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Original Article

네트워크 분석에 기반한 항암화학요법으로 유발된 말초신경병증의 최적 경혈 조합

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Optimal Combination of Acupoints Based on Network Analysis for Chemotherapy-Induced Peripheral Neuropathy

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Objectives This study aimed to identify optimal combinations of acupoints used to treat chemotherapy-induced peripheral neuropathy (CIPN).
Methods We searched four international databases (MEDLINE, EMBASE, the Allied and Complementary Medicine Databases [AMED], and China National Knowledge Infrastructure [CNKI]) and five Korean databases (DBpia, Research Information Sharing Service [RISS], Korean Studies Information Service System [KISS], Oriental Medicine Advanced Searching Integrated System [OASIS], and KoreaMed) to identify randomized controlled trials (RCTs) that used acupuncture to treat CIPN. Network analysis was performed on the acupoints used in more than three included articles. We constructed a network by calculating the Jaccard similarity coefficient between acupoints and applied minimum spanning tree. Then, modularity analysis, degree centrality (Cd), and betweenness centrality (Cb) were used to analyze properties of the acupoints.
Results A total of 25 articles were included. 24 acupoints were extracted from 25 articles. The combinations of acupoints having the highest Jaccard similarity coefficient were {EX-UE9, EX-LE10} and {ST36, SP6}. In the modularity analysis, acupoints were classified to six modules. ST40, EX-UE11, and KI6 had the highest Cd value while ST40, GB34 had the highest Cb value.
Conclusions This study found the systematic framework of acupoint combinations used in CIPN studies. This study is expected to provide new perspectives of CIPN treatment to therapists. A RCT is in progress of using the network of this study as a guideline. If significant results are derived from the RCT, it will be possible to lay the groundwork to consider acupuncture for CIPN treatment. **(J Korean Med Rehabil 2022;32(1):107-124)**

Key words Chemotherapy-induced peripheral neuropathy, Social network analysis, Acupuncture

Introduction»»»»

Cancer is the leading cause of death worldwide, and various efforts are being made to conquer cancer in each country. Cancer treatments include surgery, radiation therapy, chemotherapy, and immunotherapy, which are usually performed in combination[1]. Chemotherapy is a treatment that uses drugs to kill cancer cells, preventing the growth and division of cancer cells. Cancer cells grow and divide faster than normal cells, thus more affected by chemotherapy, but strong drugs used in chemotherapy can damage normal cells as well[2]. The human body suffers a number of side effects due to such cell damage. Chemotherapy-induced peripheral neuropathy (CIPN) is one of the side effects that is reported to affect 3~40% of patients who have undergone chemotherapy[3]. Most types of pain related to chemotherapy improves between treatments, however nerve damage often gets worse with each dose. It may take months or years to improve, and in severe cases, symptoms may remain permanently[4]. Symptoms of CIPN appear as peripheral pain, allodynia, paresthesia, numbness, tingling, and functional decline. These symptoms can degrade the quality of life, lead to discontinuation of cancer treatment, and ultimately affect survival[5]. Hence, follow-up treatment after chemotherapy is important to patients who suffer from CIPN.

Acupuncture is a widely used option among various treatments used in oriental medicine and used as a follow-up treatment after chemotherapy to improve patients' symptoms. Acupuncture has the effect on pain relief, blood circulation, and organ function regulation in the traditional viewpoint of oriental medicine[6-8]. In addition, several studies were conducted to confirm the effectiveness of acupuncture treatment in pain relief and improving nerve conduction velocity in CIPN patients. Wong and Sagar[9] reported that pain, dullness, and tingling improved after acupuncture in five CIPN patients, and Jeong et al.[7] reported that acupuncture improved peripheral nerve symptoms and nerve conduction speed. Jin et al.[10] conducted a systematic review and meta-analysis of 19 randomized clinical trials (RCTs) involving 1,174 patients and concluded that acupuncture treatment showed the effect of improving pain and nerve conduction rate in CIPN patients. It is confirmed that acupuncture is effective as a follow-up treatment after chemotherapy through these previous studies.

Based on the conclusions of previous studies that acupuncture treatment is effective in CIPN patients, we used network analysis to determine what principle is applied to the selected acupoints for CIPN treatment and which acupuncture points are significant and frequently used. Network theory was first introduced as an analysis method for social structure based on mathematical graph theory and is widely applied as a method for analyzing organic relationships between factors in natural sciences such as biology[11]. Acupuncture generally combines the specific property of each acupoint after classifying the cause of the disease by the traditional pathological viewpoint of oriental medicine. Therefore, several studies used a method of analyzing the combination and usage pattern between acupoints through network analysis. Lee et al.[12] analyzed 33 acupoints used in 53 studies related to low back pain, and Kim et al.[13] analyzed 27 acupoints in 13 studies on poor ovarian response by network analysis. Using network analysis appears to reveal the structure of acupuncture treatments for various diseases.

In this study, we constructed a network based on Jaccard similarity, and used network modularity analysis, degree centrality (Cd), and betweenness centrality (Cb) to clarify the combination and usage patterns of acupoints and principles applied in the treatment of CIPN. We analyzed 24 acupoints extracted from 25 RCTs related to CIPN treatment through the above method and visualized the information so that the relationship and importance of the acupoints used in CIPN can be grasped at a glance.

Materials and Methods

1. Extraction of data source

The articles using acupuncture treatment for CIPN were retrieved from international databases (MEDLINE, Allied & Complementary Medicine Database, EMBASE, China National Knowledge Infrastructure) and Korean databases (DataBase Periodical Information Academic, Research Information Sharing Service, Korean Studies Information Service System, Oriental Medicine Advanced Searching Integrated System, KoreaMed). The search strategies were applied by combining the keywords corresponding to the research subject and the intervention. Methods and languages suitable for each database were applied. Detailed search strategies for each database are included in Appendix I, and articles published up to September 2018 were targeted.

We screened the retrieved articles by reading the title and abstract as initial screening. Then, we performed detailed screening by reading the full text. We included RCTs using acupuncture for treatment of CIPN in this study. Articles not using acupuncture and, not corresponding to RCTs (non-RCTs, review, case series, uncontrolled observational studies) were excluded. Data on sample size/disease, intervention, control, main outcome, acupoints, and conclusion were extracted from the finally selected studies. We checked the frequency of acupoints used in the articles through the extracted data, and acupoints used more than three times were included in the study. Extracted acupoints were analyzed using network analysis (Fig. 1).

2. Acupoints combination network construction

Using the selected acupoints, a table in which X-axis and Y-axis corresponds to acupoint and reference article respectively was constructed. If the acupoint was used in the reference article, the value was expressed as 1, otherwise 0. Based on this table, to measure the similarity between two acupoints, the Jaccard similarity coefficient was used, which is one of various methods for measuring the similarity between two vectors.

