LITERATURE WATCH

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The comparative efficacy of multiple interventions for mild cognitive impairment in Alzheimer’s disease: a Bayesian network meta-analysis.
Lai X, Wen H, Li Y, Lu L, Tang C. Front Aging Neurosci. 2020;12:121.

Mild cognitive impairment (MCI) is the early phase of Alzheimer’s disease (AD). The aim of early intervention for MCI is to decrease the rate of conversion from MCI to AD. However, the efficacy of multiple interventions for MCI and the optimal methods of delivery remain controversial. Researchers from the Guangzhou University of Chinese Medicine compared and ranked treatment methods for MCI in AD, with the goal of finding an optimal intervention for MCI and a way to prevent or delay the occurrence of AD. Pairwise and network meta-analyses were conducted to integrate treatment effectiveness through direct and indirect evidence. Four English databases and 3 Chinese databases were searched for international registers of eligible published, single- or double blinded, randomized controlled trials up to September 31, 2019. Nine comparative interventions were included: pharmacologic therapies that incorporated cholinesterase inhibitors (ChEI), ginkgo (Ginkgo biloba), nimodipine, and Chinese Medicine (CM); nonpharmacologic therapies comprising acupuncture, music therapy, exercise therapy, and nutrition therapy; and a placebo group.

The primary outcome was the Mini-Mental State Examination (MMSE) score. The secondary outcome was the AD Assessment Scale—cognitive subscale (ADAS-cog). Twenty-eight trials were eligible, with a total of 6863 participants. In the direct meta-analysis of the MMSE scores, ChEIs (mean difference [MD]: −0.38; 95% confidence interval [CI]: −0.74, −0.01), CM (MD: −0.31; 95% CI: −0.75, 0.13), exercise therapy (MD: −0.50; 95% CI: −0.65, −0.35), and music therapy (MD: −1.71; 95% CI: −4.49, 1.07) were statistically more efficient than placebo. For the ADAS-cog outcomes, acupuncture (MD: 1.20; 95% CI: 0.73, 1.68), acupuncture (MD: 1.36; 95% CI: 1.28, 1.44), CM (MD: 0.61; 95% CI: 0.49, 0.73), and exercise (MD: 0.61; 95% CI: 0.49, 0.73) were better than placebo. In the network meta-analysis, the MMSE outcome ranked music therapy (59%) as the best and acupuncture (26%) as second-best. Nutrition and ginkgo treatment had the lowest ranks among all the interventions. For the ADAS-cog outcomes, acupuncture (52) was ranked the best. Among the 9 treatments studied, music therapy appeared to be the best treatment for MCI, followed by acupuncture.

This study provided new insights into potential clinical treatments for MCI due to AD, and could aid the development of guidelines for MCI in AD.

Purinergic signaling as a basis of acupuncture-induced analgesia.
He JR, Yu SG, Tang Y, Illes P. Purinergic Signal. 2020;10.1007/s11302-020-09708-z.

This review by researchers from the Chengdu University of Traditional Chinese Medicine, in China, and the University of Leipzig, in Germany, summarized experimental evidence indicating that purinergic mechanisms are causally involved in acupuncture-induced analgesia. At pain-relevant acupoints, electroacupuncture (EA) and manual acupuncture release adenosine triphosphate (ATP), which might activate purinergic P2X receptors (Rs) especially of the P2X3-type situated at local sensory nerve endings (peripheral terminals of dorsal-root ganglion [DRG] neurons). Via collaterals of ascending dorsal-horn spinal-cord neurons, the central processes of these neurons are thought to inhibit pain-relevant pathways projecting to the higher centers of the brain. In addition, during acupuncture/EAnonneuronal P2X4 and/or P2X7Rs localized at microglial cells of the central nervous system become activated at spinal or supraspinal levels. Thus, these microglia secrete bioactive compounds, such as growth factors, cytokines, chemokines, reactive oxygen species, and nitrogen species, which modulate the ascending neuronal pathways conducting painful stimuli.

Alternatively, ATP released at acupoints by acupuncture/EA might be enzymatically degraded to adenosine, stimulating in loco presynaptic A1Rs exerting an inhibitory influence on the primary afferent fibers (the abovementioned...
pain-sensing peripheral terminals of DRG neurons), which thereby fail to conduct action potentials to the spinal cord’s dorsal horn. The net effect of stimulating \( P2X3, P2X4, P2X7 \), and A1Rs by acupuncture/EA-induced release of ATP/adenosine at certain acupoints is analgesia.

