

ORIGINAL ARTICLE

Nationwide Survey of Patient Knowledge and Attitudes towards Human Experimentation Using Stem Cells or Bee Venom Acupuncture for Parkinson's Disease

Korean Movement Disorders Society Red Tulip Survey Participants,
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ABSTRACT

Objective Stem cell treatment is a well-recognized experimental treatment among patients with Parkinson's disease (PD), for which there are high expectations of a positive impact. Acupuncture with bee venom is one of the most popular complementary and alternative treatments for PD. Patient knowledge and attitudes towards these experimental treatments are unknown.

Methods Using a 12-item questionnaire, a nationwide survey was conducted of 963 PD patients and 267 caregivers in 44 Korean Movement Disorders Society member hospitals from April 2013 to June 2013. The survey was performed by trained interviewers using conventional methods.

Results Regarding questions on experimental treatments using stem cells or bee venom acupuncture, 5.1–17.7% of PD patients answered questions on safety, efficacy, and evidence-based practice incorrectly; however, more than half responded that they did not know the correct answer. Although safety and efficacy have not been established, 55.5% of PD patients responded that they were willing to receive stem cell treatment. With regard to participating in experimental treatments, there was a strong correlation between stem cell treatment and bee venom acupuncture ($p < 0.0001$, odds ratio = 5.226, 95% confidence interval 3.919–6.969). Younger age, higher education, and a longer duration of PD were all associated with a correct understanding of experimental treatments.

Conclusions Our data suggest that relatively few PD patients correctly understand the safety and efficacy of experimental treatments and that PD patients are greatly interested in new treatments. We hope that our data will be used to educate or to plan educational programs for PD patients and caregivers.

Key Words Parkinson's disease; Survey; Experimental treatment; Stem cell; Complementary alternative medicine.

Currently, evidence-based medicine (EBM) plays an important role in the treatment of Parkinson's disease (PD). Several drugs or surgical interventions are recommended as evidence-

based practices in PD. In contrast, no disease-modifying treatments have been found to be suitable for use as evidence-based practices.¹⁻⁴ Many experimental therapeutic interventions have

Received: August 22, 2014 Revised: August 26, 2014 Accepted: September 8, 2014

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been used in an attempt to modify the natural history of PD. In addition to medications, stem cell therapy, complementary and alternative medicine (CAM), and physical exercise have been studied.⁵⁻⁷ Acupuncture is the most common non-pharmacological CAM that is used in PD.⁸⁻¹² Bee venom has been suggested as a potential neuroprotective agent based on its anti-inflammatory properties.^{13,14} Following a clinical trial of bee venom acupuncture,⁵ it has become a well-recognized experimental treatment among PD patients and caregivers in Korea. Although clinical trials using stem cell therapy or bee venom acupuncture in PD have been performed, well-designed controlled trials sufficient enough to reach the standards set by EBM are lacking.^{5,15-18} Despite the great interest in stem cell therapy and the expectations for the widespread use of CAM in PD,^{8-12,19} data on patient knowledge and attitudes towards experimental treatments are lacking in the literature. Given that a majority of patients obtain information on experimental treatments from the media or the internet rather than healthcare providers,^{20,21} it is critical to understand the current level of understanding of experimental PD therapy in PD patients and their care givers. This information will aid in developing educational programs for patients and in guiding them toward evidence-based practices. Therefore, we conducted a nationwide survey to study PD patients' understand-

ing of the safety, efficacy and evidence-based practice with regard to stem cell therapy or bee venom acupuncture and to gauge their willingness to receive experimental treatments. We also analyzed factors influencing their correct understanding of the current status of the above experimental treatments.

