Workshop report

Translating Fundamental Science of Acupuncture into Clinical Practice

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Received March 10, 2019; Accepted March 26, 2019

The National Center for Complementary and Integrative Health (NCCIH) organized a 2-day workshop "Translating Fundamental Science of Acupuncture into Clinical Practice", at the National Library of Medicine, Bethesda, MD, from February 11-12, 2019. The workshop began with an overview by Dr. Helene Langevin, the director of NCCIH, focused 1) specific effect of the acupuncture intervention: neural mechanism and pathways, 2) non-specific effect of the acupuncture intervention, and 3) overcome the barriers of clinical research of acupuncture. Here we summarize the brief information on this workshop.

Specific effect of acupuncture: neural mechanism and pathways

The effect of acupuncture on reducing pain has a neural basis. Qiufu Ma, Dana Farber Cancer Institute at Harvard Medical School, gave a keynote speech on *mapping neural circuits and the neural basis of acupuncture*. Ma presented his recent work on the characterization of sensory pathways that drive the reflexive-defensive reactions to external threats and coping behaviors associated with ongoing pain, and the pathways may drive different autonomic reflexes in response to acupuncture.

Electro acupuncture (EA) may have effects on reducing pain caused by alcohol withdrawal. A study by Jiang-Hong Ye suggests that EA can alleviate hyperalgesia during alcohol withdrawal through a mechanism involving Mu Opioid Receptors (MORs) in the habenula; and EA could be of the potential treatment of hyperalgesia in alcohol dependence.

However, the effect of acupuncture may be varying with types of pain. Chronic pain biotypes predict differential analgesic response to verum and sham acupuncture. Because that not all patients with chronic pain and a given diagnosis have the same underlying pathophysiology, the existing pharmacologic and non-pharmacologic treatments are only effective for 30-40% of patients with fibromyalgia (FM), a widespread pain condition. Rick Harris from the University of Michigan presented data suggesting that the quantitative sensory testing and needling sensations at baseline can be used to identify different biotypes of patients with FM that respond differentially to sham and verum acupuncture. More sensitive patients with FM respond better to sham acupuncture; whereas less sensitive patients respond better to verum. This baseline information could be very useful for a personalized approach to the treatment of chronic pain with acupuncture. Following this talk, Jun Mao, from the Memorial Sloan Kettering Cancer Center, gave a presentation on "oncology acupuncture: precision medicine meets patient-centered care".

Lastly, in this session, Weidong Lu discussed his pilot study of a randomized clinical trial with examining the molecular mechanism and pathways through which the acupuncture may act, in the treatment of taxane-related chemotherapy-induced peripheral neuropathy (CIPN) in breast cancer. Their data suggest that increases of STATI and NF-kB expression levels in the pre-acupuncture are associated with degrees of neuropathic pain and sensory loss in breast cancer patients with CIPN. The percentage decrease in the levels of STAT1 expression was 56% in the acupuncture arm and 24% in the control arm, suggesting the involvement of transcription factors and inflammatory signaling pathways in the development of CIPN and the potential therapeutic role of acupuncture in the treatment of CIPN. He concluded that acupuncture may reduce CIPN related neuropathic pain by suppressing inflammatory signaling pathways and attenuating the over-expression of TRPV I receptors to alter the axon-degenerative process. Future research should continue to explore CIPN related molecular signaling pathways including TRPVI in humans and clinical conditions undergoing acupuncture stimulation.

Specific effect of the intervention: extra-neural mechanism and pathways

There might be some extra-neural mechanisms and pathways that explain the effect of acupuncture intervention on pain. These may include the glymphatic system, biophysical model and connective tissues, neuroinflammation, and endocrine and metabolic regulation. In session II, Maiken Nedergaard gave a keynote speech on the *glym-phatic system and pain*; and Helene Langevin discussed the biophysical model and connective tissues.

