Original Article

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Current Status of Intervention Studies on Acupuncture for Parkinson's Disease

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[Abstract]

Objectives : The purpose of this study was to investigate the effect of acupuncture treatment (AT) in the tendency of increase of the need for AT for the treatment of Parkinson's disease (PD) worldwide and to investigate the advancements in AT research in Korea and the future directions of research on this topic.

Methods : Until May 2017, the PubMed, Scopus, Medline, and four Korean databases were searched. The searched keywords were "Parkinson's disease", "Acupuncture", and "Intervention study". The intervention groups from all screened original studies were analyzed and the methods used to determine the effect of AT on PD were examined.

Results : A total of 17 studies were grouped by country on the basis of the first author's position, of which 10 studies were conducted in China, four in the United States, two in Korea, and one in Brazil. The most common type of intervention was electroacupuncture (nine studies), followed by AT (six studies), and a combination of AT and bee venom AT (two studies). The most frequently used acupoints in AT were *Baihui* (GV20), *Taichong* (LR3), *Zusanli* (ST36), *Sanyinjiao* (SP6), and *Yanglingquan* (GB34). The most commonly used tool for evaluation of PD was the Unified Parkinson's Disease Rating Scale Ⅲ, which assesses motor functions.

Conclusion : The screened studies reported that there were no adverse effects of AT on drug therapy, and AT reduced the dose of drugs used in PD treatment. Future studies on PD treatment with AT should use the acupoints GV20, LR3, ST36, SP6, and GB34, and the meridians Gallbladder meridian and Governor Vessel. Clinical studies on PD should use CONSORT or STRICTA to ensure the quality of national studies and allow the development of new tools for the assessment of the effect of AT on PD using the above criteria.

Key words :
Parkinson's disease;
Acupuncture;
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Ⅰ. Introduction

Parkinson's disease (PD) is the second-most common chronically progressive neurodegenerative disease worldwide. PD is associated with the degeneration of dopaminergic neurons and is clinically characterized by resting tremor, rigidity, bradykinesia, and postural instability[1,2]. The cause of PD is multifactorial, including a combination of genetic and environmental factors, but the exact cause is unknown[1]. Pathologic features include the death of melanin-containing dopaminergic neurons in melancholy densities. Diagnosis of PD is possible only by pathologic examination through autopsy or clinical findings. Treatment with levodopa, a precursor of dopamine, is the most effective treatment for PD to date, although non-pharmacological adjuvant therapies and surgical therapies are available[1]. However, there is no definitive treatment for PD. Furthermore, the long-term use of levodopa has adverse effects, the surgical outcome is poor, and the outcome of drug therapy has not improved[1,3].

Therefore, the interest in complementary and alternative medicine (CAM) for PD therapy in substitution for conventional therapies is increasing. More than 40% of PD patients in the United States and Europe are using CAM, and an even higher percentage is using CAM in Europe and Asia[4,5]. Acupuncture treatment (AT) is one of the most commonly used treatment modalities for PD patients, and the greatest advantage is the absence of adverse effects and acupuncture does not affect drug response. Despite these advantages, the methodological deficiencies that limit the effectiveness of AT remain unknown because of the lack of objective criteria[7]. The preclinical studies that demonstrated the effectiveness of AT, including those by Kang et al.[8], Liu et al.[9], and Wattanathorn et al.[10], serve as the basis for clinical research and are useful for the development of new treatment methods. However, the analysis of intervention methods in human studies is essential, to improve the quality of life and promote health[11].

The purpose of this study was to investigate the effect of AT in the tendency of increase of the need for AT for the treatment of PD worldwide and to investigate the advancements in AT research in Korea and the future directions of research in this field.

Ⅱ. Methods

1. Search methods

In this study, the databases PubMed, Scopus, and Medline were searched until May 2017. The studies which described studies conducted in Korea, were searched in the Korean databases DBpia, KISS, RISS, NDSL. The keywords used in the search were "Parkinson's disease", "Acupuncture", and "Intervention study". The corresponding keywords in the Korean language "*pa-kin-seun-byeong*", "*chim*", and "*jung-jae-yeon-gu*", were searched in the Korean databases. The search strategy was adjusted for each database.

2. Inclusion and exclusion criteria

A total of 55 publications were identified. After the screening of the abstracts, the studies not related to PD and those that did not assess the effect of AT on the symptoms of PD were excluded. Studies conducted before 2015, experimental researches, review articles, and non-articles were also excluded (Fig. 1).

