

The Role of Perioperative Acupoint Stimulation in the Prevention of Postoperative Cognitive Dysfunction

Shuai Yuan, and Jian-Bo Yu

ABSTRACT

From Department of Anesthesiology, Tianjin Nankai Hospital, Tianjin Medical University, Tianjin, China.

Correspondence to Dr. Jian-Bo Yu at jianboyu99@sina.com

Citation: Shuai Yuan, Jian-Bo Yu. The role of perioperative acupoint stimulation in the prevention of postoperative cognitive dysfunction. *J Anesth Perioper Med* 2016; 3: 220-4.

Aim of review: In elderly population, postoperative cognitive dysfunction (POCD) is a common complication following surgical procedures. In this article, we reviewed the research progress of POCD in the field of traditional Chinese and Western medicine and improved the understanding on the prevention of POCD by perioperative acupoint stimulation so that better perioperative management of patients with risk factors can be achieved.

Method: We first described the concept of POCD, subsequently, reviewed the recent literatures on the effect and potential mechanisms of acupoint stimulation, especially some of the new transcutaneous electrical acupoint stimulation (TEAS) strategies that may be implemented to prevent POCD.

Recent findings: Perioperative acupoint stimulation have been proven to be related to the improving of blood perfusion of brain and further strengthen the microcirculation and metabolism, and it can also exert anti-inflammation effects and change metabolism of glucose and oxygen in the brain, which can be seen as the evidence for acupoint stimulation to improve POCD under the limited researches yet.

Summary: Perioperative acupoint stimulation could exert prevention effects on POCD, but further studies are still needed to further elaborate on its potential mechanisms and transfer convincing experimental evidences into clinical therapies.

Postoperative cognitive dysfunction (POCD) is a common surgical complication which is more likely to appear in the geriatric population. Over the last a few decades, much progress in the field of both traditional Chinese and western medicine showed that perioperative acupoint stimulation therapy has effects on both reducing the dosage of anesthetics and preventing POCD in patients (1-4). We will review the causes, diagnosis and prevention strategies of POCD, and make recommendations regarding the approach of perioperative acupoint stimulation on at-risk patients to minimize the incidence of POCD in this article.

An Overview of POCD

In 1955, Based on an analysis of 1193 elderly patients, Bedford (5) found that no less than one-third of them behaved as having a cognitive dysfunction or varying degrees of dementia after undergoing a surgery. Since then, this kind of frequent neurological complication which may cause the damage of a wide variety of cognitive functions, such as memory, attention, speed of information processing, executive function and comprehension skill, has been named POCD (6, 7).

The clinical manifestations of POCD

are quite diverse, and till now, the definite mechanisms whereby surgical procedures and general anesthesia contribute to POCD are currently poorly understood. What can be ensured is that risk factors for the development of POCD include but not limited to three major aspects: patients' physical conditions, surgical procedures and general anesthesia (8). Besides, although aging itself is not regarded as a kind of disease, but it is already universally accepted as an independent risk factor of POCD (9).

Dokkedal (10) proposed that POCD could be diagnosed by a test battery, which contain the following five components: 1) the fluency in category, recitation digit span by both; 2) forward and; 3) backward, recall a 12-items list; 4) immediate and; 5) delayed. There are also some more kinds of examinations such as Mini-Mental State Examination (MMSE), Wechsler Memory Seale (WMS) and Minnesota Multiphasic Personality Inventory (MMPI), while Saczynski (11) pointed that Montreal Cognitive Assessment (MoCA) shows more sensitivity than MMSE in the assessment of advanced cognitive function.

Traditionally, β -amyloid ($A\beta$) is seemed to be a kind of biochemical marker which can be used in the diagnosis of Alzheimer's disease (AD). However, the research performed by Evered suggested that some anesthetic agents may increase the risk of AD in susceptible patients, which made biomarkers of AD have been found to be altered after anesthesia and surgery, highlighting the possible role of cerebrospinal fluid (CSF) biomarkers in predicting POCD in different surgical settings (12). Some other researchers fingered out that several kinds of biochemical markers which are interrelated to inflammation have contact with POCD as well. For example, the one who has a low preoperative density of immunoglobulin M (IgM), the possibility for him to emerge from POCD is significantly increased (13). S100A8 protein can stimulate NF-kappaB signaling pathway and change the expression of genes to raise the content of tumor necrosis factor- α (TNF- α) and interleukin- 1β (IL- 1β) by the activation of Toll-like receptor 4 (TLR4). The result of changing this pathway will be the promotion of inflammation of the nervous system and finally developing POCD (14, 15).