Transcutaneous electrical acupoint stimulation for stage 1 hypertension: protocol for a randomized controlled pilot trial.

Tian ZX, Liu CZ, Qi YS, et al. Trials. 2020;21(1):558.

Hypertension is a major pathogenic factor of cardiovascular diseases. Insufficient blood pressure (BP) control rate and suboptimal medication adherence remain challenges for effective management of hypertension. Transcutaneous electrical acupoint stimulation (TEAS) has been used to treat various diseases, including hypertension, but the scientific evidence for TEAS’ benefit remains insufficient.

Researchers from Beijing will perform a randomized, controlled clinical trial in patients with stage 1 hypertension to evaluate the effect of TEAS. The study will be a 2-arm, parallel, randomized controlled trial (RCT). Sixty patients with stage 1 hypertension will be randomly assigned to a TEAS group or a control group in a 1:1 ratio. The participants in the TEAS group will receive noninvasive acupoint electrical stimulation for 30 minutes at 4 acupoints in the upper and lower extremities at home, 4 times per week, for 12 weeks, for a total of 48 sessions. Participants in the control group will not receive any form of acupoint stimulation. All participants in both groups will receive lifestyle education on how to control high BP, including diet, weight control, and exercise.

The primary outcome measure will be the change of the mean systolic BP from baseline to 12 weeks. Secondary outcomes will include the change of mean diastolic BP, quality of life, body mass index, and physical activity level. This pilot RCT will explore the feasibility of TEAS. The trial is expected to also provide potential clinical evidence for the efficacy and safety of TEAS for treating stage 1 hypertension. The results of this study will be published in peer-reviewed journals. Furthermore, this pilot trial, as the precursor of a large-scale RCT will reveal the sample size needed for a subsequent trial.

Trial registration: Chinese Clinical Trial Registry, ChiCTR1900025042. Registered on August 8, 2019.

Effects of acupuncture on cardiovascular risks in patients with hypertension: a Korean cohort study.

Jung H, Yeo S, Lim S. Acupunct Med. 2020;6(6):96452842092 0290.

The aim of this study was to investigate the effects of acupuncture on major adverse cardiovascular events, myocardial infarction, stroke, and death in patients taking antihypertensives. Using the Korean National Health Insurance Service—National Sample Cohort (NHIS-NSC) database, this study identified 59,370 patients taking antihypertensives who had been diagnosed with hypertension between 2003 and 2006.

The patients were divided into acupuncture and non-acupuncture groups. The follow-up period for each patient ended with the diagnosis of myocardial infarction, stroke, or death. After propensity score matching (PSM), there were 18,011 patients in each group. The researchers calculated the incidence rate, hazard ratio (HR) and 95% confidence interval (CI) for major adverse cardiovascular events, myocardial infarction, stroke, and death in patients with hypertension, using a stratified Cox proportional hazard model. Secondary outcome analyses for stroke and cardiovascular mortality were also performed.

After PSM, the HRs for major adverse cardiovascular events (0.83; 95% CI: 0.80–0.86), all-cause mortality (0.73; 95% CI: 0.70–0.76), and myocardial infarction (0.85; 95% CI: 0.79–0.92) were significantly lower in the acupuncture group than in the nonacupuncture group. Moreover, the HRs for stroke-related mortality, hemorrhage stroke–related mortality, ischemic stroke–related mortality, ischemic heart disease–related mortality and circulatory system disease–related mortality were significantly lower in the acupuncture group than in the nonacupuncture group.

This observational study, with its long-term follow-up, extended the evidence base to support the effectiveness of acupuncture for managing hypertension and potentially reducing the burden of cardiovascular disease.

Analysis on the theory and clinical ideas of acupuncture and moxibustion for the prevention and treatment of coronavirus disease 2019.

Liu B, Wang H, Zhou ZY, Chang XR, Zhang W, Liu BY. Zhongguo Zhen Jiu. 2020;40(6):571–575.