3. Data extraction

The therapies used in the intervention and control groups (AT, electroacupuncture (EA), and scalp acupuncture, among others) and the methods

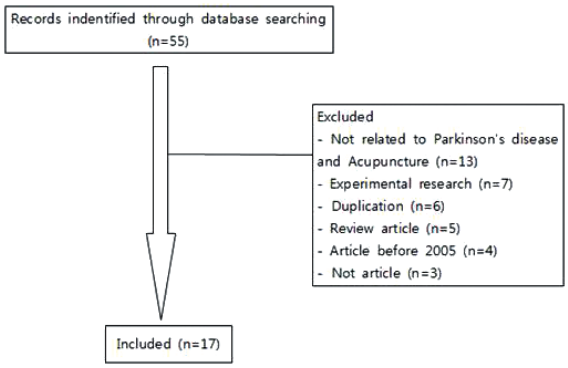

Fig. 1. Flowchart of the study selection process

used to evaluate the effect of AT on PD were analyzed in all original studies.

Ⅲ. Results

1. Publication characteristics

A total of 17 publications were grouped by country on the basis of the first author's position, of which 10 studies were conducted in China, four in the United States, two in Korea, and one in Brazil (Fig. 2).

The classification of the original studies by type indicated that most studies (N=15) were randomized clinical trials (RCTs), one was a clinical trial, and one was a pilot study (Fig. 3). Fig. 4 classifies the studies by country (Fig. 4).

For proper comparison of all searched original studies, the studies were classified by the duration of PD, sample size, evaluation method, intervention group, and control group, among other parameters (Table 1).

2. Acupuncture treatment

The most common types of Intervention were EA (N=9), AT (N=6), and AT combined with bee venom AT (N=2). Among the nine original studies that

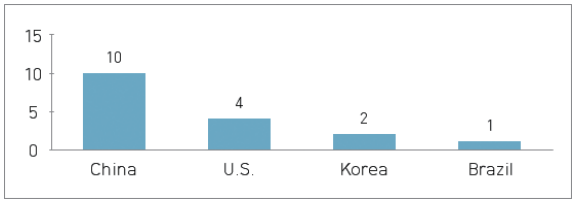

Fig. 2. Number of original studies by country

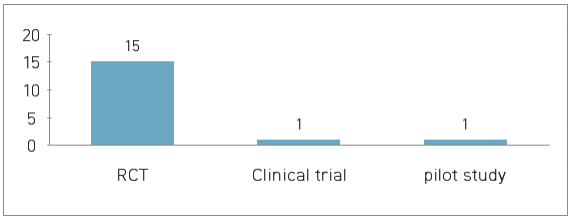

Fig. 3. Number of original studies screened by type

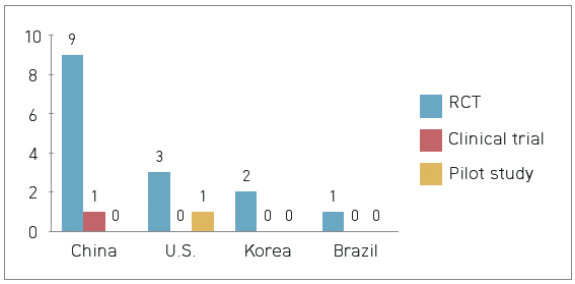

Fig. 4. Number of studies screened by country

used EA, in most studies the frequency was set to 100 Hz for the head and 4 Hz for the region below the elbow and knee (N=5), whereas in the remaining three studies frequency was set to a tolerable range. In AT, several acupoints were included or removed depending on the severity of symptoms, but the most frequently used acupoints were *Baihui* (GV20), *Taichong* (LR3), *Zusanli* (ST36), *Sanyinjiao* (SP6) and *Yanglingquan* (GB34) (Fig. 5).

The evaluation of the meridians in the searched studies (in one study, duplication of meridians used for treatment was excluded.), indicated that the most common meridians were Gallbladder meridian (GB) and Governor Vessel (GV). The use of the large intestine meridian (LI), stomach meridian (ST) and liver meridian (LR) was also common (Fig. 6).