Several decades have already passed since the first time POCD got its name, but nowadays, we still have not defined its causes completely. Based on our limited understanding of POCD, some anesthesiologist found that instead of general anesthesia, continuous epidural anesthesia or anesthetizing under bispectral index (BIS) monitoring to reduce the dose of anesthetic drugs may have a positive effect on prevention of POCD (16, 17). In animal experiments, the complying of preoperative environmental enrichment (PEE) showed improved results of abnormal object recognition test and also prevented the progress of inflammation, showing that the more external stimulation the brain received, the less chance it had to occur POCD (18).

Acupoint Stimulation in Traditional Chinese Medicine and POCD

With less progress on their own way, some researchers set their sights on traditional Chinese medicine with a quite different philosophy system from which we can infer that acupuncture therapy for the treatment of stroke may also have an effect on POCD. Although the exact role of the therapy by traditional Chinese medicine of POCD remains elusive, but from the view of traditional Chinese medicine, POCD can be classified as a kind of deficiency syndrome which is caused by spleen and kidney deficiency, blood deficiency, meridians emptiness, and even the pathogenic wind. The history of acupuncture can be dated back to thousands of years ago. The Canon of Medicine reviewed that acupuncture therapy can be used to dredge the meridians, regulate Qi and Blood to relieve pain, numbness and swelling.

Since the 1950s, research and application of perioperative stimulate acupuncture are mainly concentrated in anesthesia and analgesia, its underlying biological mechanisms are largely unknown. So far, numerous studies have confirmed the effectiveness of assisted anesthesia by acupuncture, which can reduce the amount of narcotic drugs, mitigate stress, reduce complications and improve the patients' quality of life (1).

In clinical practice, it is mainly based on the principles of consciousness-restoring resuscitation to choose acupoints from Yin and Du me-

Table. Difference of Oxygen and Glucose Contents Between Blood Samples of Arterial and Jugular Bulb (Da-jvO₂, Da-jvGlu).

| | Da-jvGlu (mg/l) | Da-jvO ₂ (ml/l) |
|--------------------|-----------------|----------------------------|
| Experimental group | 91±35 | 42±18 |
| Control group | 97±33 | 50±19 |
| *P value | P<0.05 | P<0.01 |

Statistical significance was considered when *P value<0.05.

ridians, often Taixi (KI3), Baihui (DU20), Hegu (LI4), Neiguan (PC6), Tsusanli (ST36) and Sanyinjiao (SP6) (19). The basic theory of traditional Chinese medicine called "treatment based on syndrome differentiation", stimulating acupuncture points above may regulate Qi activity and relieve Qi stagnation and Blood stasis.

With the acupoint stimulation, one research on Sprague-Dawley rat models of focal cerebral ischemia-reperfusion injury showed that the volume of cerebral infarction deeply decreased from (61.72 ± 7.12)% to (22.37 ± 4.42)% (20), which was probably based on the mechanism that acupoint stimulation showed the effect of inhibiting the intake of oxygen and glucose on neurons by monitoring its difference of oxygen and glucose contents between blood samples of arterial and jugular bulb (Da-jvO₂, Da-jvGlu) (21) (Table).

The Effect of Perioperative Acupoint Stimulation

Acupoint stimulation, especially the transcutaneous electrical acupoint stimulation (TEAS), could reduce the concentration of epinephrine and norepinephrine in patients (2), which means that the realization of curative effect may be caused by alleviating surgery-related stress response on the body. Compared with conventional anesthesia, anesthesia with acupoint stimulation together made the amount of narcotic drugs, extubation and recovery time had a significantly reduction (1, 22), which helped anesthesiologists to optimize management of patients' perioperative blood pressure (23). In another research, a conclusion can be inferred that because of the perioperative acupoint stimulation, concentrations of markers of brain injury S-100β protein in serum are also declined (24). Acupoint stimulation produces the protective effect on brain by the above-described action during the perioperative period (25), thus contributing to prevent the occurrence of POCD.