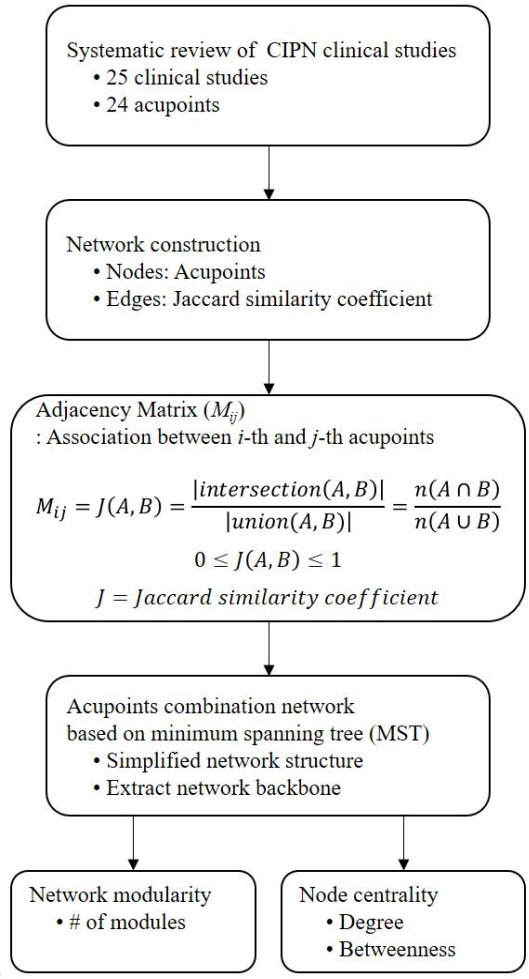

Fig. 1. The procedure of network analysis. CIPN: chemotherapy-induced peripheral neuropathy

The Jaccard similarity coefficient between the properties of acupoint A and B is defined as follows.

$$J(A,B) = \frac{|intersection(A,B)|}{|union(A,B)|} = \frac{n(A \cap B)}{n(A \cup B)}$$

$$0 \le J(A,B) \le 1$$

A network is defined as a set of nodes linked by edges in general. In this study, the nodes denote each acupoint and the edges denote connections between acupoints. These connections mean the extent of similarity between acupoints, which are represented as the

adjacency matrix (M_{ij}) that indicates Jaccard similarity coefficient between i-th and j-th acupoints.

$M_{ij} = J(A,B)$, J=Jaccard similarity coefficient

The acupoints combination network was constructed for every acupoint based on this adjacency matrix M_{ij}.

3. Modification of network for optimal network analysis

Since the constructed network was too complex to perform network analysis, the network was simplified by using a method that allows extracting the network backbone without loss of generality. Among various methods, we used minimum spanning tree (MST), which is a method that is able to avoid methodological bias, extract the network backbone, and simplify the network[14]. MST is defined as a sub-network that includes all nodes in the graph, has no cycles, and has a minimum sum of weights[15]. In this study, in order to find acupoints serving as the centers or hubs among them, the backbone structure of the acupoints combination network was extracted by the MST method using the Kruskal's algorithm. The modified network was represented in the form of an adjacency matrix.

4. Network analysis

The acupoints combination network is represented as a weighted and undirected network associated with the similarity between acupoints. To examine the topological properties of this network, we analyzed the network based on graph theory using MATLAB (Release 2017b; MathWorks Inc., Natick, MA, USA). To explore the community structure in the acupoints combination network, we calculated the modularity of the network. The modularity Q as a measure of network division denotes as follows:

$$Q = \frac{1}{l}\Sigma_{i,j\in}(M_{i,j} - \frac{k_i k_j}{l})\delta_{i,j}$$

Given a network with N nodes, where i-th and j-th node has a node degree k_i, k_j and l is the total number of edges. The adjacency matrix M_{ij} is the connection weight between i and j nodes. The membership vector δ_{ij} is 1 if i-th and j-th nodes are in same module, otherwise is 0. If modularity is closer to 1, it is classified as an optimized module[16].

To identify the most important node within the connectivity of the acupoints combination network, we considered the Cd and Cb as nodal properties of network. The Cd is a conceptually simplest measure identifying which nodes are most central. The degree (D_i) of a network with N nodes is defined as the number of linked edges at i-th node with other nodes, and it is denoted as follows.

$$D_i = \Sigma_{i\in N} M_{ij}$$

The Cb is another measure of centrality and defined as the number of edges which a given node lies on shortest paths between the other two nodes. The Cb (B_i) of i-th node of N nodes is denoted as follows,

$$B_i = \frac{1}{(n-1)(n-2)})\Sigma_{j,k\in N}\frac{\rho^i_{jk}}{\rho_{jk}}$$

where ρ_{jk} is the number of shortest paths between j-th and k-th node, and ρ^i_{jk} is the number of shortest paths between j-th and k-th nodes that pass through i-th node.

5. Network visualization

The analysis results of the acupoints combination network were visualized in four ways: (1) adjacency matrix denoted as the Jaccard similarity coefficients between acupoints; (2) backbone structure of the acupoints combination network applying MST method; (3) network topological architecture with connectivity and modularity; and (4) nodal properties as Cd and Cb.