In the case of scalp-acupuncture, the same acu-

Table 1. Summary of intervention studies on Parkinson's disease

Ref.	Duration of PD(y) (sample size) Hoehn & Yahr scale	Evaluation methods	Intervention group	Control group
Aroxa et al[12]	n.r. (11/11) HY 1–3(avg. n.r.)	(1) PDSS (2) Total efficacy	(A) AT+medication (LR3, SP6, LI4, TE5, HT7, PC6, LI11, GB20 once a week for 8weeks, 30min)	(B) Medication (n.r.)
Liu et al[13]	(A) 5.8 (B) 6.4 (C) 6.0 (45/45/45) HY 1–3(avg. 2.8)	(1) UPDRS Ⅲ (2) Total efficacy	(A) PA+medication (GB20 kakkonein extract 1㎖, once every days for 8weeks, n.r.)	(B) AT (GB20 once every days for 8weeks, n.r.) (C) Medication (Madopar)
Toosizadeh et al[14]	n.r. (10/5) HY n.r.	(1) UPDRS (Ⅰ, Ⅱ, Ⅲ) (2) Postural balance assessment	(A) EA (GV20, GV14, ST36, LI4, GB34, LR3, KI3, SP6, BL40 once a week for 3weeks, 4 or 100㎐, 30min)	(B) Sham treatment
Xia et al[15]	n.r. (30/30) HY n.r.	(1) HAMD	(A) EA+medication (GV20, EX–HN3, EX–HN1, LR3, SP6 every other day for 3months, frequency within tolerable range, 30min)	(B) Medication (Madopar)
Cho et al[16]	(A) 5.0 (B) 6.0 (C) 5.0 (15/14/14) HY 1–3(avg. n.r.)	(1) Total UPDRS (2) PDQL (3) BDI (4) BBS (5) 30m gait speed(s)	(A) BVA (GB20, LI11, GB34, ST36, LR3 0.005% 0.1㎖, twice a week for 8weeks) (B) AT (GB20, LI11, GB34, ST36, LR3 twice a week for 8weeks, 20min)	(C) None
Chen et al[17]	(A) 5.4 (B) 6.4 (30/30) HY 1–3(avg. 2.1)	(1) UPDRS Ⅲ	(A) EA+medication (GV20, EX–HN1, EX–HN3 once every days for 6weeks, frequency within tolerable range, 1hr)	(B) Medication (Madopar, tolterodine)
Huang et al[18]	(A) 5.4 (B) 6.04 (5/5) HY 1.5–3(avg. 2.0)	(1) SPECT	(A) Scalp EA+medication (MS6, MS4, MS8, MS9, MS14 once every days for 5weeks, 50㎐, 30min)	(B) Medication (levodopa)
Chae et al[19]	(A),(B),(C) 3.0 (10/10/10) HY avg. 1.6	(1) fMRI	(A) AT (GB34 inserting to 10㎜ depth, 3min)	(B) Covert placebo (GB34 non–penetrating, 3min) (C) Overt placebo
Ren et al[20]	n.r. (50/30) HY n.r.	(1) Total efficacy	(A) AT+medication (TE14, TE2, PC2, PC7 once every 3–5days, 10courses each, 30min)	(B) Medication (Madopar)
Chang et al[21]	(A) 3.4, (B) 3.6 (30/30) HY 2–3(avg. n.r.)	(1) Total UPDRS (2) Total efficacy	(A) AT+medication (GV24, GV20, EX–HN1 once every days for 30days, 30min)	(B) Medication (Madopar)
Chen et al[22]	(A) 4.85, (B) 4.65 (30/30) HY n.r.	(1) Webster scale (2) Total efficacy	(A) AT+medication (CV12, CV10, CV6, CV4, KI13, KI17, ST24 once every days for 10days, 30min)	(B) Medication (Madopar)
Huang et al[23]	(A) 5.4 (B) 6.4 (5/5) HY 1–3(avg. 2.0)	(1) SPECT	(A) Scalp EA+medication (MS6, MS4, MS8, MS9, MS14 once every days for 5weeks, 100㎐, 30min)	(B) Medication (Madopar)