There are further studies have shown that compared with the use of continuous wave electrical stimulation, the using of 2HZ-100HZ density waves performed better that may be related to the effects of fatigue of acupuncture points to electrical stimulation (3). In recent years, some clinical studies indicated that compared with the patients received general anesthesia, the incidence of POCD in those patients who received TEAS during the surgery was significantly decreased at about one to four days after surgery, but there was no significant difference in long-term (≥5 d) incidence (2-4). While the DSM-IV (26) states that it can only be diagnosed as POCD if the cognitive disturbance doesn't meet the criteria for delirium, dementia, or amnesic disorder, and in further species, an individual must has a new onset of deficits in at least two areas of cognitive functioning lasting for a period of at least 2 weeks. So, which kind of cognitive dysfunctions we observed within 4 days after surgery and how does TEAS really work on it still remains further studies to finger it out.

Some scholars' analysis showed that after a variety of surgical procedures, incidence of POCD at 7 days later was evidently higher than 30 days after (27). The result suggested that cognitive abnormality in the early postoperative stage was probably caused by stress reaction, and pharmacological effects of narcotic drugs and their effects on the nervous system had not been fully recovered. Therefore, the evaluation of POCD should be done after 3 months of the surgical procedure, so as to provide a reliable result and rule out of the impact of these factors (12).

Probable Mechanism of Acupoint Stimulation

Studies have shown that stimulation of Baihui and Neiguan can improve blood perfusion of brain and further strengthen the microcirculation and metabolism. The stimulation can also lower the expression of some kinds of inflammatory factors such as cyclooxygenase2 (COX-2), TNF and IL by inhibiting NF-κB signal transduction pathway, in order to contribute to the restoration of the cell function of central nervous system (28).

Acupuncture on Hegu can cause the activation of brain function within a broader region,

which will further showed significant sedative and analgesic effects (29).

Needling Tsusanli can regulate body movement, sensation, language, memory, learning, and the spirit and visceral activities by activating the brain mainly in the temporal lobe and some parts of the frontal, insula, parietal lobe, lingulate gyrus and cerebellum (30). The concentrations of TNF, IL-6 and human high-mobility group box-1 (HMGB1) in serum, TNF- α mRNA and protein levels in spleen were both down regulated, which showed the anti-inflammation effects of this acupoint (31-33). In addition, intervention by TEAS on Hegu and Tsusanli can reduce the metabolism of glucose and oxygen in the brain during the perioperative period, thereby increasing the tolerability of brain ischemia (21). Although there are still some disputes on whether lactate could be energy substrates of brain, some researchers have already noticed that TEAS may protect brain cells by affecting the uptake of lactate (34). In animal experiments, it showed that these two acupoints had the potential of protecting from brain injury by increasing thalamus blood flow and improving oxygen delivery obviously from (84.33 \pm 50.65) PU to (161.80 \pm 73.65) PU under deliberated hypotension when mean arterial pressure (MAP) decreased to 40% of baseline for at least 1 hour (35).

At present, except inflammatory reactions, oxygen radical has also been known as playing an important role in the genesis and development of POCD (13, 36). TAES can increase superoxide dismutase (SOD) level, inhibit malondialdehyde (MDA) gather and play a role to protect brain function. SOD is a kind of antioxidative enzyme which can scavenge oxygen radicals, thereby blocking the lipid peroxidation chain re-

action (36). MDA is a metabolic product of the peroxidation of unsaturated fatty acid in biofilm initiated by oxygen radicals. With the lower concentrations of MDA and hypersensitive C-reactive protein (hs-CRP) caused by TEAS, it can be inferred that TAES may play a role in improving postoperative cognitive function by reducing oxidative stress reactions (32).

Conclusion

So far, researches on effects of acupuncture stimulation on POCD are mostly in non-cardiac surgery patients, while the traditional view is generally considered that cardiopulmonary bypass (CPB) is a risk factor for the occurrence of POCD (37). But one research with the patients treated with off-pump coronary artery bypass grafting (OPCABG) showed that even though without CPB and TEAS therapy, the incidence of POCD was still not significantly decreased (38). This happens probably because, in such kind of patients, chronic cardiovascular diseases are commonly found with them and effects of long-term cerebral perfusion is beyond the extent of acupoint stimulation can alleviate. Chronic cardiovascular disease may also be an independent risk factor of POCD which is similar to the age.

In summary, to confirm the effects of acupoint stimulation therapy on POCD, some more researches and clinical practice are still needed, and larger, more adequately powered studies are also required to draw the best solution to stimulate acupuncture points, which may also become a breakthrough on mechanisms of POCD.

No potential conflict of interest relevant to this review was reported.