Table I. Characteristics of Included Studies

First author (year)	Sample size/disease (condition)	Intervention (experimental)	Control	Main outcome / Result	Acupoint
Chen (2018)[17]	80 patients/ Oxaliplatin-induced peripheral neurotoxicity with colorectal cancer	(A) AT (30 min, weekly treatment 5 times, total 2 weeks, n=40)	(B) Medication (intramuscular injection of mecobalamin 0.5 mg, weekly treatment 3 times, total 2 weeks, n=40)	1. Efficacy rate : Group A=70.0% (28/40), Group B=47.5% (19/40)	ST36, CV6, SP3, LI4, LI11, LR3, EX-UE9, EX-LE10 EX-UE11, ST40, SP10, SP6, KI3
Huang (2017)[18]	80 patients/ Oxaliplatin and paclitaxel-induced peripheral neurotoxicity with cancer	(A) Warm needle AT (10 days a course, total 2 courses, weeks, n=40)	(B) Medication (providing nutritional support for nerve, n=40)	1. Incidence of neurotoxicity : Group A=27.5% (11/80), Group B=42.5% (17/80) ($p<0.05$) 2. QOL : Group A significantly better than Group B ($p<0.05$)	TE3, LI4, SI3, TE5, LI11, KI6, GB39, SP6, GB34, ST36, SP6
Han (2016)[19]	104/98 patients/ CIPN with multiple myeloma bortezomib (velcade)-based chemotherapy	(A) AT plus (B) (methylcobalamin used the same way as above accompanied by 3 cycles of acupuncture, n=49)	(B) Medication (methylcobalamin, 10 times of 500 μg intramuscular methylcobalamin injection every other day followed by 2 months of oral methylcobalamin application, n=49)	1. VAS : Group A=before 5.57±0.257, after 3.23±0.170 Group B=before 5.50±0.244, after 4.25±0.197 2. FACT/GOG-NTX questionnaire : Group A=before 36.48±0.470, after 32.98±0.542 Group B=before 36.63±0.551, after 35.17±0.518 3. NCV : Group A=improved significantly Group B=no amelioration	LR3, ST43, GB41, SP6, ST36, SP10, ST25, LU5, PC6, LI4, GV14, GV12, GV11, GV9, BL13, BL17, BL58
Tian (2016)[20]	60 patients/ CIPN caused by FOL-FOX4 regimen	(A) AT (30 min, twist the needle once, 14 days a course, n=30)	(B) Medication (injected cobamamide 1 mg, once a day, 14 days a course, n=30)	1. Efficacy rate 1) Sensory nerve : Group A=70.0%, Group B=46.66% ($p<0.05$) 2) Movement nerve : Group A=13.33%, Group B=10.00% ($p>0.05$) 2. NCV (SCV, MCV) 1) SCV : statistical significance ($p<0.05$) 2) MCV : no statistical significance ($p>0.05$) 3. QOL 1) Group A ($p<0.05$) before: 33.63±2.71 after: 40.37±5.83 2) Group B ($p<0.05$) before: 33.83±2.91 after: 36.40±4.67	LI10, LI4, LI11, TE5, EX-UE9, GB34, ST36, ST40, SP6, GB40, LR3, EX-LE10, CV4, CV6, GV20
Cao (2015)[21]	60 cancer patients undergoing Vinca alkaloids chemotherapy	(A) EA (30 min, daily for 7 days, intermittent period 8 to 20 days, 21 days for 1 course of treatment, total 2 courses of treatment, n=30)	(B) AT (same acupoints, but no electricity treatment, n=30)	1. Incidence of neurotoxicity : Group A=60.0% (18/30), Group B=90.0% (27/30) ($p<0.05$) 2. KPS score : Group A=before 55.58±1.07, after=58.24±1.27 Group B=before 53.88±9.88, after=54.05±4.17 3. Body weight : Group A=before 64.82±20.53, after=77.74±25.49 Group B=before 62.32±12.68, after=62.37±13.58	LI4, LR3
Wei (2014)[22]	60 patients/ Paclitaxel-induced peripheral neurotoxicity with cancer	(A) EA plus moxibustion box (21 days was a course. The two groups received at least 2 courses of chemotherapy, n=30)	(B) Medication (cobalt amine, n=30)	1. Efficacy rate : Group A=43.3%, Group B=26.7% 2. KPS score improving rate : Group A=63.3%, Group B=33.3% 3. Incidence of neurotoxicity : Group A=50%, Group B=90% 4. Median survival time : Group A=300 days, Group B=218 days 5. 1 year survival rate : Group A=40%, Group B=20%	ST36, LI4, ST41, CV4
Wu (2014)[23]	60 patients/ Oxaliplatin-induced peripheral neurotoxicity	(A) AT (began to accept acupuncture treatment before the patients chemotherapy, totaled 6 d, acupuncture treatment once a day, n=20)	(B) Medication (accept intravenous mecobalamin once a day while giving chemotherapy, continuous 6 d, n=19) (C) No treatment (chemotherapy alone, n=19)	1. Incidence of neurotoxicity ($p<0.05$) : Group A=30.00%, Group B=36.84%, Group C=78.95% 2. Efficacy rate ($p<0.05$) : Group A=17/20, Group B=12/19, Group C=10/19	LI11, PC6, LI4, SP10, ST36, SP6, Upper: EX-UE11, EX-LE12 (bloodletting) Motor dysfunction or muscular atroph: GB34, ST40

Table I. Continued

First author (year)	Sample size/disease (condition)	Intervention (experimental)	Control	Main outcome / Result	Acupoint
Yan (2012)[24]	75 cancer patients/ CIPN with malignant tumor	(A) AT (30 min, daily for 14 days, n=36)	(B) Medication (intramuscular injection of B vitamins, n=39)	1. Efficacy rate : Group A=83.33%, Group B=51.28% (p=0.003)	LI4, LI11, EX-UE9, LR3, ST36, SP10, EX-LE10, SP9 ST40, CV6, BL17
Sun (2012)[25]	66 patients/ Oxaliplatin-induced peripheral neurotoxicity	(A) EA plus (B) (30 min, daily for 14 days, n=34)	(B) Medication (glutathione, daily for 14 days, n=32)	1. Efficacy rate : Group A=76.5% (26/34), Group B=46.9% (15/32) 2. NCV (SCV, MCV) 1) SCV (Group A>Group B, statistical significance) : bilateral ulnar nerves 2) MCV (Group A>Group B, statistical significance) : right ulnar nerve, left peroneal nerve	ST36, CV4, SP10 According to pattern identification: LI4, LI11, TE10, TE4, LI5, SI4, EX-UE9, SI3, ST35, ST34, SP6, SP9, ST41, KI3, BL60, BL62, KI6, EX-LE10, LR3
Cui (2011)[26]	62 patients/ Oxaliplatin-induced peripheral neurotoxicity	(A) Warm needle AT (10 days is a treatment cycle. evaluation of efficacy after 2 cycles of chemotherapy, n=32)	(B) Medication (glutathione, 1.5 g/d, daily for 5 days, n=30)	1. Efficacy rate : Group A=87.5%, Group B=63.33% (p<0.05)	LI11, TE5, LI4, TE3, SP9, SP6, ST36, GB34, KI6, GB39
Hou (2011)[27]	40 patients/ CIPN with malignant tumor	(A) AT (30 min, at the start of chemotherapy, once per day, 2 weeks in succession, n=20)	(B) Medication (metoclopramide injection intramuscularly, 10 mg each time, once or twice a day, granisetron Oral, 1 mg each time, once daily, peripheral nerve toxicity above degree II for adenosylcobalamin injection, n=20)	1. Incidence of neurotoxicity : Group A=60% (12/20), Group B=60% (12/20) (p>0.05) 2. Incidence of digestive tract adverse effect : Group A=70% (14/20), Group B= 85% (17/20) (p>0.05) 3. Score of digestive tract adverse effect : Group A=1.40±1.39, Group B=2.52±1.74 (p<0.05)	LI11, PC6, LI4, ST 36, SP6, GB34
Tian (2011)[28]	76 patients/ Oxaliplatin-induced peripheral neurotoxicity with gastrointestinal cancer	(A) Warm needle AT (30 min, once a day, 21 days is a course of treatment, n=38)	(B) Medication (neurotropine, n=38)	1. Neurotoxicity grade : significant difference (p<0.05) 2. QOL : improvement of KPS score - Group A=52.63% (20/38), Group B=23.69% (9/38) (p<0.05)	LI4, LI5, LI10, LI11, TE5, LR3, ST36, GB34, CV6, ST40
Wang (2011)[29]	60 patients/ Oxaliplatin-induced peripheral neurotoxicity with colorectal cancer	(A) AT (30 min, once a day, 14 days is a course of treatment, n=30)	(B) Medication (intramuscular injection of cobamamide, n=30)	1. Efficacy rate 1) Sensory nervous dysfunction : Group A=70.00%, Group B=46.67% (p>0.05) 2) Motor nervous dysfunction : Group A=13.33%, Group B=6.67% (p>0.05) 3) Therapeutic effect of different grade in group A : grade I=71.43%, grade II=66.67%, grade III=75.00% (p>0.05)	LI4, LI10, LI11, ST36, ST32, GB30, ST40, GB34, GB31, EX-LE10 Early patient: BL20, LR3 Late patient: SP6, KI3, SP10, Finger or tiptoe numbness: EX-LE12, EX-UE11 (bloodletting)
Xu (2010)[30]	64 patients/ Paclitaxel or oxaliplatin-induced peripheral neurotoxicity	(A) AT (30 min, once a day, 14 days is a course of treatment, n=32)	(B) Medication (intramuscular injection of cobamamide, n=32)	1. Efficacy rate : Group A=66.7%, Group B=40.0% (p<0.05)	LI4, LR3, ST36, CV6, LI11, SP3, EX-UE9, EX-LE 10 Early patient: SP10 Late patient: SP6, KI3 Upper: EX-UE11, EX-LE12 (bloodletting) Motor dysfunction or muscular atroph: GB34, ST40
Liu (2009)[31]	60 patients/ CIPN with malignant tumor	(A) AT (30 min, once a day, 14 days is a course of treatment, the first 3 days of chemotherapy began, total 2 courses of treatment, n=30)	(B) Medication (intramuscular injection of B vitamins, once a day, 14 days is a course of treatment, the first 3 days of chemotherapy began, total 2 courses of treatment, n=30)	1. Efficacy rate : Group A=83.3% (25/30), Group B=60.0% (18/30) (p<0.05)	ST36, SP6, GB34, LI4, LI11, KI16, CV4, CV6 Upper extremity paralysis: HT3, LI10, LU7, LU11, TE5, PC4, TE3, SP12, EX-UE9 Lower extremity paralysis: GB30, GB31, BL40, ST40, SP6, GB38, GB40, LR4, BL60, EX-LE10
Mai (2008)[32]	60 patients/ CIPN with malignant tumor	(A) AT (Once a day, 10 days is a course of treatment, the interval of treatment was 3 days, total 3 courses of treatment, n=30)	(B) Medication (intramuscular injection of B vitamins, once a day, 10 days is a course of treatment, the interval of treatment was 3 days, total 3 courses of treatment, n=30)	1. Efficacy rate : Group A=93.3% (28/30), Group B=43.3% (13/30) (p<0.05)	GB20, TE5, ST36, BL40, GB34, ST40, SP6, LR3, SP10