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Wang et al[24]	(A) 2.6 (B) 2.2 (37/39) HY 2–3(avg. n.r.)	(1) Measuring of SOD, LPO	(A) Scalp EA+medication (EX–HN1, GB6, GV21, GB5, GV17, GV16, BL9, BL10, GB19, GB20 once every days for 30days, frequency within tolerable range, 30min	(B) Medication (Madopar)
Jiang et al[25]	(A) 5.4, (B) 6.4 (15/15) HY 1.5–3(avg. 2.2)	(1) Webster scale (2) UPDRS Ⅲ (3) Total efficacy	(A) Scalp EA+medication (MS6, MS4, MS8, MS9, MS14 5times weekly for 6weeks, 100Hz, 30min)	(B) Medication (Madopar)
Cristian et al[26]	n.r. (7/7) HY 2–3(avg. n.r.)	(1) UPDRS Ⅲ (2) PDQ–39 (3) GDS	(A) EA (KI3, KI10, BL60, LR3, ST41, ST36, GB34, LI4, GV20 inserting into muscle, 4Hz, 20min)	(B) Sham EA (nonacupoint, inserting just under the skin, 4Hz, 20min)
Kluger et al[27]	n.r. (47/47) HY 1–4(avg. 2.3)	(1) MFIS (2) UPDRS Ⅲ (3) PDQ–39	(A) AT (GV20, GV24, CV6, LI10, HT7, ST36, SP6 biweekly for 6weeks, 30min)	(B) Sham AT (nonacupoint)
Lei et al[28]	(A) 6.2 (B) 5.2 (10/5) HY avg. 2.9	(1) UPDRS (Ⅰ, Ⅱ, Ⅲ) (2) Gait evaluation	(A) EA+medication (GV20, GV14, LI4, ST36, GB34, BL40, SP6, KI3, LR3 once a week for 3weeks, 4 or 100Hz, 30min)	(B) Sham EA (nonacupoint, inserting just under the skin, 0 or 4 or 100Hz, 30min)

n.r.=Not reported, AT=Acupuncture treatment, HY=Hoehn and Yahr scale, avg.=average, BVA=Bee venom acupuncture, PA=Pharmacoacupunctre, EA=Electroacupuncture, UPDRS=Unified Parkinson's Disease Rating Scale, BBS=Berg Balance Scale, PDQL=Parkinson's Disease Quality of Life Questionnaire, BDI=Beck Depression Inventory. SPECT=Single Photon Emission Computed Tomography.

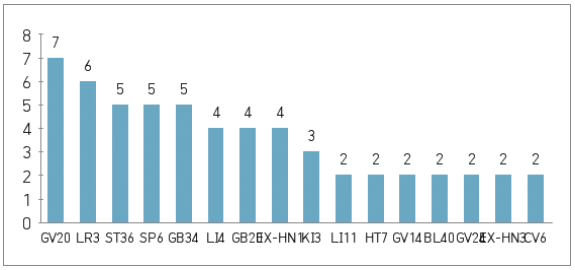

Fig. 5. Number of acupoints used in the screened studies

Fig. 6. Number of meridians used in the screened studies

points (MS6, MS4, MS8, MS9, and MS14) were used in three studies (Huang et al.[18], Huang et al.[23], and Jiang et al.[25]).

3. Evaluation methods

The tool used by most original studies (9 out of 17) for the evaluation of PD was the Unified Parkinson's Disease Rating Scale (UPDRS) Part Ⅲ, which assesses motor functions. Six studies used the total efficacy score and comprehensively assessed the patient's condition, and three studies used the Parkinson's Disease Quality of Life Questionnaire (PDQL) and the shorter version of PDQL (PDQ–39) (Fig. 7).

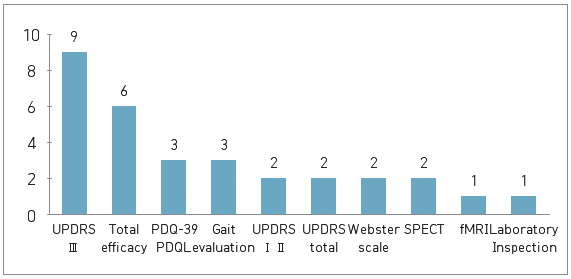

Fig. 7. Evaluation methods used in the screened studies

4. Comparison with the control group

Among the 17 original studies, most studies (N=11) used drug monotherapy for the control groups, including Madopar (N=9), and levodopa (N=1). One study did not specify the active ingredient or drug name. In addition, four studies evaluated sham AT and one study did not evaluate any treatment.

