The aim of this study was to review clinical efficacy of acupuncture treatment of mild cognitive impairment.

Methods: Randomized controlled trials that performed acupuncture treatment for mild cognitive impairment were retrieved from 6 online databases (PubMed, Cochrane Library, EMBASE, CNKI, NDSL, OASIS) on September 30th, 2018. Studies were selected according to inclusion and exclusion criteria, and were reviewed by Risk of Bias assessment.

Results: In total, 21 studies were included in this review. All studies were Chinese (19 studies published in Chinese and 2 in English). The sample size, 50 to 100, and the number of treatment times, 20 to 30, were the largest range in all studies. The most treatments performed was 30. The longest treatment period was 56 days, which accounted for 33% of the studies. The most frequently used evaluation index was the Mini Mental State Examination followed by the Montreal Cognitive Assessment, each used 17 times and 15 times, respectively. The most frequently used acupoints were GV20, EX-HN1, GB20, and GV24, which accounted for 47% of total number of acupoints used. In 48% of the studies, needle retention time was 30 minutes. Western medicine treatment was the most common control group. Most studies reported that the intervention group was statistically significantly different to the control group.

Conclusion: These results suggest that acupuncture for mild cognitive impairment was effective. However, it is difficult to confirm this conclusion because the quality of most of these studies were of low quality.

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Introduction

As the elderly population increases, the prevalence of dementia also increases, provoking interest in the prevention of dementia and mild cognitive impairment (MCI) [1]. Mild cognitive impairment is a condition that occurs as a result of normal aging, an intermittent stage that may lead to mild dementia [2], identified by Petersen, a psychiatrist in the United States in 1966. A clinical study has shown that 44% of patients diagnosed with MCI developed dementia within 3 years [3]. Thus, the need for treatment of MCI is important to reduce the potential progression to dementia.

Currently there is no approved drug to treat MCI in Western medicine. Alzheimer’s drugs such as donepezil, rivastigmine, and cholinesterase inhibitors, have been evaluated as potential treatments for MCI in a number of clinical trials [4-6]. Alternatively, there are studies that suggest non-drug treatment, such as cognitive training or physical exercise therapy may be helpful [7,8], but further research is needed.

There is also no defined treatment for MCI in traditional oriental medicine [9,10], which have reportedly less side effects than Western drug treatment. Several randomized controlled trials (RCT) [11-31] have been reported where acupuncture treatment of MCI has been evaluated including systematic review [32-34]. However, in the study by Hu et al [32], EMBASE and Cochrane databases were absent. Studies by Mai and Zheng [33] and Wang...
also excluded EMBASE, and there were some inconsistencies
in the analysis. Among these systematic reviews, there were no
studies including Korean databases.

The purpose of this study was to investigate the effectiveness
of acupuncture treatment in MCI by using 6 online databases
including the Korean database and EMBASE (PubMed, Cochrane
Library, EMBASE, CNKI, NDSL, OASIS).

Materials and Methods

Data sources

To investigate the efficacy of acupuncture treatment of MCI,
database searches were performed to retrieve studies published
until September 30, 2018. The databases included were PubMed/
MEDLINE, Cochrane, EMBASE, the China National Knowledge
Infrastructure (CNKI) for international publications, the National
Digital Science Library (NDSL), and the Oriental Medicine
Advanced Searching Integrated System (OASIS) for Korean
publications.

Keywords were used for the database searches with minor
adjustments for each database: (“mild cognitive impairment”
or “cognitive dysfunction”), (“acupuncture” or “acupuncture
therapy” or “chiropractic” or “acupuncture points” or “acupuncture
analgesia” or “electroacupuncture” or “scalp acupuncture”)

Eligibility criteria

Inclusion criteria

RCTs were included that reported on acupuncture treatment of
patients with mild cognitive impairment, with no differentiation
placed on the method of acupuncture treatment. In addition,
there were no restrictions in the control group and on the year of
publication.

Exclusion criteria

Studies that were not RCT’s, case studies, systematic reviews,
literature reviews, articles, and protocols were all excluded.
Furthermore, vascular MCI, and MCI due to stroke or brain
damage were excluded. Studies with only abstracts available or
studies whose original text was unavailable, were also excluded.