Table I. Continued

First author (year)	Sample size/disease (condition)	Intervention (experimental)	Control	Main outcome / Result	Acupoint
Wu (2015)[33]	90 patients/ CIPN with malignant tumor	(A) AT + moxa plus (B) AT: 30 min, daily for 7 days Herbal medicine: 21 days was a course of treatment and they were treated for 2 courses, n=30	(B) Herbal medicine (Hwanggigyejiomul-tang [Huangqiguizhiwuwu-tang], n=30) (C) No treatment (n=30)	1. Efficacy rate : Group A=90.0%, Group B=53.3%, Group C=6.6% (p<0.001) 2. KPS score : Group A=90±10, Group B=80±10, Group C=70±10 (p<0.05) 3. Neurotoxicity classification 1) NK cells, IL-10 factors=significant difference (p<0.05) 2) T cell subgroups, IL-2=no statistical signifiance (p>0.05)	LI4, LR3
Li (2012)[34]	40 patients/ CIPN with malignant tumor	(A) EA plus (B) (The first 3 days of chemotherapy began and ended on the 3rd day after the end of chemotherapy, 14 d was a course of treatment, n=40)	(B) Herbal medicine (Bibosinhaedog-bang [Pibushenjiedu-fang], n=40)	1. Incidence of neurotoxicity : Group A=before 50% (20/40), after 15% (6/40) Group B=before 45% (18/40), after 35% (14/40) 2. Karnorfsy score : Group A=before 68.33±8.98, after 86.57±7.03 Group B=before 67.25±10.42, after 73.23±6.24 3. QOL : Group A=before 23.61±5.37, after 50.10±5.36 Group B=before 22.88±4.99, after 40.81±4.23 4. Weight : Group A=before 48.34±7.52, after 55.23±7.06 Group B=before 49.45±9.42, after 55.48±10.68	ST36, SP6, LI11, GV20, CV4, CV6
Luo (2008)[35]	40 patients/ Paclitaxel or oxaliplatin-induced peripheral neurotoxicity	(A) EA plus (B) (30 min, daily for 5 days a week, from the day before chemotherapy, to the end of the day after the end of chemotherapy. The use of traditional Chinese medicine in patients with oral administration during oral administration of herbal medicine, n=40)	(B) Herbal medicine (n=40)	1. Incidence of neurotoxicity : Group A=before 50.0%, after 15.0% Grop B=before 45.0%, after 35.0% 2. Weight : Group A=before 48.35±7.52, after 55.23±7.06 Group B=before 49.45±9.42, after 55.48±10.68 3. Chinese symptom score chart, Karnorsfy score, life quality score : result of Group A is better than Group B	ST36, SP6, LI4, GV20, CV4, CV6
Wang (2011)[36]	63 patients/ CIPN with malignant tumor	(A) AT plus herbal medicine (Boyanghwano-tang [Buyanghaiwu-tang], 30 min, daily for 15 days, n=32)	(B) Medicatin (intramuscular injection of B vitamins, n=31)	1. Efficay rate : Group A=96.9% (31/32), Group B=77.4% (24/31) (p<0.05)	LI11, LI4, TE5, HT7, ST36, ST41, SP10, SP6, LR3, GB34, GB39
Rostock (2013)[37]	60 patients /cancer patients with CIPN	(A) EA 8±1 sessions of EA	(B) Hydroelectric baths (C) High doses of vit B1, B6 (D) Placebo	1. NRS improved : Group A=0.8±1.2, Group B=1.7±1.7, Group C=1.6±2.0, Group D=1.3±1.3 (p=0.705) 2. Neuropathy score, NCV, NCI-CTC, EORTC-QLQ C30 : no significant difference	LV3, SP9, GB41, GB34, LI4, LI11, SI3, HT3
Zhong (2012)[38]	50 patients/ CIPN with malignant tumor	(A) AT plus (B) (20 min, d1, d3, d5, d7, 14d was a course of treatment, n=23)	(B) External washing herbal medicine (principle of Hexue Tongbi, first 1 days of chemotherapy began for 7 days, 14 d was a course of treatment, n=27)	1. Efficacy rate : Group A=1st day 13%, 3rd day 21.7%, 5th day 30.4% Group B=1st day 0%, 3rd day 7.4%, 5th day 11.1% (p<0.05) Group A=7th day 34.7%, 14th day 47.8% Group B=7th day 29.6%, 14th day 44.4% (p>0.05) 2. Curative effect after 7 day : Group A=20/23, Group B=18/27 (p<0.05)	LI11, TE5, LI4, TE3, SP9, ST36, GB34, SP6, GB39
Xiong (2016)[39]	90 patients /CIPN with breast cancer	(A) Acupuncture group (n=30) At the acupoint such as LI11, LI4, ST36, SP6, SP10 bilaterally (each group, once every three days)	(B) Mecobalamin group (n=30) (C) Acupoint inject group (n=30)	1. Efficacy rate : Group A=78.6%, Group B=83.3%, Group C=93.1% (p<0.01) 2. NCV : improvement in Group C was obviously superior (all p<0.01) 3. Hemorrheology indicator : improved in Group A and Group C (p<0.05)	(A) Bilaterally LI11, LI4, ST36, SP6, SP10 (B) Intramuscular injection with 1 mL of mecobalamin injection was conducted (C) Acupoint selection was the same as group A 0.1 mL of mecobalamin injection was injected into each acupoint, respectively.