MATERIALS & METHODS

Since 2006, the Korean Movement Disorders Society (KMDS) has held annual nationwide campaigns and lectures regarding PD ("Red Tulip Campaign") to educate PD patients and caregivers in KMDS member hospitals. A survey of 1230 participants (PD patients and caregivers), organized by the KMDS, was performed at 44 sites from 48 secondary- or tertiary-referral hospitals in Korea from April 2, 2013 to June 14, 2013. No specific inclusion or exclusion criteria were applied, except that the patients were required to participate voluntarily and to be capable of answering the questionnaire. Trained interviewers collected demographic data from patients or caregivers and administered the 12-item questionnaire in face-to-face interviews with the participants at each site. Participants answered all questions with one of three answers (Yes, No, and Unknown). Demographic data included age, gender, PD duration, diagnosis of parkinsonian

Table 1. A questionnaire used to examine Parkinson's disease patient knowledge of and attitudes towards stem cell treatment and bee venom acupuncture

Item	Questions
1	Parkinson's disease is caused by a reduction in dopamine-producing neurons
2	Parkinson's disease is the same disorder as Alzheimer's disease
3	Parkinson's disease patients are improved by medical treatment including levodopa
4	Late complications of Parkinson's disease can be improved by the surgical treatment deep brain stimulation
5	Stem cell treatment for Parkinson's disease has been proven safe
6	Stem cell treatment for Parkinson's disease has been proven efficacious
7	Stem cell treatment for Parkinson's disease has been proven globally, and it is currently used as a standard therapy for Parkinson's disease
8	Although stem cell treatment for Parkinson's disease is an experimental treatment without proof of safety and efficacy, I am willing to receive this experimental treatment if there is a chance
9	Acupuncture with bee venom for the treatment of Parkinson's disease has been proven safe
10	Acupuncture with bee venom for the treatment of Parkinson's disease has been proven efficacious
11	Acupuncture with bee venom for the treatment of Parkinson's disease has been proven globally, and it is currently used as a standard therapy for Parkinson's disease
12	Although acupuncture with bee venom for the treatment of Parkinson's disease is an experimental treatment without proof of safety and efficacy, I am willing to receive this experimental treatment if there is a chance

disorders, years of education, and the most disabling symptoms. Survey questionnaires developed by the executive committee of the KMDS was comprised of three parts (Table 1). The first section of the questionnaire (4 questions) was designed to estimate the participant's knowledge of the pathogenesis and the medical and surgical treatments available for PD. The second section (3 questions) covered the safety and efficacy of stem cell therapy, and whether stem cell therapy was used worldwide as an evidence-based practice. Questions in the final section were similar to those in the second section, except that the questions referred to bee venom acupuncture treatment rather than stem cell therapy. Two questions asked the participants whether they were willing to receive stem cell therapy or bee venom acupuncture treatment despite the fact that they were not safe, effective or acknowledged as a standard treatment around the world. For all questions, participants answered using the responses yes, no, or unknown. Other demographic data, such as age upon participation in the survey, gender, duration of PD, years of education, category of PD diagnosis and the most disabling symptom, were also collected in parallel. The categories of PD diagnosis comprised PD, Parkinson plus syndrome, and an unknown diagnostic parkinsonism category. The most disabling symptoms included tremor, rigidity, bradykinesia, postural instability (falls), gait disturbance, and others.

Statistical analyses were performed after converting participant responses into correct, incorrect,

and unknown responses. The degree of accuracy of the understanding of PD between patients and caregivers was compared using chi-squared tests. Factors affecting an accurate understanding of PD treatment were analyzed using univariate logistic regression analyses. All statistical analyses were performed using the SAS program.

RESULTS

The demographic data are summarized in Table 2. Nine hundred and sixty three parkinsonian patients and 267 caregivers responded. Of the patients, 91.3% had PD, 4.5% had Parkinson plus syndrome, and 4.3% did not know whether they had PD or PD plus syndrome. The mean age of the patients was 69.8 ± 7.9 years, and the mean duration of PD was 4.4 ± 4.2 years. The mean duration of education was 11.1 years. In approximately two-thirds of patients, tremor or postural instability and gait disturbances were the most disabling symptoms. Other non-motor symptoms including memory decline, dizziness/giddiness, and musculoskeletal issues, such as back pain, anxiety or depressive mood, were considered the most disabling symptoms in 17.1% of patients.