Acupuncture and moxibustion have a wealth of experience in prevention and control of epidemic diseases since ancient times. These modalities have also been used to address all kinds of acute infectious diseases in modern times, and the efficacy of these modalities has been reported clearly and reliably. This article proposed the theoretical feasibility and reliability of acupuncture and moxibustion interventional prevention and treatment, discussing the recognition of coronavirus disease 2019 (COVID-19) from the perspectives of acupuncture and moxibustion. A unique “acupuncture and moxibustion program” for addressing COVID-19 was presented, including treatment at different stages, selecting acupoints by distinguishing meridians, and applying needle techniques by various methods.

This article also offered a new understanding of acupuncture and moxibustion at related acupoints on the surface of the body that can affect the “moyuan” to treat the disease directly.
Do acupuncture trials have lower risk of bias over the last five decades? A methodological study of 4715 randomized controlled trials.

Long Y, Chen R, Guo Q, Luo S, Huang J, Du L. PLoS One. 2020;15(6):e0234491.

The aim of this study was to evaluate changes in risk of bias of acupuncture randomized controlled trials (RCTs) in the past 5 decades. Multiple databases were searched. The researchers included RCTs identified from systematic reviews of acupuncture. General characteristics and risk-of-bias judgments for each domain were extracted. The proportions of RCTs at high and unclear risks of bias were calculated, and the changes were examined by the Mann–Kendall test.

The researchers included 368 systematic reviews, encompassing 4715 RCTs. The rates of RCTs at unclear risk of bias were the highest in allocation concealment (63%) and the lowest in incomplete outcome data (35%). In the last 5 decades, statistically significant reductions were found for random sequence generation (P < 0.001) and selective reporting (P = 0.01), and increases for blinding of participants and personnel (P < 0.001), blinding of outcome assessment (P < 0.001), and incomplete outcome data (P = 0.04). For the proportions of RCTs at high risk of bias, blinding of participants and personnel (47%), and blinding of outcome assessment (35%) were the poorest domains. There were no significant differences in changes for all domains.

Although improvements concerning unclear risk were noted for random sequence generation and selective reporting, major issues remain for allocation concealment and blinding. It is imperative to use valid randomization, specify how it is conducted, and try to test for selection bias and the success of masking by using the Berger–Exner test.

An evidence mapping and analysis of registered COVID-19 clinical trials in China.

Lu L, Li F, Wen H, et al. BMC Med. 2020;18(1):167.

This article summarized the key characteristics of registered trials of 2019 novel coronavirus (COVID-19), in terms of their spatial and temporal distributions, types of design and interventions, and patients’ characteristics among other factors. A comprehensive search of registered COVID-19 trials was performed on platforms, including the ClinicalTrials.gov, World Health Organisation–International Clinical Trials Registry Platform (WHO-ICTRP), Chinese Clinical Trials Registry (ChiCTR), Australian Clinical Trials Registry, Britain’s National Research Register (BNRR), Current Control Trials (CCT), and GlaxoSmithKline Register.

Trials registered at the first 8 weeks of the COVID-19 outbreak were included, without language restrictions. For each study, the registration information, study design, and administrator information were collected and summarized. A total of 220 registered trials were evaluated as of February 27, 2020 from researchers from China and the United States. Hospital-initiated trials were the majority and accounted for 80% of the sample. Among the trials, pilot studies and phase 4 trials were more common and represented 35% and 19.1% of the sample, respectively. The median sample size of the registered trials was 100, with an interquartile range of 60–240. Furthermore, 45.9% of the trials mentioned information on a data-monitoring committee, and 54.5% of the trials did not specify disease severity among patients they intended to recruit.

Four types of interventions were most common in the experimental groups across the registered studies: antiviral drugs; Traditional Chinese Medicine (TCM); biologic agents; and hormone drugs. Among these interventions, TCM and biologic agents were frequently used in pilot studies and corresponded to a variety of primary endpoints. In contrast, trials with antiviral drugs had more targeted primary outcomes such as “COVID-19 nucleic acid test” and “28-day mortality.” The researchers provided evidence mapping and analysis of registered COVID-19 clinical trials in China.

In particular, it is critical for ongoing and future studies to refine their research hypotheses, and identify their intervention therapies and their corresponding primary outcomes better. It is also imperative for multiple public health divisions and research institutions to work together for integrative clinical data capture and sharing, with a common objective of improving future studies to evaluate COVID-19 interventions.

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