Table I. Continued

First author (year)	Sample size/disease (condition)	Intervention (experimental)	Control	Main outcome / Result	Acupoint
Wong (2016)[40]	23 patients into each group/ Eligible cancer patients had a < 2 ECOG performance score, received neurotoxic chemotherapy, CIPN symptoms for >two months	(A) ALTENS group Twice weekly for 12 treatments for 6 to 8 weeks.	(B) Acupuncture group Using 34 G (0.25 mm), 40-mm sterilized acupuncture needles No electrical stimulation	1. mTNS scores : baseline=7.1, treatment completion=4.0, 3 months follow-up=3.6, 6 months follow-up: 3.1 (p<0.001) 2. Numbness scores : significantly improved at 6 months (p<0.001) 3. ESAS pain scores and perception of well-being scores : inconclusive	(A) T7, L3, LI4, LIV3, LI11, ST36 (B) LI4, LIV3, LI11, ST36, CV6, SP6, Bafeng, Baxie, Jing
Greenlee (2016)[41]	48 patients with stage I-III breast cancer who scheduled to receive taxane therapy	(A) EA group (n=25) (Weekly treatments concurrents with taxane treatment) 2 Hz of mixed pulsatile intervals for a total of 30 minutes	(B) SEA group (n=23)	1. BPI-SF Week 12: Group A=2.6, Group B=2.8 (p=.86) Week 16: Group A=3.4, Group B=1.7 (p=.03) increase at week 16: Group A is 1.62 points higher than Group B (p=.04) 2. FACT-NTX : no differences at week 12 3. NPS-4 : Group A worse pain at week 16 (p=.03)	(1) General GB34, ST36, LI4, LI10 (2) Lower limb L3, L5 (3) Upper limb C5, C7

AT: acupuncture, QOL: quality of life, CIPN: chemotherapy induced peripheral neuropathy, VAS: visual analog scale, FACT/GOG-NTX: functional assessment of cancer therapy/gynecologic oncology group-neurotoxicity, NCV: nerve conduction velocity, FOL-FOX4: oxaliplatin-5-fluorouracil-leucovorin, SCV: sensory nerve conduction velocity, MCV: motor nerve conduction velocity, EA: electroacupuncture, KPS: Karnofsky performance scale, NK: natural killer, IL: interleukin, NRS: numeric rating scale, NCI-CTC: National Cancer Institute-common toxicity criteria, EORTC-QLQ: European organization for research and treatment of cancer-quality of life questionnaire, ECOG: eastern cooperative oncology group, ALTENS: acupuncture-like transcutaneous electrical nerve stimulation, mTNS: modified total neuropathy score, ESAS: Edmonton symptom assessment score, SEA: sham electroacupuncture, BPI-SF: brief pain inventory-short form, FACT-NTX: functional assessment of cancer therapy-taxane neurotoxicity subscale, NPS: neuropathic pain scale.

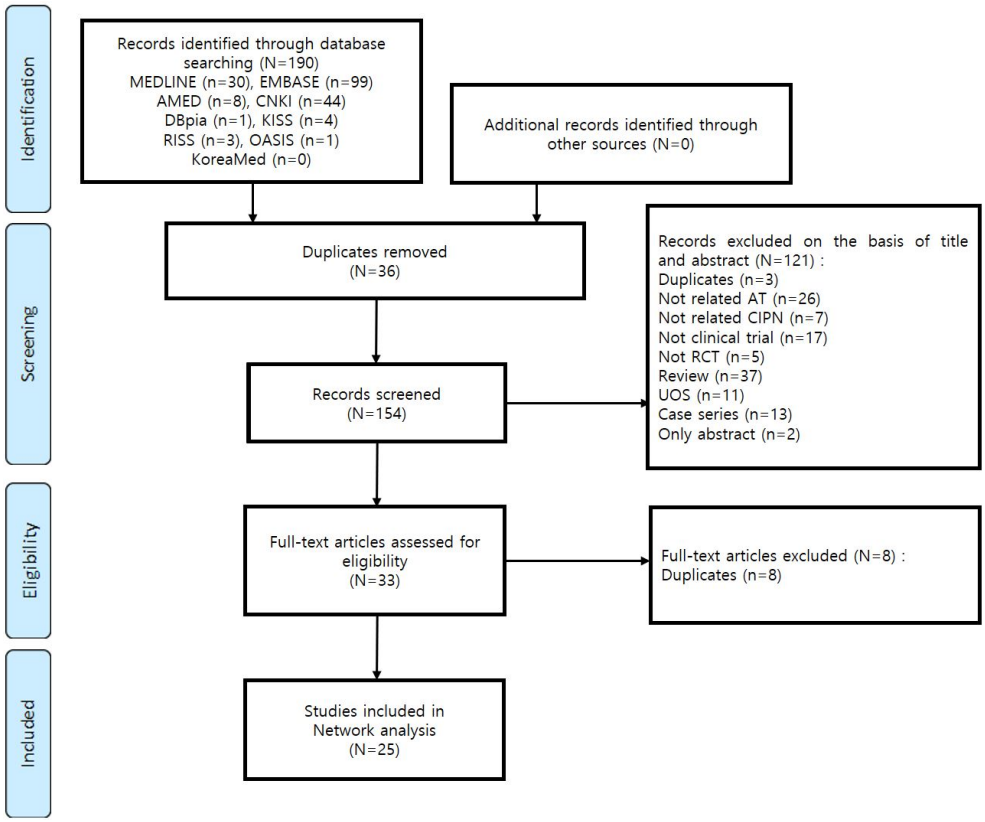

Fig. 2. PRISMA diagram for the included studies. AMED: Allied and Complementary Medicine Databases, CNKI: China National Knowledge Infrastructure, KISS: Korean Studies Information Service System, RISS: Research Information Service System, OASIS: Oriental Medicine Advanced Searching Integrated System, AT: acupuncture, CIPN: chemotherapy-induced peripheral neuropathy, RCT: randomized controlled trial, UOS: uncontrolled observational study.

Results»»»»

1. Extraction of data source

A total of 190 articles were retrieved from the databases, of which 36 duplicates were removed. After screening titles and abstracts, 26 articles not related to acupuncture treatment, 7 articles not related to CIPN, 83 articles not RCTs, 2 articles having only abstract, 3 duplicates were excluded. Full-texts of the remaining 33 articles were assessed in detail, and 8 articles were excluded. Finally, total 25 international articles (Chinese 21, English 4) were included, and no article meeting the conditions was retrieved from Korean databases (Fig. 2). Data were extracted from the included articles (Table I)[17-41]. Identifying the frequency of acupoints used in the articles, the acupoints used more than three times were included in this study (Table II). A total of 24 acupoints were included, and the combination of these acupoints were analyzed.

2. Network construction based on Jaccard similarity coefficient

Table II represents the relationship between acupoints and the reference article. Number 1 means usage of acupoint in the article, otherwise 0. Based on this table, Jaccard similarity coefficient was calculated between each acupoint. The network based on similarity was constructed and shown in the form of an adjacency matrix (Fig. 3). Then, we applied MST to the network as shown in Fig. 4.

As a result of analyzing the adjacency matrix applied MST, {EX-UE9, EX-LE10} and {ST36, SP6} showed the highest Jaccard similarity coefficient. The acupoints combination {EX-UE11, EX-LE12}, {LI4, LI11}, {LI4, ST36} also showed high similarity (Fig. 4; yellow cells). Of these acupoints, EX-UE9, EX-LE10, EX-UE11 and EX-LE12 were used less frequently in CIPN studies (Table II), but they were usually used in combination with each other, hence similarity were high.