Ⅳ. Discussion

PD is the second most common neurodegenerative disease after Alzheimer's disease. The most common clinical symptoms are motor symptoms, including bradykinesia, rest tremor, rigidity, and postural and gait impairment. Non-motor symptoms include neuropsychiatric features, dysautonomia, sleep disorders, sensory dysfunction, pain, and fatigue, and the prevalence of these symptoms is increasing[29]. At present, drug therapy based on levodopa, a precursor of dopamine, is the treatment of choice for PD. However, the amount of levodopa or dopamine agonist usually is increased during therapy as PD advances because the disease is progressive and levodopa does not prevent disease progression. Symptoms such as non-motor wearing-off and motor fluctuations may occur with the long-term use of levodopa. Dopamine agonists may cause adverse effects such as nausea, vomiting, orthostatic hypotension, leg swelling, anorexia, and sleepiness[1].

Although AT is one of the most commonly used alternative therapies for PD, few studies evaluated the effects of AT in PD patients[6]. Park et al[30] and Kang et al[31] reported that AT prevented 6-hydroxydopamine-induced neuronal death and inhibited microglial activation in PD animal models. Bee venom AT was also associated with neuroprotection[32,33]. In addition, Jia et al[34] reported that AT improved the motor symptoms of PD by normalizing GABA levels in the midbrain. Other studies demonstrated the effect of AT on PD in animal models. However, Lee et al[7] and Baek et al[35] found no evidence of the effectiveness of AT, EA, and scalp acupuncture on PD. In fact, few studies evaluated the effectiveness of AT in PD patients[6,19].

Of the screened original studies, ten were conducted in China, including nine RCTs and one clinical trial, in which AT was used and the control group was screened; 3 RCTs, 1 pilot study, were conducted in the United States, two RCTs were from Korea, and one RCT was from Brazil. Few intervention studies from Korea evaluated the effectiveness of AT in PD treatment. The retrieved articles were classified by the duration of PD, sample size, evaluation methods, intervention group, and control group. The most common interventions were EA (N=9) and, in these cases, the frequency was set to 4 Hz or 100 Hz or to a frequency that the patient could withstand. In 12 of the 17 original studies, AT was combined with drug therapy using Madopar or levodopa, and no adverse effects were observed in the evaluated studies. In this context, Ren et al[20] suggested that AT might be effective in reducing the dosage of drugs used in PD treatment. Six original studies used AT alone and two studies used pharmacoacupuncture. Liu et al[13] injected kakkonein extract into *Fengchi* (GB20) in combination with drug therapy to improve patient's behavior, emotion, and activities of daily living, and observed short-term and long-term benefits. Moreover, Cho et al[16] reported that bee venom AT was a promising adjunctive therapy for PD by injecting 0.1 mL of bee venom (0.001%) into acupoints *Fengchi* (GB20), *Quchi* (LI11), *Yanglingquan* (GB34), *Zusanli* (ST36), and *Taichong* (LR3).

The most commonly used acupoints and meridians in the intervention groups were GV20 (7 studies), followed by LR3, ST36, SP6, and GB34. GB and GV were the most commonly used meridians (8 studies). These acupoints and meridians should be used as a criterion for the selection of high-quality studies on AT for PD patients.

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The UPDRS[36] is the most widely used scale to assess the effect of clinical interventions on PD. It has four sections (I to VI), and section Ⅲ evaluates motor functions[37]. UPDRS III is used most often because the total UPDRS score is inefficient in many cases. Although it was used in most screened studies (9 out of 17), UPDRS III does not evaluate the effect of AT on PD, and thus a new standard should be developed[38,39]. Some studies reported that the evaluation of the effect of AT on PD is limited by the sample size[7,35,40]. In addition, the effectiveness of AT could be assessed because the quality of the studies was poor. Therefore, high-quality clinical studies are necessary to evaluate the effectiveness of AT and thus provide valuable information to physicians and patients. The methodological deficiencies can be overcome by using Consolidated Standards of Reporting Trials (CONSORT)[41] and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)[42] to ensure the quality of research.

Ⅴ. Conclusions

The purpose of this study was to provide directions for research on AT in PD patients in Korea by reviewing national and international intervention studies.

1. AT for PD improves all aspects of daily life functions, including motor and neurological symptoms.
2. The screened studies reported that there were no adverse effects of AT on drug therapy, and AT reduced the dose of drugs used during PD treatment.
3. Future studies on AT for PD should use acupoints *Baihui* (GV20), *Taichong* (LR3), *Zusanli* (ST36), *Sanyinjiao* (SP6), and *Yanglingquan* (GB34) and meridians GB and GV.
4. Clinical studies on PD should use CONSORT or STRICTA to ensure the quality of national studies and allow the development of new tools to evaluate the effect of AT on PD using the above criteria.

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