy, from −2 to −3 moderate neuropathy and lower than −3 severe neuropathy. By this definition diabetic neuropathy was present in 29 of the 44 (66%) subjects (an average individual Z-Score <−1).