Data collection and risk of bias

Studies that satisfied the inclusion criteria were selected
and 2 reviewers performed data extraction and assessment
independently. In cases of disagreement, the matter was reassessed
by a 3rd reviewer. The risk of bias in RCT’s was assessed using the
Cochrane risk of bias tool [35].

Results

A total of 359 studies were retrieved from 6 online databases
until September 30, 2018. Of the 359 articles retrieved, PubMed
had 50, Cochrane 55, EMBASE 42, CNKI 167, NDSL 40 and
OASIS 5. From the 359 studies, 62 duplicates were removed, along
with 205 non-related studies, and 24 non-clinical studies. Of the
68 studies remaining, 15 studies were excluded as they did not
have the original text, and 53 studies were excluded because 12
were not RCT, 2 were case studies, 6 were systematic reviews, 9
were literature reviews, 1 was an article, and 2 were protocols. This
provided a final study sample of 21 (Table 1; Fig. 1). All 21 studies
were published in China, of which 19 were in Chinese and 2 were
in English.

Year of publication

Analysis by year showed that 21 studies used acupuncture to
treat MCI from 2009 to 2017 (Fig. 2).
Table 1. Details of the Final Study Samples Included for Analysis.

<table>
<thead>
<tr>
<th>No. author (y)</th>
<th>N</th>
<th>Intervention</th>
<th>Control</th>
<th>Treatment No.</th>
<th>Period</th>
<th>Evaluation index</th>
<th>Result (A &gt; B, C, D)</th>
<th>Adverse events</th>
<th>Acupoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.Liu (2009)</td>
<td>26</td>
<td>A: Atx</td>
<td>B: W-med (n = 8)</td>
<td>30</td>
<td>30 d</td>
<td>1.ADL, 2.CDR, 3.MMSE, 4.CMS</td>
<td>1. p &lt; 0.05, 2.p &lt; 0.05, 3.p &lt; 0.05, 4.p &lt; 0.05</td>
<td>NR</td>
<td>Ex-HN1, HT7, GB20, BL23, K13, GB39</td>
</tr>
<tr>
<td>02.Sun (2009)</td>
<td>60</td>
<td>A: E-Atx + B</td>
<td>B: W-med (n = 30)</td>
<td>30</td>
<td>30 d</td>
<td>1.MMSE</td>
<td>1.p &lt; 0.01</td>
<td>NR</td>
<td>GV20, PC6, SP6</td>
</tr>
<tr>
<td>03.Wang (2009)</td>
<td>60</td>
<td>A: Atx</td>
<td>B: W-med (n = 30)</td>
<td>28</td>
<td>28 d</td>
<td>1.MMSE, 2.ADL, 3.TCM syndrome table</td>
<td>1. p &lt; 0.05, 2.p &lt; 0.05, 3.p &lt; 0.05</td>
<td>NR</td>
<td>GV20, Ex-HN1, GV24, GB20, BL23, K13</td>
</tr>
<tr>
<td>04.Zhang(2009)</td>
<td>60</td>
<td>A: Atx + B</td>
<td>B: W-med (n = 30)</td>
<td>30</td>
<td>30 d</td>
<td>1.MMSE, 2.MoCA</td>
<td>1.p &lt; 0.05</td>
<td>NR</td>
<td>GV20, GV24, ST8, PC6, SP6</td>
</tr>
<tr>
<td>05.Jin (2010)</td>
<td>30</td>
<td>A: E-Atx</td>
<td>B: W-med (n = 16)</td>
<td>45</td>
<td>45 d</td>
<td>1.CMS, 2.MoCA, 3.MRS</td>
<td>1.p &lt; 0.01, 2.p &lt; 0.01, 3.p &lt; 0.05</td>
<td>NR</td>
<td>Ex-HN1, BL23, GB20, K13</td>
</tr>
<tr>
<td>06.Liu (2010)</td>
<td>45</td>
<td>A: E-Atx</td>
<td>B: W-med (n = 19)</td>
<td>30</td>