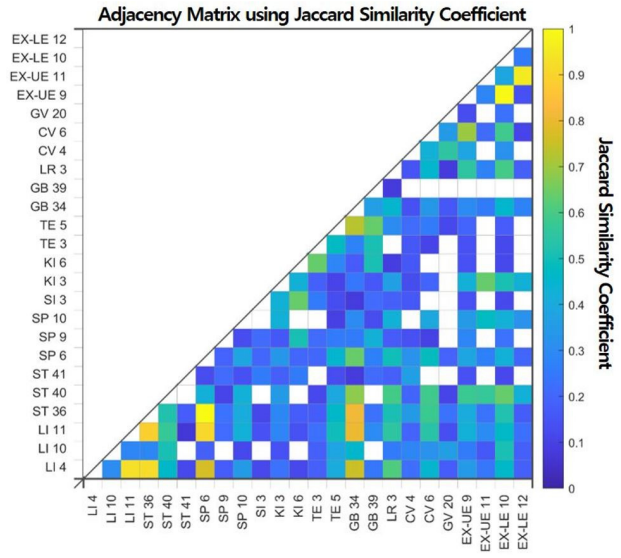

Fig. 3. Adjacency matrix using Jaccard similarity coefficient.

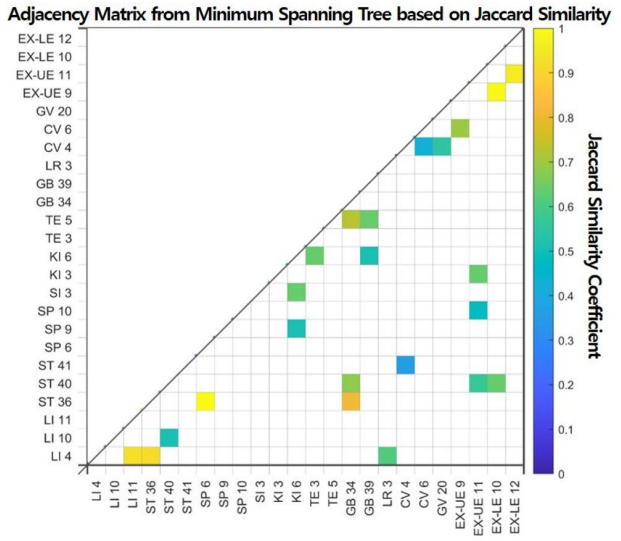

Fig. 4. Adjacency matrix from minimum spanning tree based on Jaccard similarity coefficient.

3. Modularity analysis

We performed network modularity analysis to explore the community structure in the acupoints combination network. As a result, the 24 acupoints used in the CIPN studies were categorized into six modules (Fig. 5). The network modularity was visualized by circular layout, and the acupoints belonging to the same module were assigned the same color (Fig. 5). Module 1 consisted of

Table II. Acupoints Used in Articles and Frequency of Acupoints

Acupoints	Chen, 2018	Huang, 2017	Han, 2016	Xiong, 2016	Tian, 2016	Greenlee, 2016	Cao, 2015	Wei, 2014	Wu, 2014	Rostock, 2013	Yan, 2012	Sun, 2012	Cui, 2011	Hou, 2011	Tian, 2011	Wang, 2011	Xu, 2010	Liu, 2009	Mai, 2008	Wu, 2015	Li, 2012	Luo, 2008	Wang, 2011	Zhong, 2012	Wong, 2016	Frequency
LI4	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	0	1	1	1	1	21
LI10	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0	5
LI11	1	1	0	1	1	0	0	0	1	1	1	0	1	1	1	1	1	1	0	0	1	0	1	1	1	17
ST36	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	22
ST40	1	0	0	0	1	0	0	0	1	0	1	0	0	0	1	1	1	1	1	0	0	0	0	0	0	9
ST41	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	3
SP6	1	1	1	1	1	0	0	0	1	1	0	1	1	1	0	1	1	1	1	0	1	1	1	1	1	19
SP9	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	4
SP10	1	0	1	1	0	0	0	0	0	0	1	0	0	0	0	1	1	0	0	0	0	0	1	0	0	7
SI3	0	1	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	3
KI3	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	5
KI6	0	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	3
TE3	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	3
TE5	0	1	0	0	1	0	0	0	0	0	0	0	1	0	1	0	0	1	1	0	0	0	1	1	0	8
GB34	0	1	0	0	1	1	0	0	1	0	1	0	1	1	1	1	1	1	1	0	0	0	1	1	0	14
GB39	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1	0	4
LR3	1	0	0	0	1	0	1	0	0	1	1	1	0	0	1	1	1	0	1	1	0	0	1	0	1	13
CV4	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0	0	0	1	0	0	1	1	0	0	0	6
CV6	1	0	1	0	1	0	0	0	0	0	1	0	0	0	1	0	1	1	0	0	1	1	0	0	1	10
GV20	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	4
EX-UE9	1	0	0	0	1	0	0	0	0	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	1	7
EX-UE11	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	4
EX-LE10	1	0	0	0	1	1	0	0	0	0	1	1	0	0	0	1	1	1	0	0	0	0	0	0	1	9
EX-LE12	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	3

1 means usage of acupoint in the article, otherwise 0.
2. Network construction based on Jaccard similarity coefficient.

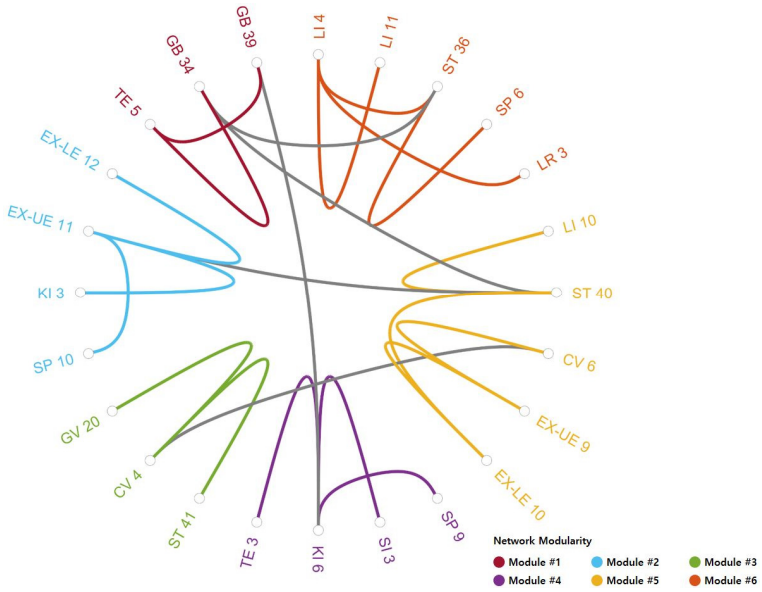

Fig. 5. Network topology with modularity.

GB39, GB34, TE5 (Fig. 5, red lines), Module 2 consisted of EX-LE12, EX-UE11, KI3, SP10 (Fig. 5, light blue line), Module 3 consisted of GV20, CV4, ST41 (Fig. 5, green lines), Module 4 consisted of TE3, KI6, SI3, SP9 (Fig. 5, purple lines), Module 5 consisted of EX-LE10, EX-UE9, CV6, ST40, LI10 (Fig. 5, yellow lines), Module 6 consisted of LR3, SP6, ST36, LI11, LI4 (Fig. 5, orange lines), and {GB34, ST36}, {GB34, ST40}, {GB39, KI6}, {EX-UE11, ST40}, and {CV4, CV6} connected different modules (Fig. 5, gray lines). In addition, we have classified the modules by the characteristics of acupoints constituting the module: the acupoints around the local pain area (Modules 2 and 5); acupoints to make the flow of qi (Modules 1, 4); and acupoints to promote normal body function (Modules 3, 6).