The mean number of correct answers in the first section of the survey questionnaire, which collected information regarding the participants' general knowledge of Parkinson's disease, was 2.3 ± 1.2 for PD patients and 2.5 ± 1.2 for caregivers. The percent of correct answers was highest for questions on dopamine deficits in PD, medical treatment of PD using dopaminergic drugs, discrimination of PD from Alzheimer's disease and surgical treatment of PD. The proportion of correct, incorrect and unknown responses was similar between PD patients and caregivers for questions 1–3 (Figure 1). However, more caregivers answered the question on surgical treatment of PD correctly than PD patients ($p < 0.01$, chi-squared test). Factors predicting correct answers for Q1–4 are summarized in Supplement Table 1 (in the online-only Data Supplement). Younger age-at-onset, higher levels of education, and a longer duration of disease were significant, independent predictors of correct answers for Q1, Q2, and Q4 but not for Q3. Logistic regression analyses demonstrated that younger age-at-onset, longer periods of education and a longer duration of disease were significant, independent predictors of

Table 2. Demographic and clinical characteristics of the survey participants

	Patient	Caregiver
Survey participants, <i>n</i> (%)	963 (78.4)	267 (21.6)
Gender (M:F)	580:383	143:124
Age (years), mean (SD)	69.8 (7.9)	64.9 (13.6)
PD duration (years), mean (SD)	4.4 (4.2)	
Diagnosis (PD:PD plus:unknown)	879:43:41	
Education (year), mean (SD)	11.1 (4.3)	12.7 (4.7)
Most-disabling symptom*		
Tremor, <i>n</i> (%)	298 (30.9)	
Gait disturbances/falls, <i>n</i> (%)	325 (33.7)	
Rigidity, <i>n</i> (%)	111 (11.5)	
Bradykinesia, <i>n</i> (%)	182 (18.9)	
Others, <i>n</i> (%)	165 (17.1)	

*one hundred and thirty four patients responded with multiple answers that were the most-disabling symptom. PD: Parkinson's disease, SD: standard deviation.

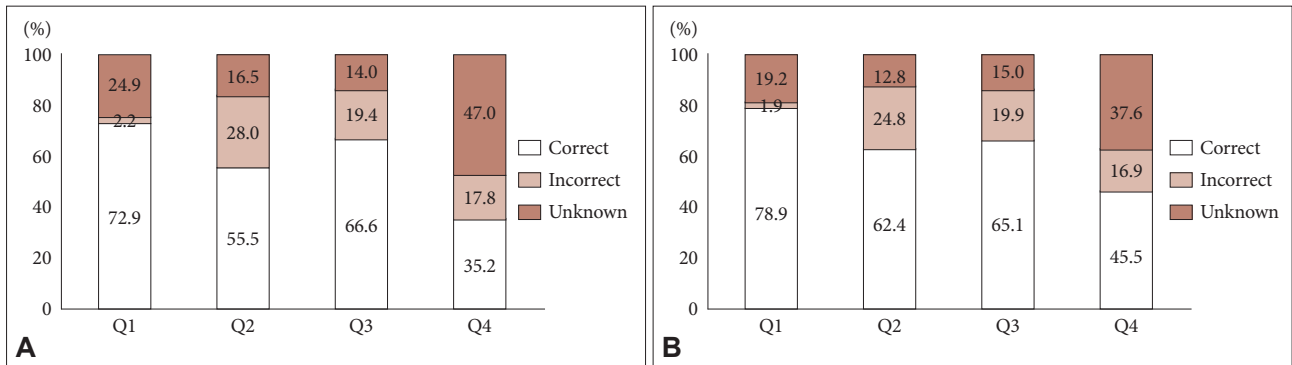


Figure 1. Bar graphs showing categories of answers to questions on the pathogenesis and treatment of Parkinson's disease in parkinsonian patients (A) and caregivers (B). Q1, Q2, Q3, and Q4 refer to the question items. Q1: Parkinson's disease is caused by a reduction in dopamine-producing neurons. Q2: Parkinson's disease is the same disorder as Alzheimer's disease. Q3: Parkinson's disease patients are improved by medical treatments including levodopa. Q4: Late complications of Parkinson's disease can be improved by surgical treatment via deep brain stimulation.

correct answers for all questions except question #3. A clinical diagnosis of atypical parkinsonism (Parkinson plus syndrome or unknown diagnostic category of parkinsonism) was a significant predictor of incorrect answers for levodopa responsiveness in PD. Table 2 summarizes the logistic regression results of the factors predicting correct answers.