<td>30 d</td>
<td>1.MMSE, 2.MoCA, 3.MRS</td>
<td>1.p &lt; 0.05</td>
<td>NR</td>
<td>Yu’s scalp clustering acupuncture</td>
</tr>
<tr>
<td>07.Wang (2010)</td>
<td>60</td>
<td>A: E-Atx + B</td>
<td>B: Cognitive training</td>
<td>48</td>
<td>56 d</td>
<td>1.MoCA</td>
<td>1.p &lt; 0.05</td>
<td>NR</td>
<td>Yu’s scalp clustering acupuncture</td>
</tr>
<tr>
<td>08.Wang (2011)</td>
<td>60</td>
<td>A: E-Atx + B</td>
<td>B: Cognitive training</td>
<td>48</td>
<td>56 d</td>
<td>1.MoCA</td>
<td>1.p &lt; 0.05</td>
<td>NR</td>
<td>Ex-HN1, GV20, GV24, GB20</td>
</tr>
<tr>
<td>09.Yu (2010)</td>
<td>112</td>
<td>A: E-Atx</td>
<td>B: W-med (n = 56)</td>
<td>24</td>
<td>56 d</td>
<td>1.MMSE, 2.WMS, 3.CDT</td>
<td>1.p &lt; 0.05, 2.p &lt; 0.01, 3.p &lt; 0.05</td>
<td>NR</td>
<td>Ex-HN1, GV20, GV24, GB20</td>
</tr>
<tr>
<td>10.Chen (2011)</td>
<td>252</td>
<td>A1: E-Atx</td>
<td>B: W-med (n = 84)</td>
<td>24</td>
<td>56 d</td>
<td>1.MMSE, 2.WMS, 3.CDT</td>
<td>1.p &lt; 0.05, 2.p &lt; 0.05, 3.p &lt; 0.05</td>
<td>NR</td>
<td>GV20, Ex-HN1, GB20, GV24</td>
</tr>
<tr>
<td>11.Li (2011)</td>
<td>60</td>
<td>A: E-Atx</td>
<td>B: W-med (n = 20)</td>
<td>24</td>
<td>28 d</td>
<td>1.MMSE, 2.MoCA, 3.ERP</td>
<td>1.p &lt; 0.05</td>
<td>NR</td>
<td>GV20, Ex-HN1, GB20, GV24</td>
</tr>
<tr>
<td>12.Li (2012)</td>
<td>60</td>
<td>A: E-Atx</td>
<td>B: W-med (n = 30)</td>
<td>28</td>
<td>28 d</td>
<td>1.MMSE, 2.MoCA, 3.ERP</td>
<td>1.p &lt; 0.05</td>
<td>NR</td>
<td>GV20, Ex-HN1, GB20, GV24</td>
</tr>
<tr>
<td>13.Zhang(2012)</td>
<td>120</td>
<td>A: E-Atx</td>
<td>B: W-med (n = 65)</td>
<td>10</td>
<td>3 mo</td>
<td>1.MoCA</td>
<td>1.p &lt; 0.01</td>
<td>NR</td>
<td>GV20, Ex-HN1</td>
</tr>
<tr>
<td>14.Zhao (2012)</td>
<td>60</td>
<td>A: E-Atx</td>
<td>B: W-med (n = 30)</td>
<td>32</td>
<td>56 d</td>
<td>1.MMSE, 2.MoCA, 3.ERP</td>
<td>1.p &lt; 0.05</td>
<td>NR</td>
<td>Ex-HN1, GB20, GV20, GB15</td>
</tr>
<tr>
<td>15.Zhang(2013)</td>
<td>252</td>
<td>A1: E-Atx</td>
<td>B: W-med (n = 75)</td>
<td>24</td>
<td>56 d</td>
<td>1.MMSE, 2.WMS, 3.CDT</td>
<td>1.p &lt; 0.01</td>
<td>NR</td>
<td>GV20, Ex-HN1, GB20, GV24</td>
</tr>
<tr>
<td>17.Wang (2015)</td>
<td>120</td>
<td>A: E-Atx</td>
<td>B: W-med (n = 30)</td>
<td>45</td>
<td>3 mo</td>
<td>1.MMSE</td>
<td>1.p &lt; 0.01</td>
<td>NR</td>
<td>GV20, GV24, GB41, EX-HN5, GB20</td>
</tr>
<tr>
<td>18.Li (2016)</td>
<td>60</td>
<td>A: E-Atx</td>
<td>B: W-med (n = 30)</td>
<td>45</td>
<td>3 mo</td>
<td>1.MMSE, 2.MoCA</td>
<td>1.p &lt; 0.01, 2.p &lt; 0.05</td>
<td>NR</td>
<td>GV20, GV24, GB15, GB17, GV20, EX-HN5, GB20</td>
</tr>
<tr>
<td>21.Tan (2017)</td>
<td>32</td>
<td>A: E-Atx</td>
<td>B: Sham Atx (n = 16)</td>
<td>20</td>
<td>28 d</td>
<td>1.MMSE, 2.MoCA</td>
<td>1.p &lt; 0.05</td>
<td>NR</td>
<td>Ex-HN1, DU29, PC6, K13, ST40, LR3</td>
</tr>
</tbody>
</table>