References

1. Liu X, Li S, Wang B, An L, Ren X, Wu H. Intraoperative and postoperative anaesthetic and analgesic effect of multipoint transcutaneous electrical acupuncture stimulation combined with sufentanil anaesthesia in patients undergoing supratentorial craniotomy. *Acupunct Med* 2015;33:270-6.
2. Tang L, Ma C, You F, Ding L. Impacts of the low-frequency electric stimulation at the acupoints on the content of plasma 5-HT and NE in the patients with post-stroke insomnia. *Zhongguo Zhen Jiu* 2015;35:763-7.
3. Lin SY, Gao J, Yin ZL, Zhou LJ, Chen X. Impacts of the different frequencies of electroacupuncture on cognitive function in patients after abdominal operation under compound anesthesia of acupuncture and drugs. *Zhongguo Zhen Jiu* 2013;33:1109-12.
4. Gao XQ, Zhang ZY, Ma WH. Effects of electroacupuncture assistant general anesthesia on postoperative cognitive dysfunction of aged patients. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2012;32:591-3.
5. Bedford PD. Adverse cerebral effects of anaesthesia on old people. *Lancet* 1955;269:259-63.
6. Zhang J, Tan H, Jiang W, Zuo Z. Amantadine alleviates postoperative cognitive dysfunction possibly by increasing glial cell line-derived neurotrophic factor in rats. *Anesthesiology* 2014;121:773-85.
7. Qiu LL, Ji MH, Zhang H, Yang JJ, Sun XR, Tang H, et al. NADPH oxidase 2-derived reactive oxygen species in the hippocampus might contribute to microglial activation in postoperative cognitive dysfunction in aged mice. *Brain Behav Immun* 2016;51:109-18.
8. Rundshagen I. Postoperative cognitive dysfunction. *Dtsch Arztebl Int* 2014;111:119-25.
9. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* 2008;108:18-30.
10. Dokkedal U, Hansen TG, Rasmussen LS, Mengel-