With regard to questions on the safety and efficacy of treatment with stem cells or acupuncture with bee venom, 18.9–37.8% of PD patients answered correctly and 5.1–17.7% answered incorrectly. Intriguingly, more than half of PD patients responded with “unknown”. Despite the fact that the safety and efficacy have not been established, 55.5% of PD patients were willing to receive experimental treatments with stem cells (Figure 2). PD patients showed a similar tendency of interest in experimental treatments with acupuncture using bee venom. PD patients who were interested in stem cell therapy were also interested in receiving acupuncture treatment with bee venom ($p < 0.0001$, odds ratio = 5.226, 95% confidence interval 3.919–6.969).

We analyzed the factors associated with an accurate understanding of experimental treatments by performing univariate logistic regression analyses of question items 5–12 (Table 3). Older age was associated with an incorrect understanding of experimental treatment with stem cells or bee venom acupuncture. A higher level of education was associated with a correct understanding of the safety and efficacy of stem cell therapy. More PD plus patients answered questions on the efficacy of stem cell treatment incorrectly than PD patients. A longer duration of PD was also associated with an improved understand-

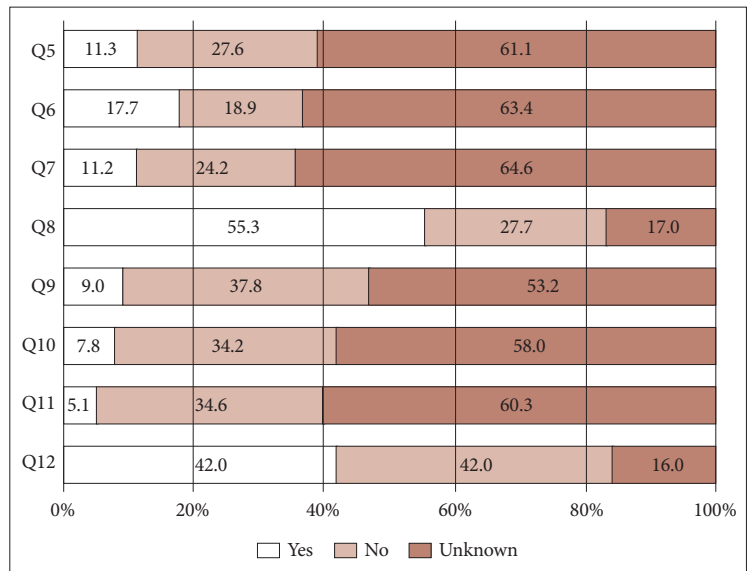


Figure 2. Bar graphs showing the categories of answers to questions on Parkinson's disease patient knowledge and attitude towards experimental treatments. Q5 to Q12 refer to question items. Q5–8 focused on stem cell treatment, and Q9–12 focused on acupuncture using bee venom. Questions regarding safety (Q5 and Q9), efficacy (Q6 and Q10) and whether these treatments are used in evidence-based practice (Q7 and Q11) were also included. For Q8 and Q12, patients were asked whether they were interested in receiving experimental treatments despite a lack of evidence of the safety and efficacy for the given experimental treatment.

ing of the safety of stem cell therapy, and whether it was an acknowledged treatment. This trend for an association between a correct understanding and higher education or longer duration of PD was similar for questions regarding bee venom acupuncture treatment; however, statistical significance was found only for the associations between a safety question (Questions #9) and education and PD duration, and the acknowledgment of the experimental nature of stem cell therapy (Questions #11) and PD duration.