ADL, activities of daily living; Atx, acupuncture treatment; BDNF, brain derived neurotrophic factor; CDT, clock drawing test; CMD, Chinese medical diagnosis; CMS, clinical memory scale; C-med, Chinese medicine; ERP, event-related potentials; E-Atx, electric acupuncture treatment; MMSE, mini mental state examination; MoCA, Montreal cognitive assessment; MRS, magnetic resonance spectroscopy; n, sample size; NR, not reported; TCM, traditional Chinese medicine; WMS, Wechsler memory scale; W-med, western medicine / *Etc., Alzheimer’s disease assessment scale-cognitive (ADAS-Cog); Digit symbol task; digit span task; Word recall; fMRI, functional magnetic resonance imaging.
**Sample size of study**

The total number of patients in the experimental group and control groups was analyzed. Of the 21 studies, 5 studies (24%) had less than 50 patients, 11 studies (52%) had 50 to 100 patients, 3 studies (14%) had 100 to 200 patients, and 2 studies (10%) had more than 200 patients (Fig. 3).

**Treatment number of times and period**

The number of acupuncture treatments ranged from 10 to 48, with 24 and 30 treatments being the most common. When expressed as a range, there was 1 study (5%) with 10 to 20 treatments, 8 studies (38%) with 20 to 30 treatments, 6 studies (28%) with 30 to 40 treatments, and 6 studies (29%) with 40 to 50 treatments (Fig. 4).

The most frequent treatment period was 56 days which was observed in 7 studies (33%), This was followed by 28 days and 30 days which were used in 5 studies each (24%), 45 days in 1 study (5%), and 3 months in 3 studies (14%; Fig. 5).

**Evaluation index**

In a single study at least 1 evaluation indicator was used and at the most 7 were used. A total of 1,610 patients were evaluated for 16 evaluation indices, in a total of 21 studies. There were 17 studies that used the mini mental state examination (MMSE) as the evaluation index. There were 15 studies that used the Montreal cognitive assessment (MoCA), 4 studies that used the activities of daily living (ADL), 3 studies that used Wechsler memory scale (WMS), clock drawing test (CDT), magnetic resonance imaging (MRI), 2 studies that used event-related potentials (ERP), clinical memory scale (CMS), respectively, and 8 other evaluation indices were used once for each scoring scale (Fig. 6).

**Analysis of acupuncture treatment**

There were 17 studies that used acupoints and the most frequently used acupoint was Baihui (GV20), which was used in 14 studies. Sishencong (EX-HN 1) and Fengchi (GB20) were used in 11 studies, Shenting (GV24) in 10, Taixi (KI3) in 7, Shenyeu (BL23)
in 6, Neiguan (PC6) in 5, Xuanzhong (GB39) in 4, and Sanyijniao (SP6) and Taichong (LR3) were used in 3 studies. The acupoints were used 1 or 2 times, and over the course of treatment the acupoints were used 23 times in total (Fig. 7).

In the 17 studies that used acupoints, the needle retention times were 30 minutes in 10 studies, 20 minutes in 3 studies, 40 minutes in 3 studies and 6 hours in 1 study (Fig. 8).

There were 9 monotherapy groups in the treatment group, and 12 in the combination therapy group. In the monotherapy group, 6 studies used electroacupuncture, and 3 studies acupuncture alone. In the combination therapy group, 7 studies combined treatment with Western medicine, 3 with Chinese medicine, and 2 with cognitive training. Among the combination therapy group, 2 studies used electroacupuncture and 10 studies used acupuncture alone.