Rurong Ji, from Duke University, presented on the modulation of neuroinflammation and neuropathic pain by electroacupuncture. Increasing evidence suggests that neuroinflammation in the peripheral nervous system such as dorsal root ganglion (DRG) plays a more critical role in the pathogenesis of CIPN. Paclitaxel treatment induces not only neuropathic pain symptom but also cause sex-dependent neuroinflammation in DRGs, including infiltration and activation of macrophages and T cells and associated increases in the proinflammatory cytokines (e.g., IL-1β and IL-17). However, Electro-acupuncture (EA) at hindpaw acupoints in lightly anesthetized mice, before paclitaxel injecttion, effectively prevented the development of neuropathic pain (mechanical allodynia) and reduced the signs of neuroinflammation; and auricular EA stimulation was also effective in preventing the development of CIPN. In contrast, post-treatment of hEA after the development of CIPN did not reverse the established neuropathic pain. Ji presented a study showing that EA treatment during the early phase development of CIPN may be able to prevent or delay CIPN in cancer patients. Mechanistically, EA promotes the

resolution of neuroinflammation in part by increasing the production of specialized pro-solving mediators (SPMs).

Suzanna Zick discussed mechanistic clinical studies of chronic pain and cancer-related fatigue. In the presentation, Zick showed evidence from their studies examining inflammatory markers, spectroscopy, and connectivity in fatigued and non-fatigued, self-acupressure in breast cancer survivors and other acupuncture research to probe the usefulness and validity of this model. Future directions for which peripheral markers may prove useful in future human research. In addition, Elisabet Stener-Victorin from Karolinska Institutet gave a talk through video conference on acupuncture for Infertility in women with polycystic ovary syndrome.

Non-specific effects of the acupuncture interventions

Ted Kaptchuk, from Harvard Medical School, talked about "Placebo effects of acupuncture: clinical and genomic findings". Placebo effects are rarely mentioned in the classical East Asian or Chinese medicine. Acupuncture is believed to be effective based on the observation of individual patients report before and after treatment. He discussed the existing evidence of placebo acupuncture including the genetics of placebo acupuncture. Effective strategies to separate acupuncture from placebo effects are still an active concern in research.

Neuroimaging is used to examine the effect of acupuncture. One talk by Jian Kong focused on neuroimaging study of placebo effect of acupuncture; a talk by Vitaly Napadow was about "brain concordance supports patient/acupuncturist therapeutic alliance and modulates analgesia" based on a hyperscan functional magnetic resonance imaging (fMRI) approach.

Overcoming Barriers for Clinical Research of Acupuncture

This session began with a talk by Hugh MacPherson, from University of York in U.K, on the challenge of evaluating specific and non-specific effects in clinical trials of acupuncture.

Richard Niemtzow discussed how to overcome the barriers of acupuncture research for both clinician and researchers. The selected acupuncture procedure should be evidence-based, safe, and has the potential to demonstrate its value in achieving desired outcomes based on evaluating reviews, trials, and practical clinical experience.

Paul Crawford discussed how to the propagation of acupuncture research findings by creating teams of clinicians and scientists to achieve the next level. First, pain is the most common complaint/symptoms for which individuals seek outpatient care in the United States. It is surprising to know that medical care for the 50 million patients with chronic patients and secondary disability exceeds $ 100 billion annually. Despite significant demand for chronic pain management, pain care in the United States is highly variable. In addition, studies have demonstrated that acupuncture effective at treating chronic pain, and patients treated with acupuncture use less opioid. While this is encouraging, the mechanism of this reduction in opioid use is not clear. Understanding this mechanism could lead to some breakthrough in discovering novel pharmacological and non-pharmacological treatment of pain. To achieve this, it requires collaboration between clinicians and scientist. Finally he pointed out that a standardized protocol is needed to be developed for the purpose of a mechanistic study.

Songping Han, Peking University, presented "acupuncture and related techniques for pain relief and treatment of heroin addiction: mechanisms and clinical application." The vast amount of evidence suggests that primary afferent fibers, the descending inhibitory pathways and the central opioid peptides mediate the effect of acupuncture; and EA treatment has profound therapeutic effects on acute withdrawal syndrome in heroin addicts. Han pointed out the over-expression of cholecystokinin octapeptide in the CNS may be the mechanisms of acupuncture tolerance caused by frequent and prolonged EA treatments. It may also be responsible for the non-responders to EA treatment observed in clinical settings.

Rosa Schnyer presented that important insights can be derived from the clinical practice of acupuncture to inform the design of clinical trials. A bidirectional approach to a translational research strategy highlights critical gaps in building an acupuncture evidence framework. The gaps include the need for early phase research, standards to optimize the selection. Implementation and delivery of treatment protocols, more precise articulation of research questions and inclusion of hypothesis-driven secondary outcomes that better assess the impact of acupuncture in improving the patient's capacity to manage a specific condition.