4. Network analysis

We analyzed the Cd and Cb of each acupoint used in the treatment of CIPN (Table III). Cd and Cb were visualized by forced layout and scale of value was indicated by the size of circle. As a result of Cd analysis, ST40, EX-UE11, and KI6 had the most abundant edges, and these acupoints were used frequently in combination

Table III. Degree Centrality and Betweenness Centrality of Acupoints in Minimum Spanning Tree Network

Acupoints	Degree	Betweenness
LI4	3	0.16996
LI10	1	0
LI11	1	0
ST36	3	0.312253
ST40	4	0.656126
ST41	1	0
SP6	1	0
SP9	1	0
SP10	1	0
SI3	1	0
KI3	1	0
KI6	4	0.249012
TE3	1	0
TE5	2	0.355731
GB34	3	0.640316
GB39	2	0.300395
LR3	1	0
CV4	3	0.16996
CV6	2	0.237154
GV20	1	0
EX-UE9	2	0.300395
EX-UE11	4	0.249012
EX-LE10	2	0.355731
EX-LE12	1	0

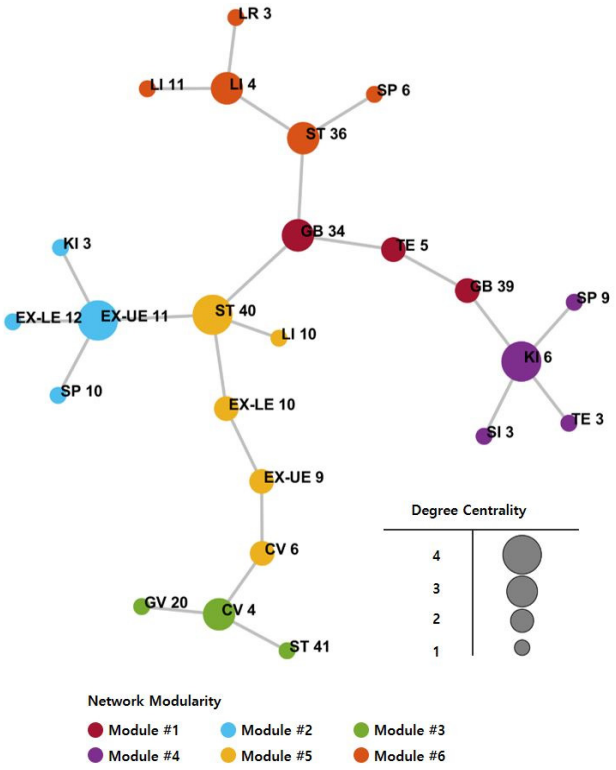

Fig. 6. Degree centrality represented by acupoints combination network.

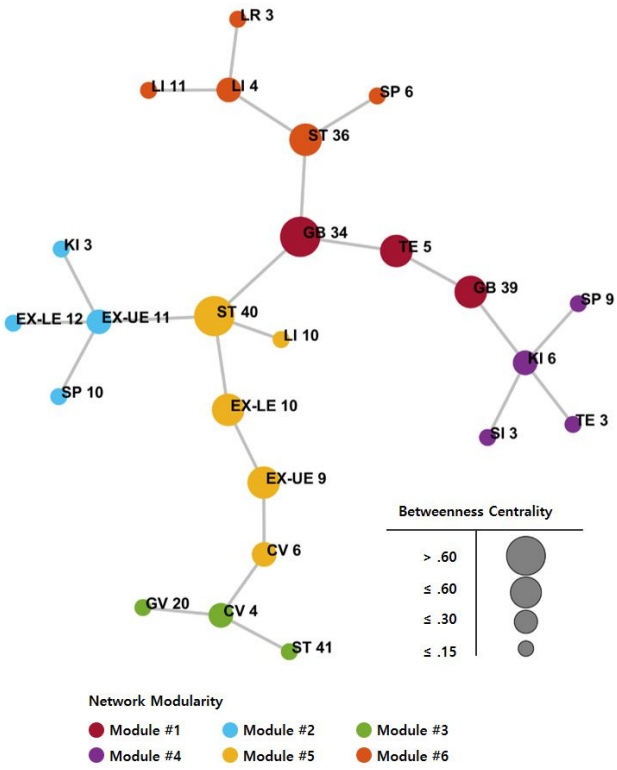

Fig. 7. Betweenness centrality represented by acupoints combination network.

with other acupoint for the CIPN treatment (Fig. 6). Fig. 7 shows Cb of each acupoints. GB34 and ST40 had the highest Cb value, and TE5, GB39, EX-LE10, EX-UE9, and ST36 also had a higher Cb value than other nodes. These acupoints play an important role as a mediator node in connecting vertices to other points.

Discussion»»»»

CIPN patients suffer from symptoms such as pain and allodynia in the peripheral area, resulting in poor quality of life and discontinuation of treatment. Acupuncture is used as a treatment for CIPN patients, and several studies have reported its effectiveness. In this study, to identify what principles are applied to selecting acupoints to treat CIPN and help combining and selecting optimal acupoints, we constructed a network based on Jaccard similarity coefficient, and performed a systematic network analysis using network modularity analysis, Cd analysis, and Cb analysis. Through this process, we examined correlations, patterns, and significance in network of selected acupoints for treatment of CIPN.

The network was constructed based on Jaccard similarity coefficient. Nodes corresponded to acupoints, and edges corresponded to similarity in this network. Degree of similarity was expressed by color in the adjacency matrix, so we could identify which edge is more weighted in the network. {EX-UE9, EX-LE10}, {ST36, SP6} had the highest similarity and {EX-UE11, EX-LE12}, {LI4, LI11}, {LI4, ST36} also had higher similarity than other edges. A high Jaccard similarity coefficient means two acupoints are frequently used in combination regardless of the frequency of each acupoint used independently. The similarity calculated in this network may provide information about much used acupoints combination for patient treatment or clinical research.

In oriental medicine, acupoints are usually used in

combination rather than independently. Researchers combined multiple acupoints in CIPN RCTs, so network representing relationship of acupoints combination used in 24 studies took a very complex form. This form represents all unimportant edges and is unsuitable for performing network analysis. Also, when visualized for its complexity, it is difficult to grasp the relationship between acupoints intuitively. In order to overcome these problems, we extracted the network backbone through simplification in this study. MST, known as the method to avoid methodological bias and extract the network backbone, was used, in order to modify the network to a form that is simple and representing of key points compared to previous studies.