Treatment of control group

The most common control group was Western medicine which was used in 17 studies. There were 2 studies that used cognitive training as a control, 1 that used sham acupuncture as a control, and 1 that used acupuncture, Chinese medicine, western medicine respectively (Fig. 9).

Therapeutic effect

Efficacy of acupuncture treatment was measured in the 21 selected studies, the experimental and control groups (n = 47) were analyzed and evaluation indices in the acupuncture treated groups showed improvement after treatment in 13 studies, (3 studies showed that only the experimental group improved after treatment). The comparison between the experimental group and the control group was made to assess the therapeutic effects. In 16 studies, the experimental group showed a statistically significant improvement for each evaluation index compared to the control group. In the remaining 5 studies, Wang et al [13] showed that treatment with traditional Chinese medicine (TCM) when using the syndrome table, had a statistically significant beneficial effect in the experimental group compared to the control group, but there was no significant difference between the 2 groups when using the MMSE and the ADL evaluation indices. In the study by Liu et al [16], only the experimental group showed improvement after treatment when using the MMSE and MoCA evaluation indices, and there was a significant difference compared to the control group after treatment. However, in the NAA/Cr (left hippocampus), there was no significant difference between the 2 groups after treatment. In the NAA/Cr and the CHO/Cr (left temporal lobe), only the experimental group showed improvement after treatment. There was a significant difference between the 2 groups after treatment. In the study by Yu et al [19], the MMSE and the WMS evaluation indices showed improvement after treatment in both experimental and control groups. There was a significant difference between the 2 groups after treatment, but only the control group showed improvement in the CDT evaluation index after treatment. There was no significant difference between the 2 groups. In the study by Zhang et al [25], the MMSE and the CDT evaluation indices showed improvement after treatment in both experimental and control groups. There was a significant difference in the experimental group compared to the control group, but only in the experimental group was there improvement after treatment in the WMS evaluation index. There was a significant difference between the groups. In the study by Liu et al [30], the MMSE and the MoCA evaluation indices showed improvement after treatment in both experimental and control groups, and there was a significant difference in the experimental group compared to the control group, but in the Barthel evaluation index, there was no significant beneficial effect after treatment in both experimental and control groups.
**Adverse reaction**

None of the 21 studies reported any adverse reactions.

**Risk of bias assessment**

The risk of bias was assessed for 21 studies using Cochrane risk of bias tool (Figs. 10, 11).

**Random sequence generation**

Low risk was observed in 9 studies (43%) where 6 studies used a random number table, and 3 studies used computers for random sequence generation. In the remaining 12 studies (57%), the level of risk was unclear because of the random division of the group without description of the randomization method.

**Allocation concealment**

Low risk was observed in 2 studies (10%) which used sealed envelopes with serial numbers. The remaining 19 studies (90%) were classified as having an unclear risk because there was no mention of concealment or lack of judgment.

**Blinding of participant and personnel**

All 21 studies (100%) were categorized as high risk because the studies were not blinded, due to the characteristics of acupuncture treatment.

**Blinding of outcome assessment**

Four studies (19%) were classified as low risk because of the presence of a separate evaluator and blinding of the study. In the other 17 studies (81%), all of them were classified as unclear risk because there was no mention of blinding of outcome assessment.

**Incomplete outcome data**

Low risk was observed in 18 studies (86%) where there were 4 studies with incomplete outcome data, but these 4 studies did not affect the outcome significantly, and there were 14 studies that had complete data. High risk was observed in 2 studies (10%), and it was judged that the incomplete data outcome could affect the results because there was no mention that it did not significantly affect the outcome. Unclear risk was observed in 1 study (5%), which stated that they did not know if there was an incomplete outcome.

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Fig. 10. Risk of RCT bias. RCT, randomized controlled trial.

![Risk of RCT bias](image)

Fig. 11. Risk of RCT bias summary. (+): Low risk of bias, (-): High risk of bias, (?) : Unclear of risk. RCT, randomized controlled trial.
Selective reporting
All 21 studies (100%) were categorized as unclear risk because there was no report of protocols and predefined plans.