Table 3. Factors associated with correct answers on questions of experimental PD treatments for patients with PD

	Stem cell treatment				Acupuncture with bee venom			
	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
Age	0.95*** (0.94–0.97)	0.97** (0.95–0.99)	0.95*** (0.93–0.97)	0.98* (0.96–0.99)	0.97** (0.96–0.99)	0.98* (0.97–1.00)	0.98* (0.97–1.00)	0.97** (0.96–0.99)
Gender	0.85 (0.63–1.13)	0.99 (0.71–1.38)	0.88 (0.65–1.20)	0.95 (0.73–1.24)	1.00 (0.77–1.30)	1.05 (0.81–1.37)	0.92 (0.71–1.20)	0.93 (0.71–1.21)
Education	1.09*** (1.05–1.13)	1.07** (1.03–1.11)	1.12*** (1.08–1.17)	0.99 (0.96–1.02)	1.05** (1.02–1.08)	1.02 (0.99–1.05)	1.03 (1.00–1.06)	1.01 (0.98–1.04)
Diagnosis								
PD plus vs. PD	1.12 (0.57–2.17)	0.30*** (0.09–0.99)	0.49 (0.20–1.17)	1.23 (0.66–2.30)	0.88 (0.47–1.62)	0.65 (0.34–1.24)	0.57 (0.29–1.12)	1.06 (0.57–1.97)
Unknown PDism vs. PD	0.39 (0.15–1.01)	0.61 (0.24–1.60)	0.68 (0.29–1.56)	0.72 (0.38–1.39)	0.65 (0.33–1.27)	0.62 (0.31–1.24)	0.76 (0.38–1.51)	0.48 (0.23–1.00)
PD duration	1.05*** (1.01–1.08)	1.02 (0.99–1.06)	1.06** (1.03–1.10)	1.06** (1.03–1.10)	1.06** (1.03–1.10)	1.03 (1.00–1.06)	1.04* (1.01–1.08)	1.00 (0.97–1.03)
Most-disabling symptom								
Tremor	0.95 (0.69–1.29)	0.81 (0.57–1.17)	0.85 (0.61–1.17)	0.93 (0.71–1.23)	0.93 (0.71–1.23)	0.96 (0.73–1.27)	0.92 (0.69–1.22)	0.90 (0.69–1.19)
Rigidity	1.49 (0.98–2.27)	1.14 (0.70–1.86)	1.52 (0.99–2.34)	0.95 (0.64–1.41)	1.04 (0.70–1.55)	1.15 (0.78–1.72)	1.13 (0.76–1.69)	0.82 (0.55–1.24)
Bradykinesia	1.17 (0.82–1.67)	1.49* (1.01–2.19)	1.11 (0.77–1.61)	1.07 (0.77–1.48)	1.11 (0.80–1.53)	1.05 (0.76–1.45)	0.89 (0.64–1.24)	0.99 (0.71–1.37)
PIGD	0.89 (0.66–1.21)	0.99 (0.70–1.39)	1.14 (0.84–1.56)	1.48* (1.12–1.94)	0.98 (0.75–1.28)	0.90 (0.69–1.18)	0.93 (0.71–1.22)	1.25 (0.95–1.63)
Others	0.63 (0.42–0.95)	0.69 (0.43–1.10)	0.62* (0.40–0.96)	0.64* (0.46–0.90)	0.76 (0.54–1.07)	0.94 (0.67–1.32)	0.99 (0.70–1.39)	0.91 (0.65–1.28)

Q5 to Q12 refer to question items. Q5–8 focused on stem cell treatments, and Q9–12 focused on acupuncture using bee venom. Briefly, questions were focused on safety (Q5 and Q9), efficacy (Q6 and Q10) and whether the experimental treatments were used in evidence-based practice (Q7 and Q11). In Q8 and Q12, patients were asked whether they were interested in receiving experimental treatments despite the lack of evidence of safety and efficacy of the given experimental treatment. Values are odds ratio with 95% confidence intervals in parenthesis. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.0001$. PD: Parkinson's disease, Unknown PDism: diagnostic category of parkinsonism unknown, PIGD: postural instability and gait disturbance and falls, Others: other non-motor symptoms.

Patients with a longer duration of PD were more willing to receive stem cell therapy, but this association was not found for acupuncture therapy with bee venom. Patients who complained that postural instability and gait disturbance and falls (PIGD) was the most disabling symptom were more willing to receive stem cell therapy. In contrast, only older age was associated with a willingness to be treated with acupuncture using bee venom.