- From J, Christensen K. Cognitive functioning after surgery in middle-aged and elderly Danish twins. *Anesthesiology* 2016;124:312-21.
11. Saczynski JS, Inouye SK, Guess J, Jones RN, Fong TG, Nemeth E, et al. The Montreal cognitive assessment: creating a crosswalk with the mini-mental state examination. *J Am Geriatr Soc* 2015;63:2370-4.
 12. Evered L, Silbert B, Scott DA, Ames D, Maruff P, Blennow K. Cerebrospinal fluid biomarker for alzheimer disease predicts postoperative cognitive dysfunction. *Anesthesiology* 2015;124:353-61.
 13. Lu SM, Yu CJ, Liu YH, Dong HQ, Zhang X, Zhang SS, et al. S100A8 contributes to postoperative cognitive dysfunction in mice undergoing tibial fracture surgery by activating the TLR4/MyD88 pathway. *Brain Behav Immun* 2014;44:221-34.
 14. Bassil F, Fernagut PO, Bezdard E, Meissner WG. Insulin, IGF-1 and GLP-1 signaling in neurodegenerative disorders: targets for disease modification? *Prog Neurobiol* 2014;118:1-18.
 15. Cape E, Hall RJ, van Munster BC, de Vries A, Howie SE, Pearson A, et al. Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1 β in delirium after hip fracture. *J Psychosom Res* 2014;77:219-25.
 16. Zhao T. Effects of general anesthesia, general compound epidural anesthesia on postoperative cognitive dysfunction in elderly patients with non-cardiac surgery. *Modern Medicine Journal of China* 2014;16:52-4.
 17. Chan MT, Cheng BC, Lee TM, Gin T, CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol* 2013;25:187-90.
 18. Kawano T, Eguchi S, Iwata H, Tamura T, Kumagai N, Yokoyama M. Impact of preoperative environmental enrichment on prevention of development of cognitive impairment following abdominal surgery in a rat model. *Anesthesiology* 2015;123:160-70.
 19. Chen S, Xu M, Li H, Liang J, Yin L, Liu X, et al. Acupuncture at the Taixi (KI3) acupoint activates cerebral neurons in elderly patients with mild cognitive impairment. *Neural Regen Res* 2014;9:1163-8.
 20. Liang DD, Wang HF, Zhang MX, Dai QX, Liu HC, Mo YC, et al. Local adenosine A1 receptor of baihui acupoint mediate cerebral ischemia tolerance induced by electroacupuncture. *Zhonghua Yi Xue Za Zhi* 2013;93:537-40.
 21. Wang JL, Ren QS, Pei SL. Effect of transcutaneous acupoint electrical stimulation on brain oxygen and glucose metabolism in the perioperative period of the craniocerebral operation. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2008;28:201-5.
 22. Wang H, Xie Y, Zhang Q, Xu N, Zhong H, Dong H, et al. Transcutaneous electric acupoint stimulation reduces intra-operative remifentanyl consumption and alleviates postoperative side-effects in patients undergoing sinusotomy: a prospective, randomized, placebo-controlled trial. *Br J Anaesth* 2014;112:1075-82.
 23. Jones AY, Kwan YL, Leung NT, Yu RP, Wu CM, Warburton DE. Electrical stimulation of acupuncture points and blood pressure responses to postural changes: a pilot study. *Am J Crit Care* 2011;20:67-74.
 24. Lin SY, Yin ZL, Gao J, Wen HM, Zhou LJ. Influences of acupuncture anesthesia on postoperative cognitive dysfunction and S-100 β protein level of the elderly patients of colorectal cancer resection. *Chinese Acupuncture & Moxibustion* 2013;33:63-6.
 25. Liu Z, Shen YJ, Lian LL, Sha XM, Fang JQ. Inflammatory-modulating mechanism of transcutaneous electrical acupoint stimulation combined with general anesthesia or controlled hypotension on postoperative hippocampal neuroprotection. *Zhongguo Zhen Jiu* 2013;33:149-55.
 26. American Psychiatric Association. Diagnostic criteria from DSM-IV-TR. Washington, D.C.: American Psychiatric Association, 2000.
 27. Evered L, Scott DA, Silbert B, Maruff P. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesth Analg* 2011;112:1179-85.
 28. Liu F, Fang J, Shao X, Liang Y, Wu Y, Jin Y. Electroacupuncture exerts an anti-inflammatory effect in a rat tissue chamber model of inflammation via suppression of NF- κ B activation. *Acupunct Med* 2014;32:340-5.
 29. Kong SP, Tan QW, Liu Y, Jing XH, Zhu B, Huo YJ, et al. Specific correlation between the Hegu Point (LI4) and the Orofacial Part: evidence from an fMRI study. *Evid Based Complement Alternat Med* 2015; 2015:585493.
 30. Yi G, Wang J, Bian H, Han C, Deng B, Wei X, et al. Multi-scale order recurrence quantification analysis of EEG signals evoked by manual acupuncture in healthy subjects. *Cogn Neurodyn* 2013;7:79-88.
 31. Jiang SH, Tu WZ, Zou EM, Hu J, Wang S, Li JR, et al. Neuroprotective effects of different modalities of acupuncture on traumatic spinal cord injury in rats. *Evid Based Complement Alternat Med* 2014; 2014:431580.
 32. Guo AS, Li AH, Chen X, Chen WG, Sun L. Effect of acupoint catgut embedding on motor function and serum high sensitivity C-reactive protein and IL-6 levels in patients with acute cerebral infarction. *Zhen Ci Yan Jiu* 2013;38:224-8,58.
 33. Lim HD, Kim MH, Lee CY, Namgung U. Anti-inflammatory effects of acupuncture stimulation via the vagus nerve. *PLoS One* 2016;11:e0151882.
 34. Urroz P, Colagiuri B, Smith CA, Cheema BS. Effect of acute acupuncture treatment on exercise performance and postexercise recovery: a systematic review. *J Altern Complement Med* 2012;19:9-16.
 35. Shao XM, Fang JQ, Zhou CL, Guo XQ, Zhang LL, Jin L. Effect of deliberate hypotension on thalamus regional blood flow during general anesthesia combined with transcutaneous electrical acupoint stimulation. *J Clin Anesthesiol* 2012;28:599-601.
 36. Yuan S, Zhang X, Bo Y, Li W, Zhang H, Jiang Q. The effects of electroacupuncture treatment on the postoperative cognitive function in aged rats with acute myocardial ischemia-reperfusion. *Brain Res* 2014;1593:19-29.
 37. Hudetz JA, Amole O, Riley AV. Elevated biochemical markers of myocardial injury are not associated with postoperative cognitive dysfunction after coronary artery surgery. *J Anesth Clin Res* 2011;2:134.
 38. Zhou J, Zhao YH. Effects of electroacupuncture on neiguan on postoperative cognitive dysfunction in patients undergoing off-pump coronary artery bypass grafting. *Journal of Clinical Anesthesiology* 2011;27:1188-9.