Other bias
High risk was observed in 5 studies (24%). Among them, 1 study found that the number of patients initially recruited, and the number of patients assigned to the experimental group and the control group did not match, and there was no mention of the cause. There were 4 studies, which did not report the needle retention time, and were classified as high risk because it was considered that there was potential bias. In the remaining 16 studies (76%), the possibility of additional bias was not found and were classified as low risk.

Discussion
To evaluate the efficacy of acupuncture treatment for MCI, 6 online databases were searched and 21 RCT’s were selected for systematic review. All 21 studies were published in China, of which 19 were in Chinese and 2 in English. The largest sample size range was 50 to 100, all of which was 60 patients, accounting for 52% of all RCT studies. The largest number of treatment times range was 20 to 30, accounting for 38% of all studies. The highest number of treatments was 24 and 30. The longest treatment period was 56 days, which accounted 33% of the RCT’s. The results of these RCT’s suggests that acupuncture treatment performed 3 or 4 times per week may have a beneficial therapeutic effect against MCI.

A total of 1,610 patients were evaluated using 16 indices across 21 studies. The most frequently used evaluation was the MMSE, followed by the MoCA where each was used 17 and 15 times, respectively. This implies that the MMSE and the MoCA were the most common measures to evaluate the acupuncture treatment of MCI. In the 17 studies that used acupoint the most commonly used acupoint was Baihui (GV20), which was used 14 times. Sishencong (EX-HN 1) and Fengchi (GB20) were used 11 times. Shenting (GV24) was used 10 times. These 4 acupoints accounted for 46 out of 97 times (47%) acupoints, implying that these 4 acupoints were commonly used and were thought to have a more beneficial therapeutic effect than other acupoints. In these 17 studies, 10 selected the needle retention times as 30 minutes which was the longest time period over the total 17 RCT’s. Therefore, it was the most common retention time and may be the most effective time for acupuncture treatment. There were 9 monotherapy treatment groups, and 12 combination therapy groups. In the monotherapy group, 6 studies used electroacupuncture, 3 studies used only acupuncture. In the combination therapy group, 7 studies combined treatment with Western medicine, 3 with Chinese medicine, and 2 with cognitive training. Among the combination therapy groups, 2 studies used electroacupuncture, 10 studies used only acupuncture. In the control group setting, it was observed that 17 of the studies used Western medicine to determine the efficacy of acupuncture treatment of MCI. In the 21 studies, the experimental group and the control group were compared. In each evaluation index of 16 studies, the experimental group showed a statistically significant difference compared with the control group, indicating that acupuncture treatment was a beneficial treatment for MCI. In the remaining 5 studies, the difference between the control group and the treatment group was not statistically significant for each evaluation index tested.

There were no reports of adverse reactions in any of the 21 studies suggesting that acupuncture treatment was a safe treatment for MCI.

Bias is a systematic error where the findings have deviated from the true value of the outcome or estimation. Understanding bias may reveal an underestimation or overestimation of the intervention effect. In this study, the risk of bias was evaluated in 7 areas using Cochrane's risk of bias (RoB) tool [35] (random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias). The overall risk assessment of bias was unclear for most of the 21 studies. Only 9 out of 21 studies described random sequence generation, and only 2 studies described allocation concealment. Blinding of either patient and staff was difficult due to the nature of acupuncture treatment. Selective reporting areas were not mentioned in all studies. Analysis of bias risk showed that in most studies, explanations of research methods were overly concise, or not even described in the random sequence generation, allocation concealment or selective reporting area and so bias could not be avoided. These results suggested that researchers require greater awareness of bias when conducting RCT’s. Thus, in order to demonstrate the efficacy of acupuncture treatment for MCI, improved design of clinical studies with low bias will be required by referring to RCT guidelines such as CONSORT 2010 [36]. However, there is a limit to effectively designing a blinded trial due to the interventional nature of acupuncture treatment, therefore future research will be needed to improve study designs and controls for acupuncture research studies.

In conclusion, these results suggest that acupuncture treatment for MCI was effective and statistically significantly different to the control group, such as Western medicine or cognitive training. However, the quality of most of the studies was low.

Conflicts of Interest
The authors have no conflicts of interest to declare.

Acknowledgments
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