The acupoints of the network were classified into six modules by modularity analysis. As a result of examining the property of modules, two modules were paired and each pair had a specific property. First, module 2, 5 are the main combination of acupoints around the affected area (Fig. 5). Patients with CIPN are commonly known to have pain in the fingertips and tiptoes. For example, EX-UE11 and EX-LE12 in module 2 are 10 acupoints respectively at the fingertips and toes, and EX-UE9 and EX-LE10 in module 5 are each located near the metacarpophalangeal joints and metatarsophalangeal joints. Module 1, 4 consists of acupoints that communicate meridians and help the flow of qi smoothly (Fig. 5). In particular, TE5 of module 1 and KI6, SI3 of module 4 belong to confluence points of the eight vessels. These acupoints are located where twelve main meridians and eight extra meridians communicate with each other to help the flow of qi[42]. Module 3, 6 are groups of acupoints that protect and reinforce the fragile body. In particular, the acupoints in module 6 are representative of the acupoints used in oriental medicine to control and protect the intestinal dysfunction, which is consistent with the pathological concept that disease occurs in a weak condition of the human body. ST36 of module 6 is one of lower sea points of the six bowels that treat six bowels[42]. LI4 and SP6 are two acupoints representing yin and yang respectively, and six viscera and six bowels belong to yin and yang, respectively[42]. In traditional pathology of oriental medicine, CIPN can be defined as Bi syndrome (a term meaning paralysis, blockage, joint pain, etc.)[43]. Bi syndrome is a disease of concept that occurs due to the weakness of the body invading bad energy from outside and the circulation of the whole body is not made smoothly, so that muscles, veins, and joints do not function properly[44,45]. In acupuncture treatment, acupoints are combined according to the following three basic principles; 1) acupoints around the affected area are effective in treating diseases around it; 2) each acupoint has specific properties and can be used in combination of acupoints according to the feature of the disease; and 3) acupuncture can regulate the function of certain organs and can cure diseases caused by the deterioration of them[46-48]. Thus, in order to treat Bi syndrome with acupuncture treatment, it is necessary to treat the vicinity of the area affected by disease, promote circulation, and regulate organ functions to protect and strengthen the weakened body so that muscles, veins, and joints can function properly. Acupoints were uncategorized prior to modularity analysis. Nevertheless, therapeutic properties of modules classified by modern statistical analysis method were consistent with traditional oriental medicine concept of Bi syndrome treatment. Classified modules in this study are not only meaningful statistically, but also consistent with the clinical concept of oriental medicine, and hence may be helpful for selecting optimal acupoint combination.

We performed network analysis using Cd and Cb to identify acupoints which plays an important role in the network (Figs. 6 and 7). Figs. 6 and 7 represent the results of Cd and Cb, respectively. acupoints with higher value are indicated by a larger circle and acupoints with lower value are indicated by a smaller circle. Cd is related to the number of links incident to each node. Therefore, ST40, EX-UE11, KI6, GB34, ST36, LI4, and CV4, which show high degree centralities are the major acupoints in each module. Cb is an indicator to see how

well the nodes play a role as a mediator. As shown in Fig. 7, GB34 and ST40, which show a high degree of betweenness centrality, are important acupoints that serve as “hubs” that connect different modules.

To summarize the network structure of this study, the network consists of six modules with three therapeutic properties, seven acupoints with high Cd value are major acupoints of each module, and two acupoints with high Cb value connect different modules. This structure was visualized in Figs. 6 and 7. EX-UE9 and EX-LE10, and ST36 and SP6 had the highest Jaccard similarity coefficient, which corresponds to edge of the network. This study constructed and analyzed the acupoint combination network, and figured out the systematic framework of acupoint combinations used in CIPN studies. This study is meaningful in that acupuncture, a traditional treatment accumulated empirically for a long time, was analyzed through a modern network theory, and it is expected to contribute to selecting optimal acupoint combination for CIPN treatment.

In this study, there is a limitation in that the significance and the difference of outcomes in each RCT were not reflected in the value of acupoints. The acupoints used in RCT were assigned the same value regardless of statistical significance and outcomes due to methodological limitation. If a method overcoming this limitation is designed in the future, the level of evidence will increase. We expect that studies with higher evidence will be performed referring to the limitation of this study.

Since this network analysis was performed based on clinical trials, the result may change according to publication of additional studies. Because of this variability, the network in this study is not absolute. Nevertheless, network analysis is meaningful in that it is a method that grasp the structure of acupoints combination used in diseases objectively as possible. Each practitioner had selected an acupoint based on different reasons as acupuncture was performed based on the practitioner’s experience or different literature in general. Despite limitation of variability, this network analysis is expected to provide statistical evidence and reveal the structure of acupoints network, and help practitioners selecting the optimal acupoint combination with better evidence. In addition, it may be guideline for designing clinical trials.

In this study, network analysis was performed based on RCTs published up to September 2018 to present the optimal combination of acupoints for CIPN treatment. It is expected that more developed evidence of CIPN treatment may be provided by performing an RCT using optimal acupoint combination based on network analysis. Based on the results of network analysis in this study and after consensus of experts, a RCT is in progress using major acupoints of CIPN treatment, ST40, GB34, EX-LE10, EX-UE11, TE5, LI4, ST36, KI6 and CV4 and additional acupoints according to symptoms. The results will be analyzed and published after the end of the study. So far, no RCT based on network analysis of CIPN treatment acupoint combination has been reported. If significant results are derived from a follow-up study, we would be able to suggest that physicians can consider acupuncture for the treatment of CIPN.

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Appendix Ⅰ. Search Strategy

A. MEDLINE

#1. Antineoplastic Agents [MeSH Terms]

#2. (chemotherapy or (antineoplastic agents) or (chemotherapeutic Anticancer drug) or (anticancer agent) or cisplatin or carboplatin or oxaliplatin or bortezomib or docetaxel or paclitaxel or taxane or taxotere or (organoplatinum compounds) or platinum or vincristine or (vinca alkaloids) or thalidomide or (proteasome inhibitor)) [Title/Abstract]

#3. #1 OR #2

#4. Peripheral Nervous System Disease [MeSH Terms]

#5. (neuralgia or paresthesia or hyperalgesia or (chemotherapy induced peripheral neuropathy) or CIPN or (peripheral neuropathy) or Polyneuropath or (chemotherapy induced neurotoxicity)) [Title/Abstract]

#6. #4 OR #5

#7. Acupuncture [MeSH Terms]

#8. Acupuncture therapy [MeSH Terms]

#9. Electroacupuncture [MeSH Terms]

#10. Acupoint [MeSH Terms]

#11. “Acupuncture and moxibustion” [Title/Abstract]

#12. OR/ #7- #11

#13. #3 AND #6 AND #12

B. EMBASE

- same to MEDLINE

C. The Allied and Complementary Medicine Databases (AMED)

- same to MEDLINE

D. China National Knowledge Infrastructure (CNKI)

#1. 癌

#2. 肿瘤

#3. 化疗

#4. OR/#1-#3

#5. 周围神经病

#6. 周围神经炎

#7. 周围神经毒性

#8. OR/#5-#7

#9. #4 AND #8

#10. 针刺

#11. 针灸

#12. 灸法

#13. 温针灸
#14. 电针
#15. 穴位埋线
#16. 穴位注射
#17. 穴位贴敷
#18. 刺血
#19. 拔罐
#20. 耳针
#21. OR/#10-#20
#22. 8 AND 21

E. Korean databases (Oriental Medicine Advanced Searching Integrated System [OASIS], DBpia, Research Information Sharing Service [RISS], Korean Studies Information Service System [KISS], KoreaMed)
#1. “암” OR “종양” OR “신생물” OR “항암화학요법”
#2. “말초신경병증” OR “말초신경병변”
#3. “침치료” OR “침술” OR “전침” OR “온침” OR “뜸”
#4. 1 AND 2 AND 3