DISCUSSION

To the best of our knowledge, this study is the first to examine patient knowledge and attitudes towards experimental treatments, specifically in a PD population. One can argue that, given the existence of several articles that support the safety and efficacy

of experimental treatments with stem cells or bee venom, the decision to judge answers as correct vs. incorrect might be misleading. However, we do not think that this approach was inappropriate because current evidence-based practice guidelines do not support the safety and efficacy of these experimental treatments.^{1,2}

In our nationwide survey of PD patients and caregivers, we observed that only approximately 10% of PD patients understood incorrectly that experimental treatments using stem cells or bee venom acupuncture were safe, efficacious or acknowledged as evidence-based treatments worldwide. However, more than half of patients responded to these questions with the term “unknown”. Still, 55.3% and 42% of patients answered that they were willing to receive experimental treatments with stem cells or bee

venom acupuncture, respectively. This result can be compared to a recent study in which 46% of chronic ischemic stroke patients desired stem cell therapy despite its unknown side effects.²¹ In our study, there was a high concordance in patients' willingness to receive either of the experimental treatments. In a cross-sectional study, Valadas et al.²² noted that in PD, the primary motivation to participate in a clinical trial was to advance science and gain access to better treatments. The major concern while participating in clinical trials was adverse events. In another study, reasons to seek CAM included management of PD motor symptom (57.6%), fatigue (19.6%), pain (4.3%), constipation (5.4%), or no specific reason (13%).⁸ These data suggest that a sizable proportion of patients with a chronic nervous system disease wish to receive experimental treatments, even with the risk of adverse events. In this study, a younger age, higher education and a longer duration of PD were in general associated with a more accurate understanding of experimental treatments. These trends were also true for questions on PD etiology and standard PD treatments. Education level was inversely associated with the use of CAM.^{8,9} It was intriguing that although our patients with a longer duration of PD understood the safety issues surrounding stem cell therapy more accurately and whether it was an evidence-based practice, they were more willing to participate in clinical trials using stem cells. This finding is consistent with previous studies in chronic stroke patients in which a longer duration of disease was associated with patients' willingness to receive stem cell therapy and to use complementary and alternative medicine more frequently.^{8,21} This finding may be due to the failure of current symptomatic treatments to meet the patient's need to control motor or non-motor symptoms that may be resistant to levodopa in advanced PD. Additional contributing factors may also be the level of dissatisfaction with health-related quality of life or the lack of availability of disease-modifying treatments. The fact that in our study, patients with disabling PIGD were more interested in receiving experimental stem cell treatment supports this theory of unmet needs. Given the high expectations for experimental treatments with stem cells or bee venom acupuncture, it is critical to expect a substantial placebo effect when interpreting the results of a clinical trial evaluating a new therapeutic intervention for

PD.²³ In studying the neuroprotective effects of a pharmacological agent, considerable progress has been made in improving study designs to overcome symptomatic effects.^{24,25} However, for clinical trials of non-pharmacological interventions, study designs and the interpretation of results may be complicated by many confounding variables, such as outcome measures, the appropriateness of the intervention, control intervention or cultural background.^{7,26,27} As suggested, strict guidelines encompassing ethical issues, regulatory control, study design, outcome measures, and specific analyses for clinical trials of non-pharmacological interventions are required for PD.²⁸

There are limitations to this study. First, demographic and clinical data were collected from patients and not from physicians. This may have led to a coding bias, particularly in the diagnostic category. Secondly, our study may include a selection bias because data were collected from patients who attended KMDs PD educational campaigns. The high level of education in our participants reflects this factor. The small number of questions and our cross-sectional design cannot explain why PD patients have false expectations of experimental treatments. Moreover, our questionnaire did not include questions about PD-related quality of life and level of satisfaction with current treatment options, which are important when considering patients' decisions to seek therapeutic interventions.

In conclusion, a small number of PD patients understand the safety and efficacy of stem cell treatment or bee venom acupuncture and that it is not used as an evidence-based practice. Approximately half of the PD patients wished to participate in a clinical trial of an experimental treatment, despite having no data on the safety or efficacy of the therapy. We hope that our data will be used to educate or plan educational programs for PD patients and caregivers.

SUPPLEMENTARY MATERIALS

The online-only Data Supplement is available with this article at <http://dx.doi.org/10.14802/jmd.14012>.

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Conflicts of Interest

The authors have no financial conflicts of interest.

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