Gary Deng, from the Memorial Sloan Kettering Cancer Center, presented a study of "reduction of opioid use by acupuncture during hematopoietic stem cell transplantation (HSCT): a randomized controlled trial." Adult patients with multiple myeloma undergoing high dose melphalan followed by autologous peripheral blood HSCT were randomized to receive either true (TA) or sham acupuncture (SA) once daily for five days starting on the gay luC'5 15 and 30 days after chemotherapy. Pain scores and use of pain medications were assessed at baseline, day 5, 15, and 30 days after transplantation. The HSCT team, patients and outcome evaluators were blinded to group assignment.

The study shows that among 60 evaluable participants, pain scores did not differ between the two groups at day 5, 15 and 30. Patients who received SA had more than fivefold odds of increasing pain medications from the baseline compared with those who received TA (OR=5.31, 95% CL: 1.35-20.93; p=0.017). Of patients who were opioid non-users at baseline, all 15 patients in the TA group remained free from opioids at the end of the study. In contrast, 20% (4 of the 20 patients) of those in the SA group started to use opioids after chemotherapy and stem cell infusion (Day 5)and 40%(8 of the 20)had become opioid users by Day30 after HSCT(Fisher exact test; p=0.006).

They conclude that true acupuncture was associated with reduced use of pain medications and prevented opioid non-users from using opioids after HSCT when compared to sham acupuncture. These findings need warrant a fur-

ther study.

Wenli Liu, from MD Anderson Cancer Center, discussed the gaps between acupuncture research and clinical practice. Liu discussed several potential issues that are very helpful in developing research protocols for conduct research on acupuncture. 1) there are gaps in translating evidence into specific and clear clinical practice; and methodological heterogeneity in acupuncture research is a significant contributor to the often inconsistent findings; 2) besides the biologic mechanism of acupuncture effect, the lack of understanding of the relationship between the defined syndromes within TCM might also contribute to differences in acupuncture approaches (i.e., point selection) in research design; 3)TCM diagnosis may be predictive of acupuncture response, and choosing appropriate comparison has been a significant barrier for acupuncture research. For example, sham acupuncture (SA) as a placebo control for real acupuncture (RA) has been considered less physiologically active than the real treatment but may not be inert; SA technique cannot be blinded to acupuncturists and may not be indistinguishable to participants who have received previous acupuncture; many others such as the number of needles to use, needle size, and level of insertion, intensity, and type of needle stimulation, retention time, and freque-cy and duration of treatments, differ among research designs; all these can contribute to divergent research findings.

Liu also suggests to improve the understanding of the relationship of the physiological and pathophysiological foundation of TCM diagnostics with those of the modern conventional medicine, which help clearly define TCM diagnoses; and evaluating the efficacy in comparison with other medications, physical therapy, and mind and body modalities that are considered the standard of care or appropriate alternatives.

Jiang-Ti Kong, Stanford University, presented preliminary results from two parallel, randomized, controlled clinical trials examining verum and sham electro acupuncture in the treatment of chronic low back pain. With 200 patients recruited from the San Francisco Bay Area, the study examined the clinical outcomes in both pain and function, and, more importantly, central pain regulatory mechanisms of electro-acupuncture approximated by quantitative sensory testing. Finally, taking advantage of 2 independent but similar clinical trials conducted around the same time, Kong developed and validated a prediction algorithm using data reduction techniques from machine learning on a large number of baseline for predicting the outcome.

Finally, a panel discussion was moderated by a group of panelists of Hugh MacPherson, Gary Deng, Wenli Liu, Jiang-Ti Kong, Baoyan Liu, Xianghong Jing, Bingmei Zhu, which focused on 1) Redefine the scope and recommendations; 2) Key barriers and building blocks for clinical trial studies of acupuncture; and key issues – blinding; specific vs. non-specific effects. In concluding the session, Dr. Helene Langevin introduced NIH Resources to support acupuncture research; Marge Good presented National Cancer Institute Clinical Trial Resources, and Linda Porter from National Institute of Neurological Disorder and Stroke (NINDS) introduced HEAL (help to end addition long-term) Initiatives Pain Basic Research Resources and Clinical Trial Networks.

How to cite this article:
Yeh H and Huang J. Translating Fundamental Science of Acupuncture into Clinical Practice. Glob Clin Transl Res. 2019; 1 (2):